# MEDICAL POLICY

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| **Medical Policy Title** | **Molecular Testing of Tumor Tissue to Identify Targeted Therapies for Cancers** |
| **Policy Number** | **2.02.51** |
| **Current Effective Date** | February 20, 2025 |
| **Next Review Date** | February 2026 |

Our medical policies are based on the assessment of evidence based, peer-reviewed literature, and professional guidelines. Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract. (Link to Product Disclaimer)

## POLICY STATEMENT(S)

I. Gene mutational analysis of tumor tissue is considered **medically appropriate** when **ALL** the following criteria are met:

A. To direct targeted therapy;

B. The results will be used to guide management of the patient;

C. In the treatment of **ANY** of the following: (CPT code examples not all inclusive)

1. **Metastatic colorectal cancer** for the following targeted genes:
   a. Kirsten rat sarcoma viral oncogene (KRAS) (CPT: 81275, 81276);
   b. Neuroblastoma RAS viral oncogene (NRAS) (CPT: 81311);
   c. B-Raf proto-oncogene (BRAF) (CPT: 81210);
   d. Human epidermal growth factor receptor 2 (HER2) amplification;
   e. Neurotrophic tyrosine receptor kinase (NTRK) gene fusions (CPT: 81191-81193, 81194);
   f. POLE/POLD1;
   g. Rearranged during transfection (RET).
   h. MSI/MMR status (if not previously done).
2. **Non-small-cell lung cancer (NSCLC)** including adenocarcinoma, large cell, squamous cell, and NSCLC not otherwise specified for the following targeted genes:
   a. Epidermal Growth Factor Receptor (EGFR) gene mutations (CPT: 81235);
   b. Anaplastic lymphoma kinase (ALK) gene rearrangement;
   c. KRAS (CPT: 81275, 81276);
   d. NTRK 1/2/3 gene fusion (CPT: 81191-81193, or 81194);
   e. ROS proto-oncogene 1 (ROS-1) gene rearrangement;
   f. BRAF point mutations (CPT: 81210);

g. Mesenchymal-epithelial transition MET exon 14 skipping variants;
h. High-level MET amplification;
i. RET gene rearrangements;
j. Erb-B2 Receptor Tyrosine Kinase 2 (ERBB2)/(HER2) gene mutation.

3. Stage III **melanoma** at high risk of recurrence, stage IV melanoma, or clinical recurrence for the following targeted gene mutations:
   a. BRAF (CPT: 81210);
   b. KIT (CPT: 81272).
4. Newly diagnosed **metastatic pancreatic cancer** or metastatic pancreatic cancer that is progressing on or after chemotherapy or immunotherapy, and have never been tested for molecular biomarker analysis for the following targeted gene mutations:
   a. Anaplastic lymphoma kinase (ALK) gene fusions;
   b. NRG1 gene fusions;
   c. NTRK 1/2/3 gene fusion (CPT: 81191-81193, or 81194);
   d. ROS-1 gene fusion;
   e. BRAF gene mutation (CPT: 81210);
   f. BRCA 1/2 gene mutation (CPT 81162);
   g. KRAS gene mutation (CPT: 81275, 81276);
   h. PALB2 gene mutation (CPT: 81307);
   i. HER2 amplifications;
   j. FGFR2 gene fusion;
   k. RET gene fusion;
   l. Microsatellite instability (MSI)/ DNA mismatch repair (MMR)
   m. TMB
5. Recently diagnosed or recurrent **ovarian cancer** for the following targeted gene mutations:
   a. BRCA 1/2 (CPT 81162);
   b. Homologous recombination deficiency (HRD) status;
   c. MSI/MMR;
   d. TMB;
   e. NTRK (CPT: 81191-81193, or 81194);

f. BRAF (CPT: 81210);
g. FRα;
h. RET.
i. HER2

6. **Metastatic prostate cancer** for the following targeted gene mutations:
   a. BRCA 1/2 (CPT 81162);
   b. ATM;
   c. PALB2 (CPT 81307);
   d. FANCA;
   e. RAD51D;
   f. CHEK2;
   g. CDK12;
   h. MSI/MMR.
   i. TMB
7. **Breast cancer** (note specific classifications by genes below) for the following targeted gene mutations:
   a. PIK3CA mutation (HR-positive/HER2-negative breast cancer) (CPT 81309);
   b. NTRK fusion (all breast cancers) (CPT: 81191-81193, or 81194);
   c. MSI/MMR (all breast cancers);
   d. TMB (all breast cancers);
   e. Estrogen Receptor 1 (ESRI) (HR-positive/HER2-negative breast cancer) at progression following prior lines of endocrine therapy;
   f. RET (all breast cancers).
8. **Primary brain tumors** for the following targeted gene mutations:
   a. Isocitrate dehydrogenase 1 (IDH1) and IDH2 (CPT: 81120, 81121);
   b. 1p19q codeletion;
   c. 6 -methylguanine-DNA methyl-transferase (MGMT) (CPT: 81287);
   d. ATRX;
   e. Telomerase reverse transcriptase (TERT) (CPT: 81345);
   f. BRAF V600 (CPT: 81210);

g. H3-3A
h. NTRK

9. **Ependymomas** for the following targeted gene mutations:
   a. ZFTA;
   b. YAP1;
   c. MYCN;
10. **Medulloblastoma** for the following targeted gene mutations:
    a. CTNNB1;
    b. GAB1;
    c. YAP1;
    d. TP53.

D. Testing for genetic alterations in any other genes than those listed above is considered **investigational**.

Other Cancers

II. Gene mutational analysis of tumor tissue to predict response to targeted therapies and to direct targeted therapy, is considered **medically appropriate** for **ALL** of the following:
   A. Testing is recommended (2A or 1) by the current NCCN Guidelines for the cancer indication;
   B. Testing should include only the number of genes necessary for therapeutic decision making;
   C. The results will be used to guide management of the patient; and
   D. Diagnosed with **EITHER** of the following
      1. Who have previous biopsy-confirmed, newly diagnosed advanced stage III or IV or metastatic cancer; **or**
      2. 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.

III. Programmed death receptor 1 (PD-1) or its ligand (PDL-1) expression analysis is considered **medically appropriate** as a technique to predict treatment response to drug therapy.

IV. Tumor tissue testing to identify targeted cancer treatment with a comprehensive genomic profiling test (e.g. FoundationOne CDx, CARIS Life Sciences MI Tumor Seek Hybrid, MSK-IMPACT, TEMPUS xT), has not been medically proven to be effective and, therefore, is considered **investigational**.

## RELATED POLICIES

Corporate Medical Policy

2.02.53 JAK2, MPL, and CALR Molecular Testing for Myeloproliferative Neoplasm

2.02.54 Measurable Residual Disease Assessment Testing

2.02.56 Circulating Tumor DNA for Management of Cancer (Liquid Biopsy)

11.01.03 Experimental or Investigational Services

## POLICY GUIDELINE(S)

I. Smaller targeted panels with actionable gene mutations and drug therapies based on the presence of a specific mutation may be approvable.

II. A negative liquid biopsy test result should be followed by reflex testing to a formalin-fixed paraffin-embedded tissue test.

III. A liquid biopsy and formalin-fixed paraffin-embedded tissue test should not be tested simultaneously.

IV. The Health Plan and its employees adhere to all State and Federal laws concerning the confidentiality of genetic testing and the results of genetic testing. All records, findings and results of any genetic test performed on any person shall be deemed confidential and shall not be disclosed without the written informed consent of the person to whom such genetic test relates. This information shall not be released to any person or organization not specifically authorized by the individual subject of the test or in compliance with applicable law.

V. Genetic testing is appropriate only when performed by a qualified laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and offered in a setting with adequately trained health care professionals who are qualified to provide appropriate pre- and post-test counseling.

VI. Genetic testing is contract dependent. Coverage only applies to members with a valid contract; coverage is not provided for family members without a valid contract.

VII. Supporting documentation required - for other cancers not listed in the policy:

The purpose of tumor tissue testing is to provide information that will assist in predicting response to targeted therapies or to direct targeted therapy. Documentation that must be submitted for review includes all of the following documentation:

A. The purpose of the test;

B. The gene mutation(s) to be tested;

C. The drug therapy plan based on results of the testing; and

D. Supportive evidence demonstrating efficacy of the proposed drug therapy for the gene mutation in patient's cancer.

## DESCRIPTION

According to the Precision Medicine Initiative, precision medicine is an emerging approach for disease treatment and prevention that considers individual variability in genes, environment, and lifestyle for each person. Research has been directed to understanding molecular variations in tumors from different cancer types so that drugs used to treat the tumors are "targeted" or directed to inhibit the function of the molecular alteration. The goal of precision medicine is to maximize efficiency and minimize side effects of therapy.

Multigene Panel Testing

Comprehensive Genomic Profiling tests evaluate between 140-300 genes in tumor tissue for which there are only a small number of FDA-approved targeted therapy options. Large panel tests contain many genes that have no actionable gene mutations, thus no targeted therapy. Molecular panel testing has been used to determine off-label drug therapy or whether or not a patient may be eligible for a clinical trial. Of those patients tested, only a small number will experience clinical utility (have a targeted therapy identified), and an even smaller number will experience clinical benefit.

## SUPPORTIVE LITERATURE

Comprehensive Genomic Profiling Tests

It is difficult to determine the clinical validity of the molecular panels because of the different mutations and the large number of potential cancers for which they can be used. Testing each gene in the panel for each of the cancer types would require extensive research potentially taking many years to complete. Consequently, the evidence on clinical validity of the molecular panels is insufficient to make any recommendations.

The evidence for clinical utility of molecular panel testing to direct targeted therapies in cancer patients has been conflicting. The SHIVA study, a randomized, open-label phase 2 trial, randomized patients with any kind of metastatic solid tumor refractory to standard of care (Le Tourneau 2015) to matched molecularly targeted treatment based on one of three molecular pathways; hormone receptor, PI3K/AKT/mTOR, and RAF/MEK (the experimental group) or physician's choice treatment (the control group). At median follow-up of 11.3 months, median progression-free survival was similar for both groups. Grade 3 to 4 adverse events were slightly higher in the experimental group. The authors concluded that progression-free survival was not improved with the use of molecularly targeted agents outside their indications, compared with the physician's choice treatment in heavily pretreated patients with cancer. Off-label use of molecularly targeted agents should be encouraged in clinical trials to assess predictive biomarkers of efficacy.

The IMPACT study (Tsimberidou 2017), a phase I study at the University of Texas, MD Anderson Cancer Center, assessed whether molecular analysis of advanced cancer and targeted therapy was associated with improved clinical outcomes. Of the 1,144 patients analyzed, 40.2% had one or more

molecular aberration in their tumor. The patients with one aberration and matched therapy had a higher overall response rate (27%) compared to those patients without matched therapy (5%). Patients with matched therapy had longer time-to-treatment failure (5.2 months) and longer survival (13.4 months) compared to those patients without matched therapy (2.2 months and 9.0 months, respectively).

## PROFESSIONAL GUIDELINE(S)

Colorectal Cancer

The Molecular Biomarkers for the Evaluation of Colorectal Cancer Guidelines from the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American society of Clinical Oncology (Sepulveda 2017) recommend RAS mutational testing for colorectal carcinoma patients being considered for anti-EGFR therapy. 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. Quality of evidence: high/intermediate). 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. Quality of evidence: intermediate/low).

The NCCN guidelines for Colon Cancer (V.5.2024) have expanded recommendations regarding biomarker testing as the role of targeted therapy for treatment of advanced or metastatic colorectal cancer (mCRC) has become increasingly prominent. Currently, determination of tumor gene status for KRAS/NRAS and BRAF mutations, as well as HER2 amplifications and MSI/MMR status (if not previously done), are recommended for patients with mCRC. The testing can be performed on formalin-fixed paraffin-embedded tissue (preferred) or blood-based assay and may be carried out for individual genes or as part of an NGS panel, although no specific methodology is recommended. NGS panels have the advantage of being able to pick up rare and actionable genetic alterations, such as neurotrophic tyrosine receptor kinase (NTRK) fusions. Based on the limited data in the colorectal cancer population, the NCCN Panel does not currently recommend TMB biomarker testing, unless measured as part of a clinical trial. Patients with known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab. BRAF V600E mutation makes response to panitumumab or cetuximab highly unlikely unless given with a BRAF inhibitor. HER2-targeted therapies are now recommended as subsequent therapy options in patients with tumors that have HER2 overexpression. Testing for HER2 amplifications for patients with metastatic colorectal cancer is recommended. If the tumor is already known to have a KRAS/NRAS or BRAF mutation, HER2 testing is not required. However, HER2-targeted therapies are still under investigation, enrollment in a clinical trial is encouraged. Anti-HER2 therapy is only indicated in HER2-amplified tumors that are also RAS and BRAF wild type. NTRK fusions were limited to cancer that were wild type for KRAS, NRAS, and BRAF. A majority of the CRCs harboring NTRK fusions were also MMR-deficient. NTRK fusion testing may be limited to those patients with wild-type KRAS, NRAS, and BRAF. There are two targeted therapies (larotrectinib and entrectinib) that have been FDA-approved for the treatment of patients with metastatic, unresectable solid tumors that have an NTRK gene fusion and no satisfactory alternative treatment options, regardless of the location of the primary

tumor. These treatment options are not appropriate for most patients due to the rarity of the NTRK fusion in CRC.

Non-Small Cell Lung Cancer

The NCCN guidelines for Non-Small Cell Lung Cancer (NSCLC) (V.11.2024) 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. If there is insufficient tissue to allow testing for all of EGFR, ALK, ROS1, BRAF, ERBB2 (HER2), KRAS, NTRK 1/2/3, MET, and RET, repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results, and, if unknown, these patients are treated as though they do not have driver oncogenes. Erlotinib is recommended, with or without chemotherapy, as first-line therapy for advanced or metastatic NSCLC in patients with known activated EGFR mutation or gene amplification. EGFR mutations were predictive of a better response in patients receiving erlotinib (53% in patients with mutations versus 18% in those without mutations). KRAS mutations are associated with intrinsic TKI resistance and KRAS gene sequencing could be useful for the selection of patients as candidates for TKI therapy. Overlapping EGFR and KRAS mutations occur in less than 1% of patients with lung cancer. Other TKIs such as, Afatinib and Osimertinib have been recommended by NCCN in patients with EGFR mutations and metastatic NSCLC. Afatinib has been recommended and FDA approved for first-line therapy in patients with metastatic non-squamous NSCLC who have sensitizing EGFR mutations. Osimertinib has been approved by the FDA for patients with metastatic EGFR T790M mutation-positive NSCLC, who have progressed on or after EGFR TKI therapy. NCCN recommends Osimertinib for individuals with stage IB NSCLC with EGFR exon 19 deletion or L858R. ROS1 gene rearrangements occur more frequently in younger women with adenocarcinoma who are never smokers and in those who are negative for EGFR mutations, KRAS mutations, and ALK gene rearrangements (also known as triple negative). Crizotinib is very effective for patients with ROS1 rearrangement with response rates of about 70% including complete responses. The FDA has approved crizotinib for patients with ROS1 rearrangements.

Other genetic alterations such as, BRAF V600E and HER2 mutations, MET amplification, and RET rearrangements have been associated with emerging targeted therapies. Targeted agents are available for patients with NSCLC who have these other genetic alterations, although they are FDA approved for other indications.

As a primary immunosuppressive driver, PD-L1 overexpression may be an important facilitator for tumor growth and metastasis. PD-L1 has been detected in up to 50% of human cancers, making the PD-L1 pathway a focus of cancer research. NCCN recommends IHC testing for PD-L1 expression before first-line treatment in patients with metastatic NSCLC with negative or unknown test results for EGFRT mutations, ALK rearrangements, and ROS1 rearrangements. Although it is not an optimal biomarker, PD-L1 expression is currently the best available biomarker to assess whether patients are candidates for pembrolizumab. PD-L1 expression is continuously variable and dynamic; thus, a cutoff value for a positive result is artificial. Patients with PD-L1 expression levels just below and just above 50% will probably have similar responses. The definition of a positive PD-L1 test result varies

depending on which biomarker assay is used. For the 2022 update, the NCCN NSCLC Panel recommends testing for ERBB2 (HER2) mutations in eligible patients with metastatic NSCLC based on clinical trial data and the FDA approval of fam-trastuzumab deruxtecan-nxki. ERBB2 (HER2) exon 20 mutations occur in approximately 3% of patients (median age, 62 years) with advanced nonsquamous NSCLC. Patients tend to be females who do not smoke cigarettes; they have a higher incidence of brain metastases than those with other actionable mutations. Emerging predictive molecular biomarkers include high-level MET amplifications. Targeted agents are available for patients with NSCLC who have high-level MET amplifications. However, there is less data to support using these agents and they may not be FDA approved for NSCLC; therefore, they are referred to as emerging biomarkers.

The College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) guidelines on molecular testing for the selection of patients with lung cancer for epidermal growth factor receptor (EGFR) recommend EGFR molecular testing in patients with lung adenocarcinoma and mixed lung cancers with an adenocarcinoma component regardless of clinical characteristics (e.g., younger age, smoking status) for EGFR-targeted TKI therapy. EGFR mutation testing should be ordered at the time of diagnosis for patients who present with advanced-stage disease who are suitable for therapy, or at time of recurrence or progression in patients who originally presented with lower stage disease but were not previously tested, or testing tumors at time of diagnosis for stage I, II, or III disease so that molecular information is available to an oncologist at the time of recurrence for a subset of patients who subsequently experience recurrence, although this decision is deferred to local laboratories and oncology teams. KRAS mutation testing is not recommended as a sole determinant of EGFR-targeted therapy.

Melanoma

The NCCN guidelines for Cutaneous Melanoma (V.3.2024) state emerging molecular technologies for cutaneous melanoma diagnosis and prognostication indications include that BRAF or next-generation sequencing (NGS) for resected stage I-II cutaneous melanoma is not recommended unless it will inform clinical trial participation. BRAF mutation is recommended for patients with stage III at high risk for recurrence for whom future BRAF-directed therapy may be an option. For initial presentation with stage IV disease or clinical recurrence, obtain tissue to ascertain alterations in BRAF, and in the appropriate clinical setting, KIT from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy. Broader genomic profiling (e.g., larger NGS panels, BRAF non-V600 mutations) is recommended if feasible, especially if the test results might guide future treatment decisions or eligibility for participation in a clinical trial. If BRAF single-gene testing was the initial test performed, and is negative, clinicians should strongly consider larger NGS panels to identify other potential genetic targets (e.g., KIT, BRAF non-V600).

BRAF and KIT mutations appear to be early genetic driver events in melanoma. Thus, repeat molecular testing upon recurrence or metastases is likely to be of low yield. Repeat testing following progression on targeted therapy (BRAF- or KIT-directed therapy) does not appear to have clinical

utility, since the mechanisms of resistance are diverse and do not have prognostic or therapeutic relevance.

Pancreatic Cancer

The NCCN guidelines for Pancreatic Adenocarcinoma (V.3.2024) recommend gene profiling of tumor tissue as clinically indicated for individuals with locally advanced/metastatic disease who are candidates for anti-cancer therapy to identify uncommon mutations. Consider specifically testing for actionable somatic findings including, but not limited to fusions (ALK, NRG1, NTRK, ROS1, FGFR2, RET), mutations (BRAF, BRCA 1/2, KRAS, PALB2), amplifications (HER2), microsatellite instability (MSI), and/or mismatch repair (MMR) deficiency. Testing on tumor tissue is preferred and may be performed if recurrence after resection if not previously performed.

Ovarian Cancer

The NCCN guidelines for Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer (V.3.2024) state comprehensive tumor testing may not be necessary for certain patients in the upfront setting, specifically those with a germline mutation in BRCA1/2 or other homologous recombination/DNA repair pathway genes. Initially molecular analysis should include BRCA1/2 status, loss of heterozygosity, or homologous recombination status, in the absence of a germline BRCA mutation. However, some patients (such as those who lack a BRCA1/2 mutation or experience disease recurrence) may benefit from a more thorough tumor molecular analysis to inform additional targeted therapy options. In the recurrence setting, tumor molecular analysis is recommended to include, at a minimum, tests to identify potential benefit from targeted therapeutics that have tumor-specific or tumor-agnostic benefit including, but not limited to, BRCA1/2, HR status, MSI, MMR, TMB, BRAF, FRα, RET, and NTRK if prior testing did not include these markers. Additional somatic tumor testing can be considered at the physician's discretion to identify genetic alterations for which FDA-approved tumor-specific or tumor-agnostic targeted therapy options exist. These additional tests may be particularly useful for patients who recurrence therapy options are limited.

Prostate Cancer

The NCCN guidelines for Prostate Cancer (V.1.2025) state 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. Clinical trials may include established and/or candidate molecular biomarkers for eligibility. Tumor molecular profiles may change with subsequent treatments and re-evaluation may be considered at time of cancer progression for treatment decision-making. Tumor testing for alterations in homologous recombination DNA repair genes, such as BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2, and CDK12, is recommended for individuals with metastatic prostate cancer and can be considered in individuals with regional (N1) prostate cancer. Tumor testing for MSI-H or dMMR is also recommended in patients with metastatic castration-resistant prostate cancer and may be considered in patients with regional or castration-sensitive metastatic prostate cancer. Early studies suggest germline and somatic mutations in these genes may be predictive of the clinical

benefit of poly-ADP ribose polymerase (PARP) inhibitors. At present, two PARP inhibitors are approved by the FDA for use in prostate cancer are Olaparib and Rucaparib.

Breast Cancer

The NCCN guidelines for Breast Cancer (V.6.2024) state for recurrent unresectable (local or regional) or stage IV disease, for HR-positive/HER2-negative breast cancer, assess for PIK3CA mutations with tumor tissue to identify candidates for alpelisib plus fulvestrant. (Category 1 Evidence). In triple negative breast cancer, PD-L1 can be assessed by IHC (Category 1 Evidence). In all types of breast cancer NTRK fusion and MSI/MMR can be assessed in tumor tissue and tumor mutational burden (TMB) by NGS (Category 2A Evidence). Larotrectinib and entrectinib are indicated for the treatment of solid tumors that have an NTRK gene fusion without a known acquired resistance mutation and have no satisfactory alternative treatments or that have progressed following treatment. Pembrolizumab is indicated for the treatment of patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, or TMB-H tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. Dostarlimab-gxly is indicated for adult patients with MSI-H/dMMR unresectable or metastatic tumors that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.

Central Nervous System Cancers

The NCCN guidelines for Central Nervous System Cancers (V.3.2024) state with the use of genetic and molecular testing, histologically similar CNS neoplasms can be differentiated more accurately in terms of prognosis and response to different therapies. The fifth edition of the WHO classification of CNS tumors was published in 2021. In this newest classification, adult diffuse gliomas are subsumed within a super category of gliomas and glioneuronal tumors and are split into three subtypes: 1) IDH-mutant astrocytoma; 2) oligodendroglioma, 1p/19q-codeleted and IDH-mutant; and 3) glioblastoma, IDH wild-type. The panel recommends IDH mutation testing in patients with glioma. Testing for 1p/19q codeletion is essential for the diagnosis of oligodendroglioma. Mutation testing for ATRX and TERT promoter are also recommended, given the diagnostic value of these mutations. Grade 3–4 gliomas should undergo testing for MGMT promoter methylation, since MGMT promoter-methylated tumors typically respond better to alkylating chemotherapy, compared to unmethylated tumors. Molecular testing of glioblastomas is encouraged by the panel, as patients with a detected driver mutation (e.g., BRAF V600E mutation or NTRK fusion) may be treated with a targeted therapy on a compassionate use basis, and these tests improve diagnostic accuracy and prognostic stratification. Recurrent or progressive disease of glioblastoma patients should be enrolled in clinical trials evaluating systemic therapy options.

Ependymomas arising in the supratentorium often contain activating fusions of ZFTA. This leads to increased NF-kappa-B signaling and more aggressive behavior. This event is more common in children than in adults, and occurs only in the supratentorium, not the posterior fossa or spine. A subset of spinal cord ependymomas show MYCN amplification. Such tumors tend to behave more aggressively and are therefore now codified as SP-EPN-MYCN. As is often the case in other tumor

types (e.g., medulloblastoma), MYCN amplification is strongly associated with more aggressive behavior and worse prognosis.

Medulloblastomas are WHO grade 4 tumors that predominantly arise from the cerebellum in pediatric patients but can also occur in adults. The WHO committee on CNS tumors now recommends subclassification of these tumors into four distinct groups: i) WNT-activated; ii) Sonic hedgehog (SHH)-activated and TP53-mutant; iii) SHH-activated and TP53- wild type; and iv) non-WNT/non-SHH. Differentiating between WNT-activated, SHH-activated, and non-WNT/ non-SHH tumors is best classified by expression arrays, DNA methylation arrays, or an IHC panel composed of beta-catenin, GAB1, and YAP1. Because there are a variety of hotspots in TP53, gene sequencing is recommended in SHH-activated medulloblastomas. SHH-pathway inhibitors that have been evaluated in phase II trials including adults with recurrent medulloblastoma include vismodegib296 and sonidegib.297 Patients in these trials with SHH-activated disease were more likely to respond than patients with non-SHH disease.

Multigene Panel Testing

The NCCN guidelines contain specific genetic testing guidelines for individual cancers, based on situations in which there is a known mutation-drug combination that has demonstrated benefits for that specific tumor type (e.g., NSCLC, ovarian cancer, colorectal cancer, and melanoma). The NCCN NSCLC Panel (V.11.2024) recommends molecular testing based on clinical trial data, but strongly advises broader molecular profiling, to identify these and other rare driver mutations for which targeted therapies may be available to ensure that patients receive the most appropriate treatment; patients may be eligible for clinical trials for some of these targeted agents. The panel defines broad molecular profiling for NSCLC as molecular testing that identifies all of the classic actionable biomarkers described in the algorithm using either a single assay or a combination of a limited number of assays—and optimally also identifies the emerging biomarkers.

The American Society of Clinical Oncology (ASCO) (Chakravarty 2022) published a clinical opinion paper regarding somatic genetic testing for metastatic or advanced solid tumor cancers. They state genomic testing should be performed when there are genomic biomarker-linked therapies approved by regulatory agencies for the type of cancer and when considering a treatment for which there is a specific genomic biomarker-based contraindication (strength of recommendation: strong). For patients with metastatic or advanced solid tumors, genomic testing using multigene genomic sequencing is preferred whenever patients are eligible for a genomic biomarker–linked therapy that a regulatory agency has approved (strength of recommendation: moderate). Multigene panel–based genomic testing should be used whenever more than one genomic biomarker is linked to a regulatory agency–approved therapy (strength of recommendation: strong). For tumors with actionable genomic alterations without approved genomic biomarker–linked targeted therapies, patient participation in clinical trials is encouraged after considering the expected efficacy of available standard-of-care options (strength of recommendation: strong). Off-label and off-study use of genomic biomarker–linked therapies approved in other diseases is not recommended when a clinical trial is available or without clinical evidence of meaningful efficacy (strength of recommendation: strong).

## REGULATORY STATUS

List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools) | FDA [accessed 2025 Jan 28]

FDA Cleared-Approved-CDx. [accessed 2025 Jan 28]

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 (CLIA). Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing.

## CODE(S)

- Codes may not be covered under all circumstances.
- Code list may not be all inclusive (AMA and CMS code updates may occur more frequently than policy updates).
- (E/I)=Experimental/Investigational
- (NMN)=Not medically necessary/appropriate

**CPT Codes**

| Code | Description |
|---|---|
| 81120 | IDH1 (isocitrate dehydrogenase 1 [NADP+], soluble) (e.g., glioma), common variants (e.g., R132H, R132C) |
| 81121 | IDH2 (isocitrate dehydrogenase 2 [NADP+], mitochondrial) (e.g., glioma), common variants (e.g., R140W, R172M) |
| 81162 | BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (i.e., detection of large gene rearrangements) |
| 81175 | ASXL1 (additional sex combs like 1, transcriptional regulator) (e.g., myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; full gene sequence |
| 81191 | NTRK1 (Neurotrophic Receptor Tyrosine Kinase 1) (e.g., solid tumors) translocation analysis |
| 81192 | NTRK2 (Neurotrophic Receptor Tyrosine Kinase 2) (e.g., solid tumors) translocation analysis |

| Code | Description |
|---|---|
| 81193 | NTRK3 (Neurotrophic Receptor Tyrosine Kinase 3) (e.g., solid tumors) translocation analysis |
| 81194 | NTRK (neurotrophic receptor tyrosine kinase 1, 2, and 3) (e.g., solid tumors) translocation analysis |
| 81210 | BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s) |
| 81235 | EGFR (epidermal growth factor receptor) (e.g., non-small cell lung cancer) gene analysis, common variants (e.g., exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q) |
| 81272 | KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (e.g., gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, targeted sequence analysis (e.g., exons 8, 11, 13, 17, 18) |
| 81275 | KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; variants in exon 2 (e.g., codons 12 and 13) |
| 81276 | KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; additional variant(s) (e.g., codon 61, codon 146) |
| 81287 | MGMT (O-6-methylguanine-DNA methyltransferase) (e.g., glioblastoma multiforme) promoter methylation analysis |
| 81307 | PALB2 (partner and localizer of BRCA2) (e.g., breast and pancreatic cancer) gene analysis; full gene sequence |
| 81309 | PIK3CA (Phosphatidylinositol-4, 5-biphosphate 3-kinase, catalytic subunit alpha) (e.g., colorectal and breast cancer) gene analysis, targeted sequence analysis (e.g., exons 7, 9, 20) |
| 81311 | NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (e.g., colorectal carcinoma), gene analysis, variants in exon 2 (e.g., codons 12 and 13) and exon 3 (e.g., codon 61) |
| 81345 | TERT (telomerase reverse transcriptase) (e.g., thyroid carcinoma, glioblastoma multiforme) gene analysis, targeted sequence analysis (e.g., promoter region) |
| 81402 | Molecular Pathology Procedure Level 3 |

| Code | Description |
|---|---|
| 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 | Solid organ neoplasm, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis |
| 81449 | Solid organ neoplasm, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants and copy number variants or rearrangements, if performed; RNA analysis |
| 81455 (E/I) | Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, 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 |
| 81456 (E/I) | Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis |
| 81457 | Solid organ neoplasm, genomic analysis panel; DNA analysis, microsatellite instability |
| 81458 | Solid organ neoplasm, genomic analysis panel; DNA analysis, copy number variants and microsatellite instability (Effective 01/01/24) |
| 81459 | Solid organ neoplasm, genomic analysis panel; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements (Effective 01/01/24) |
| 81479 | Unlisted molecular pathology procedure |

| Code | Description |
|---|---|
| 88363 | Examination and selection of retrieved archival (i.e., previously diagnosed) tissue(s) for molecular analysis (e.g., KRAS mutational analysis) |
| 0037U (E/I) | 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 (e.g., FoundationOne CDx (F1CDx), Foundation Medicine Inc) |
| 0154U | Oncology (urothelial cancer), RNA, analysis by real-time RT-PCR of the FGFR3 (fibroblast growth factor receptor 3) gene analysis (i.e., p.R248C [c.742C>T], p.S249C [c.746C>G], p.G370C [c.1108G>T], p.Y373C [c.1118A>G], FGFR3-TACC3v1, and FGFR3-TACC3v3) utilizing formalin-fixed paraffin-embedded urothelial cancer tumor tissue, reported as FGFR gene alteration status (e.g.; therascreen FGFR RGQ RT-PCR Kit, QIAGEN, QIAGEN GmbH) |
| 0155U | Oncology (breast cancer), DNA, PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha) (e.g., breast cancer) gene analysis (i.e., 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 (e.g., therascreen PIK3CA RGQ PCR Kit, QIAGEN, QIAGEN GmbH) (effective 04/01/20) |
| 0172U | Oncology (solid tumor as indicated by the label), somatic mutation analysis of BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) and analysis of homologous recombination deficiency pathways, DNA, formalin-fixed paraffin-embedded tissue, algorithm quantifying tumor genomic instability score (myChoice CDx, Myriad Genetics Laboratories, Inc) |
| 0211U (E/I) | 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 (MI Cancer Seek NGS Analysis, Caris MPI d/b/a Caris Life Sciences) |
| 0244U (E/I) | Oncology (solid organ), DNA, comprehensive genomic profiling, 257 genes, interrogation for single-nucleotide variants, insertions/deletions, copy number alterations, gene rearrangements, tumor-mutational burden, and microsatellite instability, utilizing formalin-fixed paraffin-embedded tumor tissue (Oncotype MAPTM Pan-Cancer Tissue Test, Paradigm Diagnostics, Inc, Paradigm Diagnostics, Inc) (Effective 04/01/21) |

| Code | Description |
|---|---|
| 0249U (E/I) | Oncology (breast), semiquantitative analysis of 32 phosphoproteins and protein analytes, includes laser capture microdissection, with algorithmic analysis and interpretative report (Theralink Reverse Phase Protein Array (RPPA), Theralink Technologies, Inc,) |
| 0250U (E/I) | Oncology (solid organ neoplasm), targeted genomic sequence DNA analysis of 505 genes, interrogation for somatic alterations (SNVs [single nucleotide variant], small insertions and deletions, one amplification, and four translocations), microsatellite instability and tumor-mutation burden (PGDx elio tissue complete, Personal Genome Diagnostics, Inc) |
| 0329U (E/I) | Oncology (neoplasia), exome and transcriptome sequence analysis for sequence variants, gene copy number amplifications and deletions, gene rearrangements, microsatellite instability and tumor mutational burden utilizing DNA and RNA from tumor with DNA from normal blood or saliva for subtraction, report of clinically significant mutation(s) with therapy associations (Oncomap ExTra, Exact Sciences, Inc, Genomic Health Inc) |
| 0334U (E/I) | Oncology (solid organ), targeted genomic sequence analysis, formalin-fixed paraffin embedded (FFPE) tumor tissue, DNA analysis, 84 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden (Guardant360 TissueNext, Guardant Health, Inc) |
| 0379U (E/I) | Targeted genomic sequence analysis panel, solid organ neoplasm, DNA (523 genes) and RNA (55 genes) by next-generation sequencing, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability, and tumor mutational burden (Solid Tumor Expanded Panel, Quest Diagnostics) (Effective 04/01/23) |
| 0391U (E/I) | Oncology (solid tumor), DNA and RNA by next-generation sequencing, utilizing formalin-fixed paraffin-embedded (FFPE) tissue, 437 genes, interpretive report for single nucleotide variants, splice-site variants, insertions/deletions, copy number alterations, gene fusions, tumor mutational burden, and microsatellite instability, with algorithm quantifying immunotherapy response score (Strata Select, Strata Oncology, Inc) (Effective 07/01/23) |

| Code | Description |
|---|---|
| 0414U (E/I) | Oncology (lung), augmentative algorithmic analysis of digitized whole slide imaging for 8 genes (ALK, BRAF, EGFR, ERBB2, MET, NTRK1-3, RET, ROS1), and KRAS G12C and PD-L1, if performed, formalin-fixed paraffin-embedded (FFPE) tissue, reported as positive or negative for each biomarker (LungOI, Imagene) (Effective 10/01/23) |
| 0444U (E/I) | Oncology (solid organ neoplasia), targeted genomic sequence analysis panel of 361 genes, interrogation for gene fusions, translocations, or other rearrangements, using DNA from formalin-fixed paraffin-embedded (FFPE) tumor tissue, report of clinically significant variant(s) (Aventa FusionPlus, Aventa Genomics, LLC) (Effective 04/01/24) |
| 0471U | Oncology (colorectal cancer), qualitative real-time PCR of 35 variants of KRAS and NRAS genes (exons 2, 3, 4), formalin-fixed paraffin-embedded (FFPE), predictive, identification of detected mutations (Effective 07/01/24) |
| 0473U (E/I) | Oncology (solid tumor), next-generation sequencing (NGS) of DNA from formalin-fixed paraffin-embedded (FFPE) tissue with comparative sequence analysis from a matched normal specimen (blood or saliva), 648 genes, interrogation for sequence variants, insertion and deletion alterations, copy number variants, rearrangements, microsatellite instability, and tumor-mutation burden (Effective 07/01/24) |
| 0478U | Oncology (non-small cell lung cancer), DNA and RNA, digital PCR analysis of 9 genes (EGFR, KRAS, BRAF, ALK, ROS1, RET, NTRK 1/2/3, ERBB2, and MET) in formalin-fixed paraffin-embedded (FFPE) tissue, interrogation for single-nucleotide variants, insertions/deletions, gene rearrangements, and reported as actionable detected variants for therapy selection (Effective 10/01/24) |
| 0481U | IDH1 (isocitrate dehydrogenase 1 [NADP+]), IDH2 (isocitrate dehydrogenase 2 [NADP+]), and TERT (telomerase reverse transcriptase) promoter (e.g., central nervous system [CNS] tumors), next-generation sequencing (single-nucleotide variants [SNV], deletions, and insertions) (Effective 10/01/24) |
| 0498U (E/I) | Oncology (colorectal), next-generation sequencing for mutation detection in 43 genes and methylation pattern in 45 genes, blood, and formalin-fixed paraffin-embedded (FFPE) tissue, report of variants and methylation pattern with interpretation (Effective 10/01/24) |

| Code | Description |
|---|---|
| 0499U | Oncology (colorectal and lung), DNA from formalin-fixed paraffin-embedded (FFPE) tissue, next-generation sequencing of 8 genes (NRAS, EGFR, CTNNB1, PIK3CA, APC, BRAF, KRAS, and TP53), mutation detection (Effective 10/01/24) |
| 0523U (E/I) | Oncology (solid tumor), DNA, qualitative, next-generation sequencing (NGS) of single-nucleotide variants (SNV) and insertion/deletions in 22 genes utilizing formalin-fixed paraffin-embedded tissue, reported as presence or absence of mutation(s), location of mutation(s), nucleotide change, and amino acid change (oncoReveal CDx, Pillar Biosciences, Inc) (Effective 01/01/25) |
| 0538U (E/I) | Oncology (solid tumor), next- generation targeted sequencing analysis, formalin fixed paraffin embedded (FFPE) tumor tissue, DNA analysis of 600 genes, interrogation for single nucleotide variants, insertions/deletions, gene rearrangements, and copy number alterations, microsatellite instability, tumor mutation burden, reported as actionable variant (Effective 04/01/25) |
| 0543U (E/I) | Oncology (solid tumor), next- generation sequencing of DNA from formalin fixed paraffin embedded (FFPE) tissue of 517 genes, interrogation for single nucleotide variants, multi nucleotide variants, insertions and deletions from DNA, fusions in 24 genes and splice variants in 1 gene from RNA, and tumor mutation burden (Effective 04/01/25) |



**HCPCS Codes**

| Code | Description |
|---|---|
| No specific code(s) | |

**ICD10 Codes**

| Code | Description |
|---|---|
| C18.0-C21.8 | Malignant neoplasm of colon, rectosigmoid junction, rectum, and anus and anal canal (code range) |
| C25.0-C25.9 | Malignant neoplasm of pancreas (code range) |
| C34.10-C34.92 | Malignant neoplasm of lobe, bronchus, or lung (code range) |
| C43.0-C43.9 | Malignant melanoma of skin (code range) |

| Code | Description |
|---|---|
| C50.011-C50.929 | Malignant neoplasm of breast (code range) |
| C56.1-C56.9 | Malignant neoplasm of ovary (code range) |
| C61 | Malignant neoplasm of prostate |
| C71.0-C71.9 | Malignant neoplasm of brain (code range) |
| C78.5 | Secondary malignant neoplasm of large intestine and rectum |
| C79.60-C79.63 | Secondary malignant neoplasm of ovary (code range) |
| C79.81 | Secondary malignant neoplasm of breast |
| D05.00-D05.02 | Lobular carcinoma in situ of breast (code range) |
| D05.10-D05.12 | Intraductal carcinoma in situ of breast (code range) |
| D05.80-D05.92 | Carcinoma in situ of breast, specified, unspecified (code range) |
| D07.30-D07.39 | Carcinoma in situ of other and unspecified female genital organs (code range) |
| D40.0 | Neoplasm of uncertain behavior of prostate |

## REFERENCES

Chakravarty D, et al. Somatic genomic testing in patients with metastatic or advanced cancer: ASCO provisional clinical opinion. J Clin Oncol. 2022 Apr; 40(11):1231-1258.

Cobain EF, et al. Assessment of clinical benefit of integrative genomic profiling in advanced solid tumors. JAMA Oncol. 2021:7(4):525-533.

De Bono J, et al. Olaparib for metastatic castration-resistant prostate cancer. NEJM. 2020 May 28;382(22):2091-2102.

Kieler M, et al. Interim analysis of a real-world precision medicine platform for molecular profiling of metastatic or advanced cancers: MONDTI. ESMO Open. 2019 Jul 17;4(4):e000538.

Kim SS, et al. The Society of Thoracic Surgeons expert consensus on the multidisciplinary management and resectability of locally advanced non-small cell lung cancer. Ann Thorac Surg. 2024 Oct 17:S0003-4975(24)00861-0.

Le Tourneau C, et al; SHIVA investigators. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. Lancet Oncol. 2015 Oct;16(13):1324-34.

Mateo J, et al. Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): a multicenter, open-label, randomized, phase 2 trial. Lancet Oncol. 2020 Jan;21(1):162-174.

National Comprehensive Cancer Network (NCCN) [Internet]. Clinical practice guidelines in oncology. Breast Cancer. V.6.2024. 2024 Nov 11 [accessed 2024 Dec 10]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

National Comprehensive Cancer Network (NCCN) [Internet]. Clinical practice guidelines in oncology. Central Nervous System Cancers. V.3.2024. 2024 Sep 30 [accessed 2024 Dec 10]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf

National Comprehensive Cancer Network (NCCN) [Internet]. Clinical practice guidelines in oncology. Colon Cancer. V.5.2024. 2024 Aug 22 [accessed 2024 Dec 10]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

National Comprehensive Cancer Network (NCCN) [Internet]. Clinical practice guidelines in oncology. Melanoma: Cutaneous. V.3.2024. 2024 Sept 23 [accessed 2024 Dec 10]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf

National Comprehensive Cancer Network (NCCN) [Internet]. Clinical practice guidelines in oncology. Non-Small Cell Lung Cancer. V.11.2024. 2024 Oct 15 [accessed 2024 Dec 10]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

National Comprehensive Cancer Network (NCCN) [Internet]. Clinical practice guidelines in oncology. Ovarian Cancer including fallopian tube cancer and primary peritoneal cancer. V.3.2024. 2024 July 15 [accessed 2024 Dec 10]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf

National Comprehensive Cancer Network (NCCN) [Internet]. Clinical practice guidelines in oncology. Pancreatic Adenocarcinoma. V.3.2024. 2024 Aug 02 [accessed 2024 Dec 10]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf

National Comprehensive Cancer Network (NCCN) [Internet]. Clinical practice guidelines in oncology. Prostate Cancer. V.1.2025. 2024 Dec 04 [accessed 2024 Dec 10]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

Pishvaian MJ, et al. Overall survival in patients with pancreatic cancer receiving matched therapies following molecular profiling: a retrospective analysis of the Know Your Tumor registry trial. Lancet. 2020;21(4):508-518.

Schubert L, et al. ERBB family fusions are recurrent and actionable oncogenic targets across cancer types. Front Oncol. 2023 Apr;13:1115405.

Sepulveda AR, et al. Molecular Biomarkers for the evaluation of colorectal cancer: Guideline from the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology. J Clin Oncol. 2017 May 1;35(13):1453-1486.

Shah M, et al. US Food and Drug Administration Approval Summary: Elacestrant for estrogen receptor-positive, human epidermal growth factor receptor 2-negative, ESR1-mutated advanced or metastatic breast cancer. J Clin Oncol. 2024 Apr 1;42(10):1193-1201.

Sposito M, et al. Tissue- and liquid-biopsy based NGS profiling in advanced non-small-cell lung cancer in a real-world setting: the IMMINENT study. Front Oncol. 2024 Jul 9;14:1436588.

Tsimberidou AM. Initiative for Molecular Profiling and Advanced Cancer Therapy (IMPACT) and challenges in the implementation of precision medicine. Curr Probl Cancer. 2017 May-Jun;41(3):176-181.

Tsimberidou AM, et al. Long-term overall survival and prognostic score predicting survival: the IMPACT study in precision medicine. J Hematol Oncol. 2019 Dec 30;12(1):145.

Takahashi T, et al. Predictive value of EGFR mutation in non-small-cell lung cancer patients treated with platinum doublet postoperative chemotherapy. Cancer Sci. 2022 Jan;113(1):287-296.

Vivot A, et al. Pharmacogenomic biomarkers as inclusion criteria in clinical trials of oncology-targeted drugs: a mapping of ClinicalTrials.gov. Genet Med. 2016 Aug;18(8):796-805.

Weinberg BA, et al. Molecular profiling of biliary cancers reveals distinct molecular alterations and potential therapeutic targets. J Gastrointest Oncol. 2019;10(4):652-662.

Zhu J, et al. Clinical utility of Foundation One tissue molecular profiling in men with metastatic prostate cancer. Urol Oncol. 2019 Nov;37(11):813.e1-813.e9.

## SEARCH TERMS

Molecular Panel Testing, Targeted Therapy, Foundation One, Caris Life Sciences, OmniSeq, PyroSeq

## CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Next Generation Sequencing (NGS) (NCD 90.2) [accessed 2024 Dec 10]

Molecular Pathology Procedures (LCD L35000) [accessed 2024 Dec 10]

Molecular Pathology Procedures (Article-Billing and Coding A56199) [accessed 2024 Dec 10]

Genomic Sequence Analysis Panels in the Treatment of Solid Organ Neoplasms (LCD L37810) [accessed 2024 Dec 10]

Genomic Sequence Analysis Panels in the Treatment of Solid Organ Neoplasms (Article-Billing and Coding A56867) [accessed 2024 Dec 10]

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## POLICY HISTORY/REVISION

**Committee Approval Dates**

12/21/17, 12/21/18, 10/17/19, 12/17/20, 12/16/21, 01/19/23, 01/18/24, 02/20/25

| Date | Summary of Changes |
|---|---|
| 02/20/25 | • Annual review, policy statements revised with recommended genes, intent unchanged. |
| 01/01/25 | • Summary of changes tracking implemented. |
| 12/21/17 | • Original effective date |