InformedDNA®
Genetics, Decoded.

Somatic Tumor Testing

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Scope

This evidence-based guideline addresses molecular testing, including circulating tumor DNA (ctDNA) and gene expression profiling, of solid and hematologic tumors and malignancies, for the purpose of diagnosis, selecting therapeutic agents, surveillance, and predicting risk of recurrence/prognosis.

This guideline's coverage criteria delineate medically necessary clinical scenarios for molecular testing and may include specific situations when testing is considered never medically necessary. In general, molecular testing is considered never medically necessary when evidence demonstrating its ability to improve diagnosis, management, or clinical outcomes is lacking in peer-reviewed literature.

- Please refer to the General Genetic Testing guideline, for the use of polygenic risk scores for cancer.
- Please refer to the Germline Genetic Testing for Hereditary Cancer guideline, for germline genetic testing to guide treatment selection, e.g. PARP inhibitors.

State Biomarker Legislation

Medical necessity determinations must also take into consideration controlling state coverage mandates that may supersede these guidelines when applicable. When state biomarker legislation requirements impact coverage decisions, this guideline will initially be applied to determine if criteria are met for approval. If an approval cannot be granted based on the criteria in this guideline, some or all of the following sources will be reviewed, as defined by applicable state legislation, to determine if test coverage is supported in a manner that is consistent with the state biomarker legislation requirements:

- Medicare National Coverage Determinations (NCDs)
- Medicare Local Coverage Determinations (LCDs)
- U.S. Food and Drug Administration (FDA) approved or cleared tests
- Tests indicated for an FDA-approved drug
- Nationally recognized clinical practice guidelines
- Consensus statements

Guideline Coverage Criteria

General Coverage Criteria

Somatic tumor testing is medically necessary when all of the following criteria are met:

- Identification of the specific genetic variant or gene expression profile has been demonstrated through prospective research in peer-reviewed literature to improve diagnosis, management, or clinical outcomes for the individual's tumor type and disease characteristics

- Sample type (e.g., formalin-fixed, paraffin embedded (FFPE) tissue, circulating tumor DNA, etc.) has been proven to have clinical utility based on prospective evidence in peer-reviewed literature
- Testing methodology has been clinically validated and is the most accurate method unless technical limitations (e.g., poor sample quality) necessitate the need for alternate testing strategies
- The clinical benefit of testing outweighs the potential risk of psychological or medical harm to the individual being tested
- The test is as targeted as possible for the clinical situation (e.g., common variants, genes related to phenotype)

Other laboratory tests (e.g., protein, enzymes, metabolites) are medically necessary when all of the criteria above are met.

Multi-Gene Panels

In addition to the above criteria, somatic multi-gene panels for hematology-oncology indications are medically necessary when all of the following are met (please see additional criteria below for circulating tumor DNA testing):

- Sequential testing of individual biomarkers is not practical (i.e., limited tissue available, urgent treatment decisions pending) and more than one target is indicated
- Identification of biomarkers on the panel has been demonstrated to improve diagnosis, management, or clinical outcomes for the individual's tumor type and disease characteristics
- The panel is targeted and limited to genes that are associated with the specific tumor type, unless otherwise specified in tumor site-specific criteria below

Chromosomal Microarray Analysis

In addition to the above criteria, chromosomal microarray analysis is medically necessary in any of the following clinical scenarios:

- To aid diagnosis when part of the initial work-up involves cytogenetic (karyotype) and/or FISH analyses and testing was uninformative or could not be performed
- For methylation analysis (e.g., brain/central nervous system cancer)

Never Medically Necessary Tests

(list may not be all inclusive)

- Whole exome tumor sequencing for any indication (including other genome-wide interrogation strategies, e.g. transcriptome)
- Whole genome tumor sequencing for any indication (including other genome-wide interrogation strategies, e.g. transcriptome)

Criteria listed above are based primarily on the following resources. Publications issued after this guideline's effective date will be evaluated on an individual basis until criteria are incorporated in the next iteration of this guideline.

a. Bean LJH, Funke B, Carlston CM, et al. Diagnostic gene sequencing panels: from design to report-a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2020 Mar;22(3):453-461. doi: 10.1038/s41436-019-0666-z. Epub 2019 Nov 16. PMID: 31732716.

b. Chakravarty D, Johnson A, Sklar J, et al. Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion. J Clin Oncol. 2022 Feb 17:JCO2102767. doi: 10.1200/JCO.21.02767. Epub ahead of print. PMID: 35175857.

c. Mosele MF, Westphalen CB, Stenzinger A, et al. Recommendations for the use of next-generation sequencing (NGS) for

patients with advanced cancer in 2024: a report from the ESMO Precision Medicine Working Group. Ann Oncol. 2024 Jul;35(7):588-606. doi: 10.1016/j.annonc.2024.04.005. Epub 2024 May 27. Erratum in: Ann Oncol. 2025 Apr;36(4):472. doi: 10.1016/j.annonc.2024.11.010. PMID: 38834388.
d. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Accessed at www.nccn.org.
e. Shao L, Akkari Y, Cooley LD, et al. Chromosomal microarray analysis, including constitutional and neoplastic disease applications, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021 Oct;23(10):1818-1829. doi: 10.1038/s41436-021-01214-w. Epub 2021 Jun 15. PMID: 34131312.

U.S. Food and Drug Administration (FDA) Companion Diagnostics

Molecular-based testing is considered medically necessary when the requested test is an FDA-approved companion diagnostic (CDx) for a biomarker-directed therapy that is approved for use in the patient's cancer type and stage (*please see the Solid Organ Tumors section below for medically necessary clinical scenarios*).

Molecular-based FDA CDx testing is considered never medically necessary if the patient meets the FDA-label criteria for the medication(s) under consideration without the need for biomarker information.

FDA CDx approvals/retractions issued after this guideline's effective date will be evaluated on an individual basis until criteria can be incorporated into the next iteration of this guideline.

Criteria listed above are based primarily on the following resources. Publications issued after this guideline's effective date will be evaluated on an individual basis until criteria are incorporated in the next iteration of this guideline.

a. U.S. Food and Drug Administration. List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools). Available from: https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools. [April 2025]

Solid Organ Tumors

Genetic testing for solid tumors may have clinical utility for diagnosis/prognosis or to guide therapeutic decision-making based on the patient's type and stage of cancer and treatment history. The tables below list tests/indications that meet the general coverage criteria or the FDA Companion Diagnostics criteria, when applicable, for the patient's cancer type. The tables are all inclusive. If the patient's cancer type is not listed below, please see the Testing for Tumor Agnostic Therapies section. Broad molecular profiling tests not designated as FDA-approved companion diagnostics are never medically necessary.

Tissue-Based Testing

Indication	Biomarker(s)	Test
Breast Cancer** Advanced† or metastatic	*PIK3CA/AKT1/ESR1/PTEN*	■ Single gene tests ■ FoundationOne CDx (0037U) ■ therascreen *PIK3CA* PCR Kit (0155U) ■ CARIS MI Cancer Seek CDx (0211U)
Breast Cancer Advanced† or metastatic breast cancer with progression on endocrine therapy	*ESR1*	■ Single gene tests
Central Nervous System	*IDH1, IDH2, ATRX, TERT,*	■ Single gene tests

(CNS) Cancer Suspected or confirmed	*H3-3A, HIST1H3B, BRAF* [fusion or V600E alteration], *RELA* fusion, *ZFTA* fusion, 1p and 19q codeletion, *MGMT* promoter methylation, Sonic hedgehog (*SHH*) pathway (mutational analysis), *MYC* and *MYCN* (copy number analysis)	■ Phenotype-specific CNS somatic tumor profiling panels (81445) ■ Methylation based testing (0020M) ■ Oncomine DX Target Test (0022U) ■ FoundationOne CDx (0037U)
	RNA fusions	■ RNA sequencing assays (81449) *(when FISH-based or IHC tests are insufficient to establish a diagnosis)*
Cholangiocarcinoma Advanced† or metastatic	*FGFR2*, *IDH1*	■ Single gene tests ■ FoundationOne CDx (0037U) ■ Oncomine DX Target Test (0022U)
Colorectal Cancer Metastatic	*KRAS*, *NRAS*, *BRAF*, *MLH1*, Microsatellite Instability (MSI), *MSH2*, *MSH6*, *PMS2*, *EPCAM*	■ Single gene tests ■ MSI Instability Testing (81301) ■ Targeted multigene panels (81445) ■ cobas *KRAS* Mutation Test, therascreen *BRAF* V600E RGQ PCR, therascreen *KRAS* RGQ PCR ■ CRCdx RAS Mutation Detection Kit (0471U) ■ FoundationOne CDx (0037U) ■ oncoReveal CDx (0523U) ■ Praxis Extended RAS Panel (0111U) ■ xT CDx (0473U) ■ CARIS MI Cancer Seek CDx (0211U)
Stage 0-IIIC	*MLH1*, Microsatellite Instability (MSI), *MSH2*, *MSH6*, *PMS2*, *EPCAM*	■ Single gene tests ■ MSI Instability Testing (81301) ■ Targeted multi-gene panels (81445)
Cutaneous Melanoma Advanced† or metastatic	*BRAF*, *KIT*	■ Single gene tests ■ cobas 4800 *BRAF* V600 Mutation Test, THXID *BRAF* Kit ■ FoundationOne CDx (0037U) ■ CARIS MI Cancer Seek CDx (0211U)
Endometrial Cancer (Uterine Neoplasms)	*POLE, TP53,* Microsatellite Instability (MSI), *MLH1, MSH2, MSH6, PMS2, EPCAM*	■ Single gene tests ■ MSI Instability Testing (81301) ■ Targeted multigene panels (81445) ■ CARIS MI Cancer Seek CDx (0211U)
	RNA fusions	■ RNA sequencing assays (81449) *(when uterine sarcoma is suspected or confirmed and FISH-based or IHC tests are insufficient to establish a diagnosis)*
Epithelial Ovarian, Fallopian Tube, or Primary	*BRCA1/BRCA2, KRAS*	■ Somatic *BRCA1/BRCA2* ■ MyChoice CDx (0172U)

Peritoneal Cancers Advanced† or metastatic		■ FoundationOne CDx (0037U) ■ FoundationFocus CDxBRCA Assay
Gastrointestinal Stromal Tumors (GIST) Suspected or confirmed	*KIT, PDGFRA*	■ Single gene tests ■ therascreen PDGRFA RGQ PCR Kit (81314)
	BRAF, *NF1*, *NTRK*, and *EGFR*	■ Single gene tests ■ Targeted multigene panels (81445) (*when KIT and PDGFRA are negative)*
Lung Cancer** Advanced† or metastatic non-small cell lung cancer at the time of initial diagnosis and/or at the time of progression on a new biopsy sample	*EGFR, ALK, KRAS, ROS1, ERBB2 (HER2), BRAF, RET, MET, NRG1*	■ Single gene tests ■ cobas *EGFR* Mutation test v2 (81235), therascreen *EGFR* RGQ PCR test (81235), therascreen *KRAS* RGQ PCR test (81275, 81276) ■ Targeted multigene panels (81445 and/or 81449) ■ FoundationOne CDx (0037U) ■ Oncomine DX Target Test (0022U) ■ oncoReveal CDx (0523U) ■ TruSight Oncology (TSO) Comprehensive assay ■ CARIS MI Cancer Seek CDx (0211U)
Lung Cancer Stage IB-IIIA resected non-small cell lung cancer	*EGFR, ALK*	■ Single gene tests ■ Cobas *EGFR* Mutation test v2 (81235), Therascreen *EGFR* RGQ PCR test (81235) ■ FoundationOne CDx (0037U) ■ Oncomine DX Target Test (0022U) ■ oncoReveal CDx (0523U) ■ CARIS MI Cancer Seek CDx (0211U)
Pancreatic Cancer *Advanced† or metastatic*	*NRG1*	■ Single gene tests
Prostate Cancer Metastatic, castration-resistant	*BRCA1/BRCA2* and other homologous recombination repair (HRR) genes	■ Single gene tests ■ Targeted multigene panels (81445) ■ FoundationOne CDx (0037U)
Sarcoma Suspected or confirmed	*EGFR, IDH1/IDH2 COL2A1*	■ Single gene tests *(when sarcoma of the bone is suspected or confirmed)*
	Cytogenetic abnormalities or gene fusions	■ DNA (81445) and/or RNA (81449) NGS testing (*when FISH-based or IHC tests are insufficient to establish a diagnosis of soft tissue sarcomas)*
Synovial Sarcoma Advanced† or metastatic	*HLA-A*	■ SeCore CDx HLA A Sequencing System
Salivary Gland Tumors Suspected or confirmed	Cytogenetic abnormalities or gene fusions	■ DNA (81445) and/or RNA (81449) NGS testing (*when FISH-based or IHC tests are insufficient to confirm the subtype of*

		salivary gland tumor)
Thyroid Cancer Advanced† or metastatic	*BRAF, RET*	■ Single gene tests ■ Oncomine DX Target Test (0022U)
Testing for Tumor Agnostic Therapies Advanced† or metastatic cancer	Tumor Mutation Burden (TMB), Microsatellite Instability (MSI), *NTRK, BRAF, RET*	■ Single gene tests ■ FoundationOne CDx (0037U) ■ TruSight Oncology (TSO) Comprehensive assay (0543U) ■ CARIS MI Cancer Seek CDx (0211U)
Uveal Melanoma Advanced† or metastatic	*HLA-A*	■ SeCore CDx HLA Sequencing System
Suspected or confirmed	*EIF1AX, SF3B1, BAP1, PRAME*	■ Single gene tests

† *Advanced includes unresectable, recurrent, relapsed, or refractory cancers*

***Sequential or concurrent testing alongside ctDNA testing is medically necessary*

Circulating Tumor DNA (ctDNA) Testing

Indication	Biomarker(s)	Test
Breast Cancer** Advanced† or Metastatic	*PIK3CA*	■ FoundationOne® Liquid CDx (0239U) ■ therascreen *PIK3CA* PCR Kit (0177U)
	ESR1	■ Guardant360® CDx (0242U)
Colorectal Cancer* Advanced† or Metastatic	*BRAF*	■ FoundationOne® Liquid CDx (0239U)
Lung Cancer** Advanced† or metastatic non-small cell lung cancer at the time of initial diagnosis and/or at the time of progression on a new serum sample	*EGFR, MET, ROS1, ALK, ERBB2, KRAS*	■ cobas v2 EGFR Mutation Test v2 (81235) ■ FoundationOne® Liquid CDx (0239U) ■ Guardant360® CDx (0242U) ■ Agilent Resolution ctDx FIRST
Lung Cancer* Stage IB-IIIA resected non-small cell lung cancer	*EGFR, ALK*	■ FoundationOne® Liquid CDx (0239U) ■ Guardant360® CDx (0242U) ■ cobas v2 EGFR Mutation Test v2 (81235)
Prostate Cancer* Metastatic castration-resistant)	*BRCA1/ BRCA2, ATM*	■ FoundationOne® Liquid CDx (0239U)
Tumor Agnostic* Advanced† or metastatic cancer	*NTRK*	■ FoundationOne® Liquid CDx (0239U)

† *Advanced includes unresectable, recurrent, relapsed, or refractory cancers*

**Medically necessary when tissue-based testing cannot be performed*

***Sequential or concurrent testing alongside tissue testing is medically necessary*

Gene Expression Classifier Testing

Breast Cancer
Breast cancer assays not listed below are considered never medically necessary.

Oncotype DX® Breast Recurrence Score Test is medically necessary in any of the following clinical scenarios:

- Patient has had surgery with complete pathological staging and either of the following:
    - Patient is age ≤50 or premenopausal, and
        - Breast tumor is hormone receptor positive, HER2-negative
        - Breast tumor is anatomic stage 1 or 2
        - Patient is node negative (pN0 or pN+micro)

      OR

    - Patient is postmenopausal or age >50, and
        - Breast tumor is hormone receptor positive, HER2-negative
        - Breast tumor is anatomic stage 1 or 2
        - Patient is node negative (pN0 or pN+micro) or has 1-3 positive nodes (N1).*

*If sentinel lymph node biopsy was not performed or not planned, testing is medically necessary when the patient is 50 or older, postmenopausal with tumor size of 2 cm or less, Nottingham grade 1 or 2, and the patient had a negative axillary preoperative ultrasound.

Mammaprint® or EndoPredict are medically necessary to assess the need for adjuvant chemotherapy when all of the following criteria are met:

- Patient is postmenopausal or age >50, *and*
- Breast tumor is hormone receptor (ER and/or PR) positive, *HER2*-negative
- Breast tumor is anatomic stage 1 or 2
- Patient is node negative (pN0 or pN+micro)) *OR* has 1-3 positive nodes (N1)

Prosigna™ PAM50 is medically necessary to assess the need for adjuvant chemotherapy when all of the following criteria are met:

- Patient is postmenopausal or age >50, *and*
- Breast tumor is hormone receptor (ER and/or PR) positive, *HER2*-negative,
- Breast tumor is anatomic stage 1 or 2
- Patient is node negative (pN0 or pN+micro)

The Breast Cancer Index™ test is considered medically necessary in the following clinical scenarios:

1. In individuals considering adjuvant chemotherapy when all of the following criteria are met:
    - Patient is postmenopausal or age >50, *and*
    - Breast tumor is hormone receptor (ER and/or PR) positive, *HER2*-negative,
    - Breast tumor is anatomic stage 1 or 2,
    - Patient is node negative (pN0 or pN+micro) *OR* has 1-3 positive nodes (N1)
2. In individuals considering extending endocrine therapy beyond 5 years when all of the following criteria are met:
    - Patient is postmenopausal or age >50, *and*
    - Breast tumor is hormone receptor (ER and/or PR) positive, *HER2*-negative,

- Breast tumor is anatomic stage 1 or 2,
- Patient is node negative (pN0 or pN+micro) *OR* has 1-3 positive nodes (N1)

Uveal Melanoma
DecisionDx® - UM (81552) is medically necessary for individuals with confirmed non-metastatic uveal melanoma.

Gene expression profiling is considered never medically necessary in any other clinical setting.

Hematolymphoid Tumors

Diagnostic/Prognostic Testing

The following molecular studies are medically necessary when the General Coverage Criteria or FDA Companion Diagnostics Coverage Criteria are met above.

- Targeted genomic sequencing panels (81450) on a bone marrow biopsy are medically necessary when a hematolymphoid neoplasm or cancer is known or suspected. *Hodgkin lymphoma is excluded from coverage.*
- Targeted genomic sequencing panels (81451) are medically necessary for B-cell acute lymphoblastic leukemia (ALL), T-cell ALL, acute myelogenous leukemia (AML) and eosinophilia only when a diagnosis is known or suspected based on bone marrow biopsy.
- Targeted genomic sequencing panels (*JAK2*, *CALR*, *MPL*) or single gene tests on peripheral blood are medically necessary for essential thrombocythemia or thrombocytosis; polycythemia vera; or primary myelofibrosis, pre-PMF, suspicion for PMF (i.e., myeloproliferative neoplasm is suspected) when 2022 WHO criteria are met.

Criteria listed above are based primarily on the following resources. Publications issued after this guideline's effective date will be evaluated on an individual basis until criteria are incorporated in the next iteration of this guideline.

a. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022 Jul;36(7):1720-1748. doi: 10.1038/s41375-022-01620-2. Epub 2022 Jun 22. PMID: 35732829; PMCID: PMC9214472.
b. American Society of Clinical Oncology (ASCO). ASCO Guidelines. Accessed at www.asco.org/guideilines.
c. Iams WT, Mackay M, Ben-Shachar R, et al. Concurrent Tissue and Circulating Tumor DNA Molecular Profiling to Detect Guideline-Based Targeted Mutations in a Multicancer Cohort. JAMA Netw Open. 2024 Jan 2;7(1):e2351700. doi: 10.1001/jamanetworkopen.2023.51700. PMID: 38252441; PMCID: PMC10804266.
d. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. 2022 Jul;36(7):1703-1719. doi: 10.1038/s41375-022-01613-1. Epub 2022 Jun 22. PMID: 35732831; PMCID: PMC9252913.
e. Merker JD, Oxnard GR, Compton C, et al. Circulating Tumor DNA Analysis in Patients With Cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. J Clin Oncol. 2018 Jun 1;36(16):1631-1641. doi: 10.1200/JCO.2017.76.8671. Epub 2018 Mar 5. PMID: 29504847.
f. Mosele MF, Westphalen CB, Stenzinger A, et al. Recommendations for the use of next-generation sequencing (NGS) for patients with advanced cancer in 2024: a report from the ESMO Precision Medicine Working Group. Ann Oncol. 2024 Jul;35(7):588-606. doi: 10.1016/j.annonc.2024.04.005. Epub 2024 May 27. Erratum in: Ann Oncol. 2025 Apr;36(4):472. doi: 10.1016/j.annonc.2024.11.010. PMID: 38834388.
g. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Accessed at www.nccn.org.
h. U.S. Food and Drug Administration. List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools). Available from: https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools. [April 2025]
i. Xie J, Yao W, Chen L, et al. Plasma ctDNA increases tissue NGS-based detection of therapeutically targetable mutations in lung cancers. BMC Cancer. 2023 Mar 31;23(1):294. doi: 10.1186/s12885-023-10674-z. PMID: 37004022; PMCID: PMC10063947.

Minimal Residual Disease (MRD) Monitoring

Hematologic Cancers

Next-generation sequencing (e.g., ClonoSeq, LymphoTrack) for MRD clone identification from bone marrow biopsy is medically necessary for:

- B-cell acute lymphoblastic leukemia (ALL) which is Philadelphia chromosome (*BCR*::*ABL*) negative
- Multiple myeloma

Next-generation sequencing (e.g., ClonoSeq, LymphoTrack) for MRD tracking is medically necessary for B-cell acute lymphoblastic leukemia that is Philadelphia chromosome (BCR::ABL) negative *or* multiple myeloma when all of the following criteria are met:

- A clone for MRD tracking has been identified
- The patient is at the end of a treatment stage when complete remission is likely
- Testing is completed on a bone marrow sample

Targeted molecular MRD testing with prospective evidence of clinical utility for the tumor type and disease characteristics is medically necessary.

Solid Tumors

Molecular testing for MRD (e.g., Signatera) and/or disease monitoring is never medically necessary.

Criteria listed above are based primarily on the following resources. Publications issued after this guideline's effective date will be evaluated on an individual basis until criteria are incorporated in the next iteration of this guideline.

a. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022 Jul;36(7):1720-1748. doi: 10.1038/s41375-022-01620-2. Epub 2022 Jun 22. PMID: 35732829; PMCID: PMC9214472.
b. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016 Aug;17(8):e328-e346. doi: 10.1016/S1470-2045(16)30206-6. PMID: 27511158.
c. Merker JD, Oxnard GR, Compton C, et al. Circulating Tumor DNA Analysis in Patients With Cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. J Clin Oncol. 2018 Jun 1;36(16):1631-1641. doi: 10.1200/JCO.2017.76.8671. Epub 2018 Mar 5. PMID: 29504847.
d. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Accessed at www.nccn.org.
e. Pascual J, Attard G, Bidard FC, et al. ESMO recommendations on the use of circulating tumour DNA assays for patients with cancer: a report from the ESMO Precision Medicine Working Group. Ann Oncol. 2022 Aug;33(8):750-768. doi: 10.1016/j.annonc.2022.05.520. Epub 2022 Jul 6. PMID: 35809752.
f. U.S. Food and Drug Administration. List of Nucleic Acid Based Tests. Available from: https://www.fda.gov/medical-devices/in-vitro-diagnostics/nucleic-acid-based-tests. [April 2025]

Key Terms and Definitions

Biomarker in genetics typically refers to a DNA or RNA sequence that can aid in diagnosis, prognosis, and treatment decision-making.

Chromosomes carry genetic material known as DNA; humans typically have 23 pairs of chromosomes.

Chromosomal microarray analysis is a genetic test that analyzes the entire genome for small deletions or duplications, known as copy number variants, in the DNA.

Circulating tumor DNA (ctDNA), also known as cell-free tumor DNA or liquid biopsy, refers to small fragments of DNA that originate from tumor cells and are released into the bloodstream.

Cytogenetic (karyotype) analysis is a laboratory technique used to examine and analyze the chromosomes to detect structural and numerical abnormalities.

Deoxyribonucleic acid (DNA) is a molecule that contains the genetic instructions for all living organisms and plays a crucial role in the development and susceptibility to diseases.

Fluorescent in situ hybridization (FISH) is a molecular cytogenetic technique used to visualize and map the location of specific DNA sequences on chromosomes or in cells.

Gene expression classifier testing is a molecular diagnostic technique that evaluates the activity levels of specific genes in a sample to classify or predict certain disease states or outcomes.

Gene expression profile refers to the pattern of gene activity or expression levels in a given cell or tissue sample at a specific time; this provides a snapshot of which genes are being actively transcribed and their associated levels of protein production or cellular activity.

Genes are segments of DNA that contain the instructions for specific traits, characteristics, or functions within an organism.

Genetic (molecular) testing examines a person's DNA or RNA to identify variations that can aid in the diagnosis of disease and/or provide valuable information about a person's risk of developing certain diseases.

Germline genetic testing involves examining the DNA incorporated in every cell of the body derived from reproductive cells (eggs or sperm).

Methylation analysis is a molecular technique used to study DNA methylation patterns in cells and tissue; DNA methylation occurs when a methyl group is added to a DNA segment and does not alter the DNA sequence but can affect gene expression and cellular function.

Minimal residual disease (MRD) monitoring is used to detect and track low levels of cancer cells that persist during or after cancer treatment.

Multi-gene panels simultaneously analyze multiple genes associated with a particular condition or a group of related conditions.

Next-generation sequencing is a technology that enables the rapid and cost-effective sequencing of large amounts of DNA or RNA.

Pathogenic/likely pathogenic variant(s) describe specific genetic changes that are known or highly likely to cause a particular genetic disorder, which can aid in diagnosis and/or guide treatment and management strategies.

Ribonucleic acid (RNA) is a molecule that plays a crucial role in various cellular processes within living organisms, such as cell functioning and regulation.

Somatic variants are genetic changes that arise in a person's DNA during their lifetime. Somatic variants are not inherited or passed onto offspring. Many cancers are associated with the accumulation of somatic variants in specific genes that control cell growth and division.

Somatic tumor testing is a type of genetic testing that focuses on identifying genetic changes that occur spontaneously in cancer cells.

CPT® Codes

Medical necessity review of claims may include evaluation of the submitted codes. Laboratories must accurately represent their services using the most applicable and specific CPT code(s). Tier 1 molecular pathology procedure codes or Proprietary Laboratory Analyses (PLA) codes should be used when available for the specific test. Tier 2 molecular pathology procedure codes should only be used if the American Medical Association (AMA) has specifically assigned the performed test to such a code. Genomic sequencing procedures (GSP) codes (e.g., CPT codes 81410-81471) were developed by the AMA to represent multi-gene panels utilizing DNA or RNA analysis for specific clinical scenarios (e.g., carrier screening, tumor testing, etc.) and should be utilized when applicable.

Coding guidelines can be found in the AMA's CPT manual as well as the Centers for Medicare and Medicaid Services (CMS) National Correct Coding Initiative (NCCI) policy manuals. NCCI General Correct Coding Policy states that procedures should be reported with the most comprehensive CPT code describing the services performed and that the services described by a CPT code cannot be unbundled into multiple less specific codes. Additionally, GSP codes should be utilized when appropriate for the described test and should not be submitted along with other CPT codes that represent components of the GSP code.

Claims may not be approved if the submitted codes are not the most appropriate for the described procedure (i.e., as accurate and specific as available).

The following code(s) are medically necessary when coverage criteria are met. This list is not all inclusive.

Code	Full Description
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 (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)
81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
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)

81165	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81166	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81167	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81168	CCND1/IGH (t(11;14)) (eg, mantle cell lymphoma) translocation analysis, major breakpoint, qualitative and quantitative, if performed
81170	ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (eg, acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain
81175	ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; full gene sequence
81176	ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; targeted sequence analysis (eg, exon 12)
81191	NTRK1 (neurotrophic receptor tyrosine kinase 1) (eg, solid tumors) translocation analysis
81192	NTRK2 (neurotrophic receptor tyrosine kinase 2) (eg, solid tumors) translocation analysis
81193	NTRK3 (neurotrophic receptor tyrosine kinase 3) (eg, solid tumors) translocation analysis
81194	NTRK (neurotrophic-tropomyosin receptor tyrosine kinase 1, 2, and 3) (eg, solid tumors) translocation analysis
81206	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative
81207	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative
81208	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative
81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
81218	CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (eg, acute myeloid leukemia), gene analysis, full gene sequence
81219	CALR (calreticulin) (eg, myeloproliferative disorders), gene analysis, common variants in exon 9
81233	BTK (Bruton's tyrosine kinase) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, C481S, C481R, C481F)
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)
81236	EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, myelodysplastic syndrome, myeloproliferative neoplasms) gene analysis, full gene sequence
81237	EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, diffuse large B-cell lymphoma) gene analysis, common variant(s) (eg, codon 646)
81245	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (ie, exons 14, 15)

81246	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (eg, D835, I836)
81261	IGH@ (Immunoglobulin heavy chain locus) (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); amplified methodology (eg, polymerase chain reaction)
81262	IGH@ (Immunoglobulin heavy chain locus) (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); direct probe methodology (eg, Southern blot)
81263	IGH@ (Immunoglobulin heavy chain locus) (eg, leukemia and lymphoma, B-cell), variable region somatic mutation analysis
81264	IGK@ (Immunoglobulin kappa light chain locus) (eg, leukemia and lymphoma, B-cell), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)
81270	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant
81272	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, targeted sequence analysis (eg, exons 8, 11, 13, 17, 18)
81273	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, mastocytosis), gene analysis, D816 variant(s)
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)
81277	Cytogenomic neoplasia (genome-wide) microarray analysis, interrogation of genomic regions for copy number and loss-of-heterozygosity variants for chromosomal abnormalities
81278	IGH@/BCL2 (t(14;18)) (eg, follicular lymphoma) translocation analysis, major breakpoint region (MBR) and minor cluster region (mcr) breakpoints, qualitative or quantitative
81279	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) targeted sequence analysis (eg, exons 12 and 13)
81287	MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme) promoter methylation analysis
81301	Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
81305	MYD88 (myeloid differentiation primary response 88) (eg, Waldenstrom's macroglobulinemia, lymphoplasmacytic leukemia) gene analysis, p.Leu265Pro (L265P) variant
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)
81310	NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, exon 12 variants
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)
81315	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; common breakpoints (eg, intron 3 and intron 6), qualitative or quantitative
81316	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; single breakpoint (eg, intron 3, intron 6 or exon 6), qualitative or quantitative

81320	PLCG2 (phospholipase C gamma 2) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, R665W, S707F, L845F)
81327	SEPT9 (Septin9) (eg, colorectal cancer) promoter methylation analysis
81334	RUNX1 (runt related transcription factor 1) (eg, acute myeloid leukemia, familial platelet disorder with associated myeloid malignancy), gene analysis, targeted sequence analysis (eg, exons 3-8)
81338	MPL (MPL proto-oncogene, thrombopoietin receptor) (eg, myeloproliferative disorder) gene analysis; common variants (eg, W515A, W515K, W515L, W515R)
81339	MPL (MPL proto-oncogene, thrombopoietin receptor) (eg, myeloproliferative disorder) gene analysis; sequence analysis, exon 10
81340	TRB@ (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using amplification methodology (eg, polymerase chain reaction)
81341	TRB@ (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using direct probe methodology (eg, Southern blot)
81342	TRG@ (T cell antigen receptor, gamma) (eg, leukemia and lymphoma), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)
81345	TERT (telomerase reverse transcriptase) (eg, thyroid carcinoma, glioblastoma multiforme) gene analysis, targeted sequence analysis (eg, promoter region)
81347	SF3B1 (splicing factor [3b] subunit B1) (eg, myelodysplastic syndrome/acute myeloid leukemia) gene analysis, common variants (eg, A672T, E622D, L833F, R625C, R625L)
81348	SRSF2 (serine and arginine-rich splicing factor 2) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variants (eg, P95H, P95L)
81351	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; full gene sequence
81352	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; targeted sequence analysis (eg, 4 oncology)
81357	U2AF1 (U2 small nuclear RNA auxiliary factor 1) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variants (eg, S34F, S34Y, Q157R, Q157P)
81360	ZRSR2 (zinc finger CCCH-type, RNA binding motif and serine/arginine-rich 2) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variant(s) (eg, E65fs, E122fs, R448fs)
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
81450	Hematolymphoid neoplasm or disorder, genomic sequence analysis panel, 5-50 genes, 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
81451	Hematolymphoid neoplasm or disorder, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
81456	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 sequence analysis panel, interrogation for sequence variants; DNA analysis,

	microsatellite instability
81518	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 11 genes (7 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithms reported as percentage risk for metastatic recurrence and likelihood of benefit from extended endocrine therapy
81519	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence score
81520	Oncology (breast), mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence risk score
81521	Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes, utilizing fresh frozen or formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk of distant metastasis
81522	Oncology (breast), mRNA, gene expression profiling by RT-PCR of 12 genes (8 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk score
81523	Oncology (breast), mRNA, next-generation sequencing gene expression profiling of 70 content genes and 31 housekeeping genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk to distant metastasis
81552	Oncology (uveal melanoma), mRNA, gene expression profiling by real-time RT-PCR of 15 genes (12 content and 3 housekeeping), utilizing fine needle aspirate or formalin-fixed paraffin-embedded tissue, algorithm reported as risk of metastasis
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.
0023U	Oncology (acute myelogenous leukemia), DNA, genotyping of internal tandem duplication, p.D835, p.I836, using mononuclear cells, reported as detection or nondetection of FLT3 mutation and indication for or against the use of midostaurin
0027U	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, targeted sequence analysis exons 12-15
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
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
0154U	Oncology (urothelial cancer), RNA, analysis by real-time RT-PCR of the FGFR3 (fibroblast growth factor receptor 3) gene analysis (ie, 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
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
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
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

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
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
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
0364U	Oncology (hematolymphoid neoplasm), genomic sequence analysis using multiplex (PCR) and next-generation sequencing with algorithm, quantification of dominant clonal sequence(s), reported as presence or absence of minimal residual disease (MRD) with quantitation of disease burden, when appropriate
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
0473U	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
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
0481U	IDH1 (isocitrate dehydrogenase 1 [NADP+]), IDH2 (isocitrate dehydrogenase 2 [NADP+]), and TERT (telomerase reverse transcriptase) promoter (eg, central nervous system [CNS] tumors), next-generation sequencing (single-nucleotide variants [SNV], deletions, and insertions)
0523U	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
0543U	Oncology (solid tumor), next generation sequencing of DNA from formalin-fixed paraffin-embedded (FFPE) tissue of 517 genes, interrogation for single nucleotide variants, multinucleotide variants, insertions and deletions from DNA, fusions in 24 genes and splice variants in 1 gene from RNA, and tumor mutation burden

The following code(s) are considered never medically necessary. This list is not all inclusive.

Code	Full Description
81458	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, copy number variants and microsatellite instability
81459	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements
81462	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants and rearrangements
81463	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis, copy number variants, and microsatellite instability
81464	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for

	sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements
81525	Oncology (colon), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence score
81529	Oncology (cutaneous melanoma), mRNA, gene expression profiling by real-time RT-PCR of 31 genes (28 content and 3 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk, including likelihood of sentinel lymph node metastasis
81540	Oncology (tumor of unknown origin), mRNA, gene expression profiling by real-time RT-PCR of 92 genes (87 content and 5 housekeeping) to classify tumor into main cancer type and subtype, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported
81541	Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 46 genes (31 content and 15 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a disease-specific mortality risk score
81542	Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score
0016M	Oncology (bladder), mRNA, microarray gene expression profiling of 219 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as molecular subtype (luminal, luminal infiltrated, basal, basal claudin-low, neuroendocrine-like)
0045U	Oncology (breast ductal carcinoma in situ), mRNA, gene expression profiling by realtime RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score
0047U	Oncology (prostate), mRNA, gene expression profiling by real-time RT-PCR of 17 genes (12 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a risk score
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)
0244U	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
0250U	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
0326U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 83 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
0329U	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
0334U	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
0340U	Oncology (pan-cancer), analysis of minimal residual disease (MRD) from plasma, with assays personalized to each patient based on prior next-generation sequencing of the patient’s tumor and germline DNA, reported as absence or presence of MRD, with disease-burden correlation, if appropriate

0388U	Oncology (non-small cell lung cancer), next-generation sequencing with identification of single nucleotide variants, copy number variants, insertions and deletions, and structural variants in 37 cancer-related genes, plasma, with report for alteration detection
0422U	Oncology (pan-solid tumor), analysis of DNA biomarker response to anti-cancer therapy using cell-free circulating DNA, biomarker comparison to a previous baseline pre-treatment cell-free circulating DNA analysis using next-generation sequencing, algorithm reported as a quantitative change from baseline, including specific alterations, if appropriate
0485U	Oncology (solid tumor), cell-free DNA and RNA by next-generation sequencing, interpretative report for germline mutations, clonal hematopoiesis of indeterminate potential, and tumor-derived single-nucleotide variants, small insertions/deletions, copy number alterations, fusions, microsatellite instability, and tumor mutational burden
0560U	Oncology (minimal residual disease [MRD]), genomic sequence analysis, cell-free DNA, whole blood and tumor tissue, baseline assessment for design and construction of a personalized variant panel to evaluate current MRD and for comparison to subsequent MRD assessments
0561U	Oncology (minimal residual disease [MRD]), genomic sequence analysis, cell-free DNA, whole blood, subsequent assessment with comparison to initial assessment to evaluate for MRD
0569U	Oncology (solid tumor), next generation sequencing analysis of tumor methylation markers (>20000 differentially methylated regions) present in cell-free circulating tumor DNA (ctDNA), whole blood, algorithm reported as presence or absence of ctDNA with tumor fraction, if appropriate
0585U	Targeted genomic sequence analysis panel, solid organ neoplasm, circulating cell-free DNA (cfDNA) analysis from plasma of 521 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, and microsatellite instability, report shows identified mutations, including variants with clinical actionability

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Change Summary

Version	Review Date	Effective Date	Summary of Revisions
Created	CSC: 8/11/2022 PAB: 9/12/2022	November 2022	Not applicable
v1.2023	COOC: 2/15/2023 PAB: 3/16/2023	April 1, 2023	Semi-annual review. No criteria changes.
v2.2023	COOC: 8/16/2023 PAB: 9/25/2023	October 1, 2023	Semi-annual review. FDA CDx criteria were revised to limit testing to single gene EGFR analysis in the setting of stage IB-IIIA resected NSCLC or advanced/metastatic NSCLC with progression on EGFR TKI therapy (excluding osimertinib).
v1.2024	COOC: 2/14/2024 PAB: 3/25/2024	April 1, 2024	Semi-annual review. Criteria were updated to allow concurrent tissue/ctDNA testing in metastatic breast cancer and NSCLC; 81523 is considered MN; AKT1, PTEN and ESR1 were added to the list of biomarkers for breast cancer tumor testing; additional ctDNA and tissue testing criteria were clarified. Updates were made to the scope, CPT code and reference sections.
v2.2024	COOC:08/19/2024 PAB: 09/20/2024	October 1, 2024	Semi-annual review. FDA CDx criteria were clarified. Criteria were updated to allow ALK testing for NSCLC,

			methylation based testing for CNS Cancer and the CRCdx RAS Mutation Detection Kit for metastatic colorectal cancer; repeat testing for NSCLC was clarified; FoundationOne Liquid CDx testing for BRCA1/BRCA2 was removed from the ctDNA testing table. Hematolymphoid tumor testing criteria were clarified. CPT codes and references were updated. TruSight Oncology (TSO) Comprehensive Assay was added to the Lung Cancer (Advanced or metastatic NSCLC) testing and to the Testing for Tumor Agnostic Therapies testing. 81455 was removed from the never medically necessary CPT code table. It was not added to the medically necessary table as it will only be considered medically necessary if used to code for this test.
v1.2025	COOC: 02/17/2025 PAB: 03/24/2025	July 3, 2025	Semi-annual review. Criteria were revised for repeat testing in the metastatic setting. Tissue testing table was updated to reflect FDA approvals. Gene expression profiling never medically necessary criteria were streamlined. Oncotype DX® Breast Recurrence Score Test criteria were clarified. CPT codes and references were updated.
v1.2026	COOC: 8/5/2025 PAB: 09/16/2025	January 9, 2026	Semi-annual review. A laboratory testing statement was added to general criteria. Tables delineating tissue testing and cfDNA testing were updated based on FDA designated biomarkers or CDx tests and AMA assignment of PLA codes. Gene expression classifier criteria were updated. CPT codes were updated. Key references were added as rationale under each criteria section replacing the formal reference section.