Medical Coverage Policy

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Molecular and Proteomic Diagnostic Testing for Hematology and Oncology Indications

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INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not

covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This Coverage Policy addresses testing for acquired or somatic harmful or likely harmful changes in the genetic information of cells that occur after conception, for selected cancers and blood disorders. Test results may help determine disease staging, chance of disease recurrence, and/or inform treatment planning.

Coverage Policy

Coverage for genetic testing varies across plans. Refer to the customer's benefit plan document for coverage details.

<u>General Criteria for Somatic Pathogenic or Likely Pathogenic Variant Genetic Testing</u>

Tumor Molecular Testing

General Criteria:

Molecular tumor biomarker or broad molecular profile panel testing is considered medically necessary when ALL of the following criteria are met:

- the individual is a candidate for a targeted therapy associated with a specific tumor biomarker(s) or disease site
- results of testing will directly impact clinical decision-making
- the testing method is scientifically valid and proven to have clinical utility based on prospective evidence
  - the testing method may target DNA, RNA, or DNA/RNA if performed as a single assay
- no other tumor biomarker or broad molecular profile panel has been performed on the specimen for the same indication
- disease-specific criteria are not described elsewhere in this Coverage Policy

Initial Evaluation

Tissue-Based Testing:

Initial tissue-based testing is considered medically necessary when the general criteria above and ANY of the following criteria are met:

- identification of the specific biomarker has been validated by the National Comprehensive Cancer Network® (NCCN ®) as a category 1, 2A or 2B recommendation for the individual's tumor type

- identification of the specific biomarker has been demonstrated in published peer-reviewed literature to improve diagnosis, management or clinical outcomes for the individual's condition
- the "Indications and Usage" section of the US Food and Drug Administration (FDA) label requires biomarker confirmation by an FDA-approved or cleared test
- broad molecular profile panel testing for **ANY** of the following:
    - advanced, metastatic solid tumors
    - recurrent cutaneous melanoma
    - non-small cell lung cancer (NSCLC)
    - recurrent pancreatic cancer
    - epithelial ovarian cancer
    - fallopian tube cancer
    - primary peritoneal cancer
    - recurrent or unresectable salivary gland tumors
    - unresectable biliary tract cancer
    - confirmed or suspected acute myeloid leukemia
    - confirmed or suspected myelodysplastic syndrome
    - myeloproliferative disease
    - multiple myeloma
    - systemic mastocytosis
    - diagnosis of cancer with at least five tumor markers included in the panel that individually meet criteria for the individual's tumor type, based on the medical necessity criteria for individual tumor markers listed above
    - tumor mutational burden (TMB) testing is recommended in the NCCN management algorithm for the individual's cancer type* and all other requirements are met
        - *Note: TMB testing must be explicitly included in the guidelines (not solely included in a footnote as an intervention that may be considered)

Cell-free (ctDNA) DNA Testing (Liquid Biopsy):

Initial cell-free (ctDNA) DNA testing is considered medically necessary when the general criteria above are met, tissue testing is not available or contraindicated, and EITHER of the following:

- advanced or metastatic solid tumors
- the "Indications and Usage" section of the US FDA-approved prescribing label requires biomarker confirmation by an FDA approved or cleared test prior to initiating therapy

Concurrent Tissue-based and ctDNA Testing:

Concurrent tissue-based and ctDNA genomic sequencing (ordered within 30 days of each other) is considered medically necessary when results will directly impact clinical decision making in the following scenarios:

- metastatic breast cancer
- metastatic non-small cell lung cancer

Repeat or Subsequent Evaluations:

Repeat tissue-based or ctDNA-based genomic sequencing (i.e., tissue- or ctDNA-based genomic sequencing has been previously performed on the individual's

cancer) is considered medically necessary when the general criteria above and ALL of the following are met:

- the individual has an advanced or metastatic solid tumor
- a new tissue biopsy sample or ctDNA sample is being collected on which the testing will be performed
- the individual has progressed on systemic therapy or has had clinical non-response after systemic therapy

Molecular tumor biomarker or broad molecular profile panel testing (either tissue or ctDNA) for hematology and oncology indications is considered not medically necessary if the criteria described above are not met.

Minimal Residual Disease (MRD)

Testing of bone marrow samples for minimal residual disease (MRD) using high-throughput immunosequencing is considered medically necessary for ANY of the following indications or when designated by NCCN as a category 1, 2A or 2B recommendation:

- multiple myeloma (MM)
- B-cell acute lymphoblastic leukemia (ALL)
- chronic lymphocytic leukemia (CLL)
- peripheral and cutaneous T-cell lymphoma (TCL)

Other testing (e.g., non-high-throughput immunosequencing) for MRD using a validated technology when recommended by NCCN as a Category 1, 2A, or 2B recommendation is considered medically necessary.

Molecular testing for hematology and oncology indications is not covered or reimbursable if the criteria described above are not met.

Tumor Profile/Gene Expression Classifier Testing

Gene-Expression Classifiers (GEC)

Tissue-based gene expression classifier (GEC) testing is considered medically necessary when ALL of the following criteria are met:

- the individual is a candidate for a targeted therapy associated with a specific disease site
- disease-specific criteria are not described elsewhere in the Coverage Policy
- results of testing will directly impact clinical decision making
- the testing method is scientifically valid and proven to have clinical utility based on prospective evidence
- **ANY** of the following:
  - risk assessment using a GEC has been validated by the NCCN as a category 1, 2A or 2B recommendation for the individual's tumor type of disease
  - use of a GEC has been demonstrated in published peer-reviewed literature to improve diagnosis, management or clinical outcomes for the individual's condition being addressed

Gene expression classifier testing is considered not medically necessary if the criteria described above are not met.

Proteomic Testing

Proteomic testing is considered medically necessary when ALL of the following criteria are met:

- results of testing will directly impact clinical decision making
- the testing method is considered to be scientifically valid and proven to have clinical utility based on prospective evidence
- testing has been validated by the NCCN as a category 1, 2A or 2B recommendation for the individual's tumor type or disease
- disease-specific criteria are not described elsewhere in the Coverage Policy

Proteomic testing is considered not medically necessary if the criteria described above are not met.

Circulating Tumor Cells Testing

AR-V7 testing from circulating tumor cells is considered medically necessary for a male with metastatic castrate resistant prostate cancer (mCRPC) considering second line therapy when BOTH of the following criteria are met:

- progression on androgen receptor–signaling inhibitor (ARSi) therapy (i.e., enzalutamide (Xtandi), abiraterone (Zytiga))
- nuclear expression of AR-V7 will be assessed to guide subsequent therapeutic decision making

Detection of circulating whole tumor cells for any other indication is considered not medically necessary.

Myeloproliferative Neoplasms

Polycythemia Vera (PV)

Genetic testing for JAK2 common variants (CPT codes 81270, 81279), MPL common variants (CPT codes 81338, 81339), and CALR exon 9 common variants (CPT code 81219) is considered medically necessary for the diagnosis of polycythemia vera (PV) when BOTH of the following criteria are met:

- genetic testing would impact medical management of the individual being tested
- **ONE** of the following:
    - hemoglobin >16.5 g/dL in men, >16.0 g/dL in women
    - hematocrit >49% in men, >48% in women
    - increased red cell mass (RCM) more than 25% above mean normal predicted value

Essential Thrombocythemia

Genetic testing for JAK2 common variants (CPT codes 81270, 81279), MPL common variants (CPT codes 81338, 81339), and CALR exon 9 common variants (CPT code 81219) is considered medically necessary for the diagnosis of essential thrombocythemia or thrombocytosis (ET) when BOTH of the following criteria are met:

- results will impact medical management
- **EITHER** of the following criteria is met:
  - platelet count ≥ 450 x 10^9/L
  - bone marrow biopsy showing: proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei; no significant increase or left shift in neutrophil granulopoiesis or erythropoiesis; and very rarely minor (grade 1) increase in reticulin fibers

Primary Myelofibrosis (PMF)

Genetic testing for JAK2 common variants (CPT codes 81270, 81279), MPL common variants (CPT codes 81338, 81339), and CALR exon 9 common variants (CPT code 81219) is considered medically necessary for the diagnosis of primary myelofibrosis (PMF) when BOTH of the following criteria are met:

- results will impact medical management
- primary myelofibrosis is suspected but not confirmed, based on results of conventional testing

ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, and SF3B1 testing is considered medically necessary for the diagnosis of primary myelofibrosis (PMF) when ALL of the following criteria are met:

- above criteria are met
- results will impact medical management
- bone marrow findings of: megakaryocytic proliferation and atypia, without reticulin fibrosis >grade 1, accompanied by increased age-adjusted bone marrow cellularity, granulocytic proliferation, and often, decreased erythropoiesis
- testing will be completed on bone marrow sample
- JAK2, CALR and MPL mutation analysis was previously completed and was negative

Chronic Myelogenous Leukemia (CML) and Philadelphia Chromosome Positive (PH+) Acute Lymphoblastic Leukemia (ALL)

BCR-ABL T315-I pathogenic variant testing (CPT code 81170) is considered medically necessary in individuals with chronic myelogenous leukemia (CML) or Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL) when ANY of the following are met:

- inadequate initial response to tyrosine kinase inhibitor therapy (i.e., failure to achieve complete hematological response at 3 months, minimal cytogenetic response at 6 months or major cytogenetic response at 12 months)
- loss of response to tyrosine kinase inhibitor therapy (i.e., hematologic relapse, cytogenetic relapse, loss of major molecular response [MMR])
- progression to accelerated or blast phase CML while on tyrosine kinase inhibitor therapy

Experimental/Investigational/Unproven

mRNA gene expression profiling and algorithmic analysis (i.e., 12 genes) (CPT code 0011M) to predict high-grade prostate cancer risk score is considered experimental, investigational or unproven.

Not Covered or Reimbursable

The following tests do not meet medical necessity criteria outlined above and are additionally not covered or reimbursable:

- Adrenal Mass Panel (24-hour urine) (CPT code 0015M)
- ClarityDx Prostate (CPT code 0550U)
- ColoScape™ Colorectal Cancer Detection (CPT code 0368U)
- EpiSwitch® CiRT (CPT code 0332U)
- EpiSwitch® Prostate Cancer Detection Test (PSE) (CPT code 0433U)
- HelioLiver Dx (CPT code 0333U)
- HPV-SEQ (CPT code 0470U)
- M-inSight® Patient Definition Assay (CPT code 0450U)
- M-inSight® Patient Follow-Up Assessment (CPT code 0451U)
- miR Sentinel™ Prostate Cancer Test (CPT codes 0343U, 0424U)
- NavDx® (CPT code 0356U)
- Northstar Response® (CPT code 0486U)
- OncoAssure Prostate (CPT code 0497U)
- OptiSeq™ Colorectal Cancer NGS Panel (CPT code 0498U)
- PROphetNSCLC™ (CPT code 0436U)
- PurIST℠ (CPT code 0510U)
- Septin9 methylation analysis (CPT code 81327)
- Tempus p-MSI (CPT code 0512U)
- Tempus p-Prostate (CPT code 0513U)

Coding Information

Notes:

1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare and Medicaid Services (CMS) code updates may occur more frequently than policy updates
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

General Criteria for Somatic Pathogenic or Likely Pathogenic Variant Genetic Testing

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	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)

CPT®* Codes	Description
81168	CCND1/IGH (t(11;14)) (eg, mantle cell lymphoma) translocation analysis, major breakpoint, qualitative and quantitative, if performed
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 receptor tyrosine kinase 1, 2, and 3) (eg, solid tumors) translocation analysis
81202	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
81203	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants
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
81229	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants, comparative genomic hybridization (CGH) microarray analysis
81232	DPYD (dihydropyrimidine dehydrogenase) (eg, 5-fluorouracil/5-FU and capecitabine drug metabolism), gene analysis, common variant(s) (eg, *2A, *4, *5, *6)
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)
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)
81242	FANCC (Fanconi anemia, complementation group C) (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A>T)
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)

CPT®* Codes	Description
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)
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 variants(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)
81278	IGH@/BCL2 (t(14;18)) (eg, follicular lymphoma) translocation analysis, major breakpoint region (MBR) and minor cluster region (mcr) breakpoints, qualitative or quantitative
81287	MGMT (0-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme), promoter methylation analysis
81288	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; 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
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)
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)

CPT®* Codes	Description
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)
81346	TYMS (thymidylate synthetase) (eg, 5-fluorouracil/5-FU drug metabolism), gene analysis, common variant(s) (eg, tandem repeat variant)
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)
81353	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; known familial variant
81500	Oncology (ovarian), biochemical assays of two proteins (CA-125 and HE-4), utilizing serum, with menopausal status, algorithm reported as a risk score

Considered Not Medically Necessary:

CPT®* Codes	Description
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
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 as a probability of predicted main cancer type and subtype
0012M	Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm reported as a risk score for having urothelial carcinoma
0080U	Oncology (lung), mass spectrometric analysis of galectin-3-binding protein and scavenger receptor cysteine-rich type 1 protein M130, with five clinical risk factors (age, smoking status, nodule diameter, nodule-spiculation status and nodule location), utilizing plasma, algorithm reported as a categorical probability of malignancy
0363U	Oncology (urothelial), mRNA, gene-expression profiling by real-time quantitative PCR of 5 genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm incorporates age, sex, smoking history, and macrohematuria frequency, reported as a risk score for having urothelial carcinoma
0391U	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
0599U	Oncology (pancreatic cancer), multiplex immunoassay of ICAM1, TIMP1, CTSD, THBS1, and CA 19-9, serum, diagnostic algorithm reported as positive or negative

Not Covered or Reimbursable:

CPT®* Codes	Description
81327	SEPT9 (Septin9) (eg, colorectal cancer) promoter methylation analysis
81350	UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, drug metabolism, hereditary unconjugated hyperbilirubinemia [Gilbert syndrome], gene analysis, common variants (eg, *28, *36, *37)
0015M	Adrenal cortical tumor, biochemical assay of 25 steroid markers, utilizing 24-hour urine specimen and clinical parameters, prognostic algorithm reported as a clinical risk and integrated clinical steroid risk for adrenal cortical carcinoma, adenoma, or other adrenal malignancy
0333U	Oncology (liver), surveillance for hepatocellular carcinoma (HCC) in high-risk patients, analysis of methylation patterns on circulating cell-free DNA (cfDNA) plus measurement of serum of AFP/AFP-L3 and oncoprotein des-gamma-carboxy-prothrombin (DCP), algorithm reported as normal or abnormal result
0356U	Oncology (oropharyngeal or anal), evaluation of 17 DNA biomarkers using droplet digital PCR (ddPCR), cell-free DNA, algorithm reported as a prognostic risk score for cancer recurrence
0368U	Oncology (colorectal cancer), evaluation for mutations of APC, BRAF, CTNNB1, KRAS, NRAS, PIK3CA, SMAD4, and TP53, and methylation markers (MYO1G, KCNQ5, C9ORF50, FLI1, CLIP4, ZNF132 and TWIST1), multiplex quantitative polymerase chain reaction (qPCR), circulating cell-free DNA (cfDNA), plasma, report of risk score for advanced adenoma or colorectal cancer
0450U	Oncology (multiple myeloma), liquid chromatography with tandem mass spectrometry (LCMS/MS), monoclonal paraprotein sequencing analysis, serum, results reported as baseline presence or absence of detectable clonotypic peptides
0451U	Oncology (multiple myeloma), LCMS/MS, peptide ion quantification, serum, results compared with baseline to determine monoclonal paraprotein abundance
0470U	Oncology (oropharyngeal), detection of minimal residual disease by next-generation sequencing (NGS) based quantitative evaluation of 8 DNA targets, cell-free HPV 16 and 18 DNA from plasma
0550U	Oncology (prostate), enzyme-linked immunosorbent assays (ELISA) for total prostate-specific antigen (PSA) and free PSA, serum, combined with age, previous negative prostate biopsy status, digital rectal examination findings, prostate volume, and image and data reporting of the prostate, algorithm reported as a risk score for the presence of high-grade prostate cancer

Tumor Profile/Gene Expression Classifier Testing

Considered Not Medically Necessary:

CPT®* Codes	Description
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)
0153U	Oncology (breast), mRNA, gene expression profiling by next-generation sequencing of 101 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a triple negative breast cancer clinical subtype(s) with information on immune cell involvement

CPT®* Codes	Description
0630U	Oncology (breast), mRNA, gene expression profiling by microarray of 80 genes (80 content and 465 housekeeping), utilizing formalin-fixed paraffinembedded tissue (FFPE), algorithm reported as an index that is diagnostic of a molecular subtype (luminal, basal, Her2)

Circulating Tumor Cells Testing

Considered Not Medically Necessary:

CPT®* Codes	Description
0490U	Oncology (cutaneous or uveal melanoma), circulating tumor cell selection, morphological characterization and enumeration based on differential CD146, high molecular–weight melanoma associated antigen, CD34 and CD45 protein biomarkers, peripheral blood
0491U	Oncology (solid tumor), circulating tumor cell selection, morphological characterization and enumeration based on differential epithelial cell adhesion molecule (EpCAM), cytokeratins 8, 18, and 19, CD45 protein biomarkers, and quantification of estrogen receptor (ER) protein biomarker–expressing cells, peripheral blood
0492U	Oncology (solid tumor), circulating tumor cell selection, morphological characterization and enumeration based on differential epithelial cell adhesion molecule (EpCAM), cytokeratins 8, 18, and 19, CD45 protein biomarkers, and quantification of PD-L1 protein biomarker– expressing cells, peripheral blood

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
86152	Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood);
86153	Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood); physician interpretation and report, when required

ICD-10-CM Diagnosis Codes	Description
C61	Malignant neoplasm of prostate
C79.82	Secondary malignant neoplasm of genital organs
D40.0	Neoplasm of uncertain behavior of prostate

Not Covered or Reimbursable:

ICD-10-CM Diagnosis Codes	Description
	All other diagnosis codes

Myeloproliferative Neoplasms

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	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)
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)
81219	CALR (calreticulin) (eg, myeloproliferative disorders), gene analysis, common variants in exon 9
81236	EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, myelodysplastic syndrome, myeloproliferative neoplasms) gene analysis, full gene sequence
81270	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant
81279	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) targeted sequence analysis (eg, exons 12 and 13)
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
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)
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)
0017U	Oncology (hematolymphoid neoplasia), JAK2 mutation, DNA, PCR amplification of exons 12-14 and sequence analysis, blood or bone marrow, report of JAK2 mutation not detected or detected

CPT®* Codes	Description
0027U	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, targeted sequence analysis exons 12-15
0040U	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis, major breakpoint, quantitative

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
0011M	Oncology, prostate cancer, mRNA expression assay of 12 genes (10 content and 2 housekeeping), RT-PCR test utilizing blood plasma and/or urine, algorithms to predict high-grade prostate cancer risk

Not Covered or Reimbursable:

CPT®* Codes	Description
0332U	Oncology (pan-tumor), genetic profiling of 8 DNA-regulatory (epigenetic) markers by quantitative polymerase chain reaction (qPCR), whole blood, reported as a high or low probability of responding to immune checkpoint-inhibitor therapy
0343U	Oncology (prostate), exosome-based analysis of 442 small noncoding RNAs (sncRNAs) by quantitative reverse transcription polymerase chain reaction (RT-qPCR), urine, reported as molecular evidence of no-, low-, intermediate- or high-risk of prostate cancer
0424U	Oncology (prostate), exosome based analysis of 53 small noncoding RNAs (sncRNAs) by quantitative reverse transcription polymerase chain reaction (RTqPCR), urine, reported as no molecular evidence, low-, moderate- or elevated-risk of prostate cancer
0433U	Oncology (prostate), 5 DNA regulatory markers by quantitative PCR, whole blood, algorithm, including prostate-specific antigen, reported as likelihood of cancer
0436U	Oncology (lung), plasma analysis of 388 proteins, using aptamer-based proteomics technology, predictive algorithm reported as clinical benefit from immune checkpoint inhibitor therapy
0486U	Oncology (pan-solid tumor), next generation sequencing analysis of tumor methylation markers present in cell-free circulating tumor DNA, algorithm reported as quantitative measurement of methylation as a correlate of tumor fraction
0497U	Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 6 genes (FOXM1, MCM3, MTUS1, TTC21B, ALAS1, and PPP2CA), utilizing formalin fixed paraffin-embedded (FFPE) tissue, algorithm reported as a risk score for prostate cancer
0498U	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
0510U	Oncology (pancreatic cancer), augmentative algorithmic analysis of 16 genes from previously sequenced RNA whole transcriptome data, reported as probability of predicted molecular subtype

CPT®* Codes	Description
0512U	Oncology (prostate), augmentative algorithmic analysis of digitized whole-slide imaging of histologic features for microsatellite instability (MSI) status, formalin-fixed paraffin embedded (FFPE) tissue, reported as increased or decreased probability of MSI-high (MSI-H)
0513U	Oncology (prostate), augmentative algorithmic analysis of digitized whole-slide imaging of histologic features for microsatellite instability (MSI) and homologous recombination deficiency (HRD) status, formalin fixed paraffin-embedded (FFPE) tissue, reported as increased or decreased probability of each biomarker

General Background

Somatic Mutation Genetic Testing
Somatic mutations are changes in the DNA of a cell that may occur in any cell of the body except the germ cells (i.e., egg and sperm). Somatic mutations differ from germline mutations, which are passed down by blood relatives; somatic mutations are not inherited. The genetic tests described in this Coverage Policy are used to identify disease-causing somatic mutations or the biological activity of genes originating in a tumor or hematologic malignancy.

Tumor markers, also known as biomarkers, are substances that are produced by cancer cells or other cells or the body in response to cancer or certain benign (noncancerous) conditions. Tumor markers are proteins or other substances that are made at higher amounts by a cancer cell than a normal cell and may be useful in determining the extent or stage of disease or recurrence, determining the most effective treatment for a specific disease and how well the disease will respond to treatment. They can be found in the blood, urine, stool, tumor tissue, or other tissues or bodily fluids of some patients with cancer (National Cancer Institute [NCI], 2023).

Published peer-reviewed evidence and professional society/organizational consensus guidelines support testing for certain tumor markers for the screening, staging, diagnosis and management of some types of cancer. However, for other tumor markers there is insufficient evidence to establish clinical utility for informing on improvement of health outcomes.

To have clinical utility the specific gene or gene biomarker for which testing has been requested, or gene expression classifier assay should be demonstrated in the published, peer-reviewed scientific literature in the form of prospective clinical trial data to improve the diagnosis, management, or clinical outcomes for the individual's tumor type or disease when the individual is a candidate for a related therapy. The identification of the gene or biomarker should also be required to initiate a related therapy that has been validated by the National Comprehensive Cancer Network® (NCCN®) as a Category 1, 2A or 2B Level of Evidence and Consensus recommendation as a standard of care. The NCCN categories of evidence and consensus are defined as:

- Category 1: Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate
- Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate

- Category 2B: Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate
- Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

Multigene panels may also provide important information regarding an individual's tumor type to direct proven therapy or support management changes for hematology-oncology indications. These tests may be clinically useful when sequential testing of individual genes or biomarkers is not feasible because of limited tissue availability, or when urgent treatment decisions are pending and sequential testing would result in a prolonged testing schedule.

There is insufficient evidence in the published, peer-reviewed scientific literature to support molecular testing when the requested gene(s) or biomarker(s) is(are) correlated with a known therapy, but that therapy has not been validated in prospective clinical trials for the specific tumor type or disease site.

Broad Molecular Profile Testing
Broad molecular profile tests, also known as molecular profiling and comprehensive genome profiling panels are large multigene tests which assess multiple genetic alterations simultaneously in a solid tumor. Several laboratory methods may be used to assess the tumor; however, next generation sequencing techniques are most commonly used. Broad molecular tests can identify alterations to base substitutions (substitution of an amino acid), insertions and deletions (amino acids are added or removed from DNA), copy number alterations (sections of DNA are repeated) and rearrangements (amino acids are rearranged in a different order). Broad molecular profile testing may be used with the goal of identifying mutations of interest for which drug therapy may be available or for enrollment in a clinical trial. Limitations to testing include testing for more alterations than have been identified for a specific type of cancer and the identification of variations of unknown significance. Nonetheless, such testing is supported by published professional society guidelines, including from the NCCN as a key component of care for a number of advanced, metastatic, refractory and recurrent cancers.

Biopsy Testing Methods
A biopsy is used as a diagnostic and monitoring tool to identify abnormalities in tissue or blood. A traditional tissue biopsy is used to sample and analyze a solid biological specimen. Tissue biopsy remains the gold standard for the confirmation and diagnosis of disease, including various cancers. Limitations include patient risk due the invasive nature of the test and limited availability of the tissue sample.

There is increasing use of plasma cell-free DNA testing, also known as a liquid biopsy, which is used to sample and analyze nucleic acids in peripheral circulation, most commonly in plasma. At present there are no standards for analytical performance and no guidelines exist for regarding the recommended performance characteristics. Cell-free DNA testing has a high specificity rate but limitations include a compromised sensitivity with up to a 30% false-negative rate. Such testing may also identify alterations that are unrelated to a lesion of interest. Nonetheless, the use of cell-free DNA testing may be considered appropriate when a patient is medically unfit for invasive tissue sampling or there is insufficient material for analysis in advanced (III or IV), metastatic, recurrent or refractory solid cancers.

There is growing evidence which indicates sequential or concurrent tissue- and ctDNA-based testing can increase detection of actionable variants in certain individuals with advanced or metastatic cancer. Data has demonstrated these methodologies can be complementary to one another in individuals with advanced or metastatic non-small cell lung cancer (NSCLC) and breast

cancer, as unique actionable variants can be identified on both methodologies (Iams, et al., 2024; Xie, et al., 2023).

Testing for Minimal Residual Disease
Minimal residual disease refers to the presence of leukemic cells below the threshold of detection by conventional morphologic methods. Patients who achieve complete response by morphologic assessment alone can harbor leukemic cells in the bone marrow. Methods frequently utilized include a multiparameter (i.e., at least 6-color) flow cytometry to detect abnormal phenotypes, real-time quantitative polymerase chain reaction (RQ-PCT) assays to detect fusion genes and high-throughput next generation sequencing (NGS)-based assays to detect clonal arrangements. An assay for minimal residual disease by high throughput sequencing methods is currently recommended as clinically useful for multiple myeloma, B-cell acute lymphoblastic leukemia, chronic lymphocytic leukemia, and peripheral and cutaneous T-cell lymphoma.

U.S. Food and Drug Administration (FDA)
FDA approval is not required for the development or marketing of specific gene tumor markers profiling tests, multigene panel tests or gene classifier tests. Many high-complexity tests are laboratory-developed in Clinical Laboratory Improvement Amendment (CLIA)-certified laboratories.

Tumor Profile/Gene Expression Classifier Testing
Gene expression classifier assays identify genetic alterations or biological activity of several genes in a tumor. Such tests may provide a more complete picture of a tumor's molecular signature and enable a better estimate of the risk of distant recurrence when considered along with other molecular signatures and clinical characteristics. They have been proposed as an adjuvant tool to assist in determining overall survival, recurrence probability, appropriate treatment options and responsiveness to chemotherapy and are not advocated as stand-alone tools. Numerous gene profiling assays are currently marketed for use in the U.S.

Professional Societies/Organizations
American Society of Clinical Oncology (ASCO): In 2022, ASCO published updated recommendations on the use of breast cancer biomarker assay results to guide adjuvant endocrine and chemotherapy decisions in early-stage breast cancer. The recommendations included the following (Andre, et al., 2022):

- "Clinicians may use Oncotype DX, MammaPrint, Breast Cancer Index (BCI), and EndoPredict to guide adjuvant endocrine and chemotherapy in patients who are postmenopausal or age > 50 years with early-stage estrogen receptor (ER)–positive, human epidermal growth factor receptor 2 (HER2)–negative (ER1 and HER2–) breast cancer that is node-negative or with 1-3 positive nodes.
- Prosigna and BCI may be used in postmenopausal patients with node-negative ER1 and HER2– breast cancer.
- In premenopausal patients, clinicians may use Oncotype in patients with node-negative ER1 and HER2– breast cancer.
- Current data suggest that premenopausal patients with 1-3 positive nodes benefit from chemotherapy regardless of genomic assay result.
- There are no data on use of genomic tests to guide adjuvant chemotherapy in patients with ≥ 4 positive nodes.
- Ki67 combined with other parameters or immunohistochemistry 4 score may be used in postmenopausal patients without access to genomic tests to guide adjuvant therapy decisions.
- BCI may be offered to patients with 0-3 positive nodes who received 5 years of endocrine therapy without evidence of recurrence to guide decisions about extended endocrine therapy.

- None of the assays are recommended for treatment guidance in individuals with HER2-positive or triple-negative breast cancer.
- Treatment decisions should also consider disease stage, comorbidities, and patient preferences."

Supportive evidence and strength of recommendation varied by indication and test.

Proteomic Testing

Proteomics involves the quantitative and qualitative study of proteins, including the function, composition and structure and the way they interact inside cells. Protein expression may be changed by environmental conditions. Proteomics can identify and monitor biomarkers by analyzing the proteins in body fluids such as urine, serum, exhaled breath and spinal fluid. Proteomics can also facilitate drug development by providing a comprehensive map of protein interactions associated with disease pathways. A proteomic profile may be used to find and diagnose a disease or condition and to see how well the body responds to treatment (National Cancer Institute [NCI], 2023; Al-Amrani, et al., 2021).

To be clinically useful the testing method must be scientifically and clinically validated and proven to have clinical utility based on prospective evidence, testing must be validated by the National Comprehensive Cancer Network® (NCCN Guidelines®) as a category 1, 2A or 2B recommendation for the individual's tumor type or disease and results of testing must directly impact clinical decision making.

Circulating Whole Tumor Cell Testing

Circulating whole tumor cells (CTCs) have been found in the peripheral blood circulation of individuals with various forms of metastatic cancer. CTCs are whole cells that have been shed by the tumor. The detection and testing of these tumor cells has been proposed as a method to stratify risk, monitor progression and monitor response to treatment.

The use of circulating whole tumor cell testing has not been proven to impact meaningful health outcomes for most cancers. There is limited evidence to establish the clinical significance of circulating whole tumor cells and how identification can improve health outcomes. Pilot studies suggest that the identification of whole tumor cells may have a role in risk stratification and monitoring responses to treatment.

However, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for prostate cancer (v2.2025) states that "androgen receptor splice variant 7 (AR-V7) testing in circulating tumor cells (CTCs) can be considered to help guide selection of therapy in the post-abiraterone/enzalutamide metastatic castration-resistant prostate cancer setting."

With the exception of testing for the AR-V7 variant in metastatic castrate-resistant prostate cancer, the role of this testing in patient management is not yet known (Antonarakis, et al., 2015; Antonarakis, et al., 2014). Larger longitudinal studies with standard techniques in clearly-defined populations of patients are needed to establish the role of such testing.

Literature Review—Breast Cancer: Smerage et al. (2014) reported on a randomized trial of patients with persistent increase in CTCs that were tested to determine whether changing chemotherapy after one cycle of first-line chemotherapy would improve the primary outcome of overall survival (OS). Five hundred ninety-five female patients were included with histologically confirmed breast cancer and clinical and/or radiographic evidence of metastatic disease. Patients who underwent chemotherapy had evaluation for CTCs at baseline and then after one cycle. Women whose CTCs remained elevated after the first cycle of therapy (arm C) (n=123) were randomly assigned to either maintain the initial treatment plan (n=64) or to change of chemotherapy (n=59). Changing to an alternate regimen had no difference in OS compared with

continuation of the initial regimen (median 12.5 versus 10.7 months, respectively, p=0.98). The CTCs did appear to have prognostic value: the median OS for arms A, B, and C were 35 months, 23 months, and 13 months, respectively. While it appears that there is prognostic value of CTCs, the role in clinical management in breast cancer has not been demonstrated.

Zhang et al. (2012) reported on a meta-analysis of published literature on the prognostic relevance of CTC, including patients with early and advanced disease. Forty-nine eligible studies with 6,825 patients were identified. The main outcomes analyzed were overall survival (OS) and disease-free survival (DFS) in early-stage breast cancer patients, as well as progression-free survival (PFS) and OS in metastatic breast cancer patients. Pooled hazard ratio (HR) and 95% confidence intervals (CIs) were calculated using the random and the fixed-effects models. The presence of CTC was significantly associated with shorter survival in the total population. The prognostic value of CTC was significant in both early (DFS: HR, 2.86; 95% CI, 2.19–3.75; OS: HR, 2.78; 95% CI, 2.22–3.48) and metastatic breast cancer (PFS: HR, 1.78; 95% CI, 1.52–2.09; OS: HR, 2.33; 95% CI, 2.09–2.60). Subgroup analyses showed that our results were stable irrespective of the CTC detection method and time point of blood withdrawal. The authors conclude that the detection of CTC is a stable prognosticator in patients with early-stage and metastatic breast cancer; however further studies are required to explore the clinical utility of CTC in breast cancer.

Bidard et al. (2012) conducted a prospective observational study that compared serum marker levels with CTC in 267 metastatic breast cancer patients. The secondary pre-planned endpoint derived from a study that previously reported on CTC as prognostic factor (Pierga, et al., 2011), compared prospectively the positivity rates and the value of CTC (CellSearch), of serum tumor markers (carcinoembryonic antigen (CEA), cancer antigen 15.3 (CA 15-3), CYFRA 21-1), and of serum non-tumor markers (lactate dehydrogenase (LDH), alkaline phosphatase (ALP)) at baseline and under treatment for PFS prediction, independently from the other known prognostic factors, using univariate analyses and concordance indexes. The study reported that a total of 90% of the patients had at least one elevated blood marker. The blood markers were correlated with poor performance status, high number of metastatic sites and with each other. CYFRA 21-1, a marker usually used in lung cancer, was elevated in 65% of patients. A total of 86% of patients had either CA 15-3 and/or CYFRA 21-1 elevated at baseline. Each serum marker was associated, when elevated at baseline, with a significantly shorter PFS. Serum marker changes during treatment, assessed either between baseline and the third week or between baseline and weeks six-nine, were significantly associated with PFS, as reported for CTC. Concordance indices comparison showed no clear superiority of any of the serum marker or CTC for PFS prediction. The authors concluded that for the purpose of PFS prediction by measuring blood marker changes during treatment, currently available blood-derived markers (CTC and serum markers) had globally similar performances. There was no clear superiority found of CTC over the other serum markers.

Liu et al. (2009) conducted on a prospective study that examined the correlation of CTCs with radiographic findings for disease progression. Serial CTC levels were obtained in patients (n=68) that were starting a new treatment regimen for progressive, radiographically measurable metastatic breast cancer. Blood was collected at baseline and three to four week intervals and radiographic studies were performed in nine to twelve week intervals. Median follow-up was 13.3 months. Patients who had five or more CTCs had 6.3 times the odds of radiographic disease progression when compared with patients who had less than five CTCs. Shorter progression-free survival was observed for patients with five or more CTCs at three to five weeks and at seven to nine weeks after the start of treatment. The CTC result was statistically significantly associated with disease progression for all patients ($p<0.001$). The association was noted to remain strong in patients treated with either chemotherapy or endocrine therapy. Potential limitations of the study include that the study included patients receiving various lines and types of therapy. The subgroup analysis for CTC-imaging correlation was performed by including biologic agents with either

chemotherapy or endocrine therapy—it was noted that each group was too small to be analyzed alone.

Nolé et al. (2008) conducted a prospective study to evaluate the prognostic significance of CTCs detection in advanced breast cancer patients. The study included 80 patients with inclusion criteria: women with histological diagnosis of breast cancer, evidence of metastatic disease from imaging studies, starting a new line of therapy and/or treated for the advanced disease with a maximum two lines of therapy. The CellSearch system was used to test for circulating tumor cell levels before starting a new treatment and after four, eight weeks, the first clinical evaluation and every two months thereafter. At baseline, 49 patients were found to have ≥ 5 CTCs. The baseline number of CTCs were associated with progression-free survival (hazard ratio [HR] 2.5; 95% confidence interval [CI] 1.2–5.4). The risk of progression for patients with CTCs ≥ 5 at the last available blood draw was five times the risk of patients with 0–4 CTCs at the same time point (HR 5.3; 95% CI 2.8–10.4). At the last available blood draw, patients with rising or persistent CTCs ≥ 5 demonstrated a statistically significant higher risk of progression with respect to patients with CTCs < 5 at both blood draws (HR 6.4; 95% CI 2.8–14.6). The authors noted that these results indicated that elevated CTCs levels measured at any time in the clinical course of a patient with metastatic breast cancer predict an imminent progression and that this analysis represents an additional step in the process of validating this method.

Literature Review—Colorectal Cancer: Groot Koerkamp et al. (2013) reported on systematic review of studies that investigated the prognostic value of tumor cells in blood (CTCs) or bone marrow (BM) (disseminated tumor cells [DTC]) of patients with resectable colorectal liver metastases or widespread metastatic colorectal cancer (CRC). A total of 16 studies with 1,491 patients were included in the review and the results of 12 studies (1,329 patients) included in the meta-analysis. Eight studies used RT-PCR methodology to detect tumor cells, nine studies applied immunocytochemistry (five with CellSearch) and one study applied both methods. The overall survival (hazard ratio [HR], 2.47; 95 % CI 1.74–3.51) and progression-free survival (PFS) (HR, 2.07; 95 % CI 1.44–2.98) were worse in patients with CTCs. The subgroup of studies with more than 35% CTC-positive patients was the only subgroup with a statistically significant worse PFS. The eight studies that had multivariable analysis identified the detection of CTCs as an independent prognostic factor for survival. Limitations of the study included a considerable degree of interstudy heterogeneity. The study does not demonstrate the clinical utility of CTC detection, or that the detection of CTCs is a predictive factor, or identify patients that may benefit from a specific treatment.

Sastre et al. (2012) reported on an ancillary study of 180 patients that was a subset of a phase III study (The Maintenance in Colorectal Cancer trial) that assessed maintenance therapy with single-agent bevacizumab versus bevacizumab plus chemotherapy in patients with metastatic colorectal cancer. The ancillary study was conducted to evaluate CTC count as a prognostic and/or predictive marker for efficacy endpoints. Blood samples were obtained at baseline and after three cycles. CTC enumeration was performed with CellSearch System. The study found that the median progression-free survival (PFS) interval for patients with a CTC count ≥3 at baseline was 7.8 months, as compared to 12.0 months found in patients with a CTC count <3 (p=0.0002). The median overall survival (OS) time was 17.7 months for patients with a CTC count >3, compared with 25.1 months for patients with a lower count (p=0.0059). After three cycles, the median PFS interval for patients with a low CTC count was 10.8 months, which was noted to be longer than the 7.5 months for patients with a high CTC count (p=0.005). The median OS time for patients with a CTC count <3 was significantly longer than for patients with a CTC count ≥3, 25.1 months compared to 16.2 months, respectively (p=0.0095).

Thorsteinsson and Jess (2011) conducted a review of studies of CTCs in colorectal cancer (CRC). Nine studies were included in the review. Detection rates of CTC in peripheral blood of patients

with non-metastatic CRC varied from 4% to 57%. Inclusion criteria included: patients diagnosed with non-metastatic colorectal cancer; CTC detected in peripheral blood samples; pre- and/or post-operative blood samples; and samples size of more than 99 patients. Seven studies applied RT-PCR and two studies used immunocytochemical methods. Seven studies found the presence of CTC to be a prognostic marker of poor disease-free survival. The authors concluded that the presence of CTC in peripheral blood is a potential marker of poor disease-free survival in patients with non-metastatic CRC and that the low abundance of CTC in non-metastatic CRC needs very sensitive and specific detection methods. They also noted that an international consensus on choice of detection method and markers is warranted before incorporating CTC into risk stratification in the clinical setting.

Rahbari et al. (2010) reported on a meta-analysis of studies to assess whether the detection of tumor cells in blood and bone marrow of patients diagnosed with colorectal cancer (CRC) can be used as a prognostic factor. Thirty-six studies were included in the review that examined the detection of free blood or bone marrow tumor cells with patient's prognosis and included various methods of techniques (e.g., reverse transcriptase-PCR [RT-PCR]) and immunologic). The review indicated that the presence of CTCs detected in peripheral blood is of strong prognostic significance in patients with CRC. There was considerable interstudy heterogeneity noted in regards to differences in the detection methods, types and numbers of target genes or antigens, sampling site and time, and in demographic or clinicopathologic status of patients.

Literature Review—Prostate Cancer: Resel Folkersma et al. (2012) reported on a prospective study that analyzed the correlation between circulating tumor cell (CTC) levels and clinicopathologic parameters (prostate-specific antigen [PSA] level, Gleason score, and TNM stage) in patients with metastatic hormone-sensitive prostate cancer (PCa) and to establish its prognostic value in overall survival (OS) and progression-free survival (PFS). The study included three arms: 30 patients with localized PCa; 30 patients with metastatic PCa; and 30 healthy volunteers. The median follow-up was 42.9 months. A significant positive correlation was demonstrated between the CTC level and all tumor burden markers (PSA and T, N, and M stage; $p<0.001$), except for Gleason score (tau=0.16). A cutoff of ≥4 CTCs/7.5 mL was chosen to distinguish patients with a poor prognosis. These patients had a significantly shorter median OS and PFS (24 compared to 45 months and 7 compared to 44 months, respectively; $p<0.001$). As the CTC level increased, the OS and PFS were noted to decrease. The risk of mortality and progression for the patients with ≥4 CTCs was 4.1 ($p=0.029$) and 8.5 ($p<0.001$) times greater. Multivariate analyses indicated that a CTC of ≥4 was an independent prognostic factor for PFS (hazard ratio 5.9, $p<0.005$).

Several observational studies have been published that correlate CTC with disease status and progression in prostate cancer (Goodman, et al. 2009; Okegawa, et al., 2009; Olmos, et al., 2009; Scher, et al., 2009; Okegawa, et al., 2008; Danila, et al., 2007; Shaffer, et al., 2007; Moreno, et al., 2005).

Professional Societies/Organizations
American Society of Clinical Oncology (ASCO): In the 2022 guidelines on the use of breast cancer biomarker assay results to guide adjuvant endocrine and chemotherapy decisions in early-stage breast cancer, ASCO made the following recommendations (Andre, et al., 2022):

- If a patient has node-negative or node-positive ER-positive, HER2-positive, or TNBC, the clinician should not use circulating tumor cells (CTC) to guide decisions for adjuvant endocrine and chemotherapy (Type: Evidence-Based; Evidence Quality: Intermediate; Strength of Recommendation: Strong).
- If a patient has node-negative or node-positive ER-positive, HER2-positive, or TNBC, the clinician should not use ctDNA to guide decisions for adjuvant endocrine and chemotherapy (Type: Evidence-Based; Evidence Quality: Intermediate; Strength of Recommendation: Strong)."

American Society of Clinical Oncologists (ASCO)/College of American Pathologists (CAP): In collaboration with CAP, ASCO published a joint review regarding circulating tumor DNA analysis in individuals with cancer (Merker, et al., 2018). The review noted some circulating DNA (ctDNA) assays have demonstrated clinical validity and utility with certain types of advanced cancer; however, there is insufficient evidence of clinical validity and utility for the majority of ctDNA assays in advanced cancer. Evidence shows discordance between the results of ctDNA assays and genotyping tumor specimens and supports tumor tissue genotyping to confirm undetected results from ctDNA tests. There is no evidence of clinical utility and little evidence of clinical validity of ctDNA assays in early-stage cancer, treatment monitoring, or residual disease detection. There is no evidence of clinical validity and clinical utility to suggest that ctDNA assays are useful for cancer screening, outside of a clinical trial.

Screening and Prognostic Tests for Early Detection of Prostate Cancer
Prostate specific antigen (PSA), an organ-specific marker, is often used as a tumor marker. The higher the level of PSA at baseline, the higher is the risk for metastatic disease or subsequent disease progression. However, it is an imprecise marker of risk. Various approaches aimed at improving the performance of PSA in early cancer detection have been tested, including the measurement of prostate biomarkers; none have yet been proven to decrease the risk of death from prostate cancer (National Cancer Institute [NCI], 2025c).

According to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for prostate cancer early detection (v2.2025), biomarkers which improve the specificity of prostate cancer detection are not yet mandated as first-line screening tests in conjunction with serum PSA. However, there may be some individuals who meet PSA standards for prostate biopsy consideration, but who would like to more precisely the estimate risk of cancer before proceeding to biopsy. The extent of validation of these biomarker tests varies across diverse populations, and it is not yet known with certainty how these biomarker tests may be used in optimal combination with magnetic resonance imaging (MRI). The NCCN guideline provides the following pre- and post-biopsy biomarker testing recommendations:

- Pre-initial biopsy
  - The probability of high-grade cancer (Grade Group ≥ 2) may be further defined prior to initial biopsy utilizing tests such as:
    - Prostate Health Index (PHI)
    - SelectMDx
    - 4Kscore
    - ExoDx Prostate Test
    - MyProstateScore (MPS)
    - MPS 2.0 (MPS2) (category 2B recommendation)
    - Stockholm3
    - IsoPSA
- Post-initial biopsy
  - Tests that improve specificity in the post-biopsy setting may be considered in patients thought to be higher risk despite a negative prostate biopsy.
  - Tests to be considered are:
    - percent-free PSA
    - 4Kscore
    - PHI
    - PCA3
    - ConfirmMDx
    - ExoDx Prostate Test
    - MPS

- MPS2 (category 2B recommendation)
- IsoPSA

Professional Societies/Organizations
American Urological Association (AUA): The 2023 AUA guideline for the early detection of prostate cancer included the following recommendations concerning biomarkers (Wei, et al., 2023a, 2023b):

- When screening for prostate cancer, clinicians should use prostate-specific antigen (PSA) as the first screening test. (Strong Recommendation; Evidence Level: Grade A)
  - Regarding the use of the Stockholm3 test as a first-line screening test for predicting the risk of GG2+ prostate cancers, the AUA noted that while the test appears promising, further validation in diverse populations to confirm initial findings is needed to move forward into practice.
- For individuals with a newly elevated PSA, clinicians should repeat the PSA prior to a secondary biomarker, imaging, or biopsy. (Expert Opinion)
- For individuals undergoing prostate cancer screening, clinicians should not use PSA velocity as the sole indication for a secondary biomarker, imaging, or biopsy. (Strong Recommendation; Evidence Level: Grade B)
- Clinicians may use adjunctive urine or serum markers when further risk stratification would influence the decision regarding whether to proceed with biopsy. (Conditional Recommendation; Evidence Level: Grade C)
  - The AUA further noted that "such biomarkers should not be used in situations in which, based on available clinical and laboratory data, the risk of GG2+ prostate cancer is so low or so high the result of adjunctive biomarkers would not influence the decision of whether to proceed with further testing (e.g., MRI and/or biopsy)".
- After a negative initial biopsy in patients with low probability for harboring GG2+ prostate cancer, clinicians should not reflexively perform biomarker testing. (Clinical Principle)
- After a negative biopsy, clinicians may use blood, urine, or tissue-based biomarkers selectively for further risk stratification if results are likely to influence the decision regarding repeat biopsy or otherwise substantively change the patient's management. (Conditional Recommendation; Evidence Level: Grade C)

Tumor Tissue-Based Molecular and Proteomic Assays for Detection of Prostate Cancer
The NCCN Guidelines® for prostate cancer (v2.2025) notes that although risk groups, life expectancy estimates, and nomograms help inform treatment decisions, there remains uncertainty regarding the risk of disease progression. Several tumor tissue-based molecular assays have been developed to improve decision-making in individuals newly diagnosed with prostate cancer, and those undergoing treatment. The NCCN guideline provides the following recommendations for such testing:

- Individuals with low or favorable intermediate disease and life expectancy ≥ 10 years may consider the use of the Decipher®, Oncotype DX® Prostate (Genomic Prostate Score), or Prolaris® genomic tests during initial risk stratification.
- Individuals with unfavorable intermediate- and high-risk disease and life expectancy ≥10 years may consider the use of Decipher® or Prolaris®.
- Decipher® may be considered to inform adjuvant treatment if adverse features are found after radical prostatectomy and during workup for radical prostatectomy PSA persistence or recurrence.

Although these tests have not been validated by prospective, randomized clinical trial data, retrospective case cohort studies demonstrate that these tests provide prognostic information independent of NCCN or Cancer of the Prostate Risk Assessment (CAPRA) risk groups which

include likelihood of death with conservative management, likelihood of recurrence after radical prostatectomy or external beam radiation therapy (EBRT), likelihood of adverse pathologic features after radical prostatectomy, and likelihood of developing metastasis after surgery or EBRT (NCCN, 2025).

Myeloproliferative Neoplasms
Polycythemia Vera (PV), Essential Thrombocythemia (ET) and Primary Myelofibrosis (PMF): Identification of the JAK2, MPL and CALR exon 9 common variants in individuals with polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) may aid in diagnosis based on diagnostic criteria for each of these diseases. For some individuals with PV, JAK2 exon 12 mutation testing may also be of benefit in disease management. Likewise, genetic testing for MPL common variants and targeted mutation analysis of CALR exon 9 may be appropriate to aid in the diagnosis and management of ET and PMF. According to 2016 World Health Organization (WHO) criteria (Arber, et al., 2016), ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2 and SF3B1 mutation analysis may aid in diagnosis of PMF.

Chronic Myelogenous Leukemia and Philadelphia Chromosome Positive (PH+) Acute Lymphoblastic Leukemia Mutation Testing: Specific mutations in the Breakpoint Cluster Region-Abelson (BCR-ABL) gene have been shown to confer resistance to imatinib both in vitro and in vivo, by affecting the binding of the drug to the tyrosine kinase enzyme (Agency for Healthcare Research and Quality [AHRQ], 2010). Of interest is the T315-I mutation, which is thought to be resistant to all current tyrosine kinase inhibitor (TKI) therapy. The mutation frequency in imatinib resistant patients with CML ranges between 2% and 20%, with variability related to detection methods as well as patient cohort characteristics and treatment. T315I mutation frequency appears to be greater in patients with Philadelphia chromosome-positive (Ph^+) ALL and likely increases with the continuation of TKI treatment (Nicolini, et al., 2009). The detection of mutations of the BCR-ABL gene has been proposed with potential impact on diagnosis and management decisions (National Cancer Institute [NCI], 2025a, 2025b; AHRQ, 2010). Evidence in the published, peer-reviewed scientific literature also supports the usefulness of testing for BCR-ABL resistance or inhibition.

Real-time quantitative PCR (RQ-PCR) is by far the most sensitive method. It provides an accurate measure of the total leukemia cell mass and the degree to which breakpoint cluster region-Abelson (BCR-ABL) transcripts are reduced by therapy, and correlates with progression-free survival. Current international recommendations for optimal molecular monitoring of patients receiving imatinib treatment include an RQ-PCR assay expressing the BCR-ABL transcript levels, which is predictive of prognosis (Bhatia, et al., 2012). In acute lymphocytic leukemia (ALL), because many patients have a different fusion protein from the one found in chronic myelogenous leukemia (CML), the BCR-ABL gene may be detectable only by pulsed-field gel electrophoresis or reverse-transcriptase polymerase chain reaction (RT-PCR). These tests should be performed whenever possible in patients with ALL, especially those with B-cell lineage disease (NCI, 2025a).

Although certain BCR-ABL mutations may be associated with TKI therapy resistance, sensitivity and specificity values in outcome studies are not suggestive of strong predictive ability, with the exception of the T315-I mutation. Early identification of this mutation may allow for alternative treatment regimens including increased dose scheduling and drug selection. Data in the published peer-reviewed scientific literature supports the clinical utility of testing for the presence of the T315-I mutation. The clinical utility of testing for other mutations to determine TKI resistance has not been established.

Literature Review: Several studies have reported associations between variations of BCR-ABL and response to drug therapy. AHRQ (2010) performed a systematic review of the published literature regarding variations of the BCR-ABL1 fusion gene and response to imatinib, dasatinib,

and nilotinib in CML. Thirty-one studies were analyzed for outcomes of interest including overall survival and cancer specific survival; progression-free or event-free survival (as defined by each study); and treatment failure. Typically, treatment failure is defined as absence of hematologic, cytogenetic, or molecular response to treatment, according to various criteria. Data was analyzed for first-, second-, and third- line TKI therapy. Second-line TKI therapy studies (four publications) demonstrated sensitivity and specificity ranges of 0.35 to 0.83 and from 0.58 to 1.00, respectively, for high-dose imatinib and imatinib-based combination. These studies were small, the calculated sensitivity and specificity values have wide confidence intervals, and a range of different mutations was identified in each of them. No robust conclusions could be made. Eight studies (nine publications) pertained to dasatinib; some had overlapping populations. Sensitivities and specificities ranged from 0.27 to 0.90 and from 0.14 to 0.87, respectively. A lack of predictive ability is suggested. For nilotinib, three studies had relevant data. Sensitivity ranged from 0.56 to 0.71 and specificity ranged from 0.42 to 0.56 for all identified mutations. Only one included study reviewed overall survival (OS). No statistically significant differences in the time-to-death among patients with, versus without mutations were found. When any breakpoint cluster region-Abelson (BCR-ABL1) mutation was considered, almost all studies reported sensitivity and specificity values that are not suggestive of strong predictive ability.

The Agency for Healthcare Research and Quality (AHRQ) noted that no study explicitly reported details on changes in treatment plans before or after testing. AHRQ determined that the presence of any BCR-ABL mutation does not appear to differentiate response to tyrosine kinase inhibitor (TKI) treatment (i.e., imatinib, dasatinib, nilotinib). AHRQ also noted that the majority of evidence pertains to the short term surrogate outcomes of hematologic, cytogenetic or molecular response. Data on overall or progression-free survival are sparse. There is consistent evidence that presence of the relatively rare T315-I mutation can predict TKI treatment failure, mainly in terms of hematologic and cytogenetic response (AHRQ, 2010).

Jabbour et al. (2009) studied 169 patients with chronic myelogenous leukemia (CML) after imatinib failure. The goals of the study were to investigate whether in vitro sensitivity of kinase domain mutations could be used to predict the response to therapy as well as the long-term outcome of patients receiving second-generation TKIs after imatinib failure. Treatment failure was defined as loss of a cytogenetic, or complete hematologic response (CHP), or failure to achieve a CHR or any hematologic response (for patients in accelerated phase or blast phase after three months of therapy, or persistence of 100% Philadelphia chromosome (Ph)–positive metaphases after 6 months of therapy, or more than or equal to 35% after 12 months). Fifty-seven patients (66%) had received prior therapy with interferon-alpha before the start of imatinib; 29 (34%) had received imatinib as their first-line therapy for CML. Mutations were detected by cDNA sequencing for mutations in the kinase domain of BCR-ABL before a change to dasatinib or nilotinib in 86 patients. Ninety-four mutations were identified in 86 patients with imatinib failure. Seven patients harbored more than one mutation. There was no difference in patient characteristics between those with mutations at the time of imatinib failure versus those with no mutations. Forty-one patients received dasatinib and 45 received nilotinib after developing failure to imatinib therapy. Hematologic and cytogenetic response rates were similar for patients without or with KD mutations. After a median follow-up of 23 months, 48 (58%) of patients without baseline mutations were alive compared with 52 (60%) with any mutation.

Nicolini et al. (2009) reported the results of a retrospective observational study of 222 patients with CML in chronic-phase, accelerated-phase, or blastic-phase and Philadelphia chromosome-positive (Ph^+) ALL patients with the BCR-ABL T315I mutation. After T315I mutation detection, second-generation TKIs were used in 56% of cases, hydroxyurea in 39%, imatinib in 35%, cytarabine in 26%, MK-0457 in 11%, stem cell transplantation in 17%, and interferon-alpha in 6% of cases. Median overall survival from T315I mutation detection was 22.4, 28.4, 4.0, and 4.9 months, and median progression-free survival was 11.5, 22.2, 1.8, and 2.5 months, respectively,

for chronic phase, accelerated phase, blastic phase, and Ph(+) ALL patients. These results suggest that survival of patients harboring a T315I mutation is dependent on disease phase at the time of mutation detection.

In an earlier study by Jabbour et al. (2006) 171 patients were screened for mutations after failing TKI therapy with a median follow-up of 38 months from start of therapy. Sixty-six mutations impacting 23 amino acids in the BCR-ABL oncogene were identified in 62 (36%) patients. Factors associated with the development of mutations were older age, previous interferon therapy and accelerated or blast phase at the start of TKI therapy. By multivariate analysis, factors associated with worse survival were development of clonal evolution and a higher percentage of peripheral blood basophils. The presence of a BCR-ABL kinase domain mutation had no impact on survival. When survival was measured from the time therapy started, non-P-loop mutations were associated with a shorter survival than P-loop mutations. The authors concluded that BCR-ABL P-loop mutations were not associated with a worse outcome. This study suggests that outcomes of individuals who fail TKI therapy may be influenced by multiple factors.

Nicolini and colleagues (2006) retrospectively analyzed the predictive impact of 94 breakpoint cluster region (BCR) - Abelson (ABL) kinase domain mutations found in 89 protein tyrosine kinase inhibitor (TKI) resistant chronic myelogenous leukemia (CML) individuals. With a median follow-up of 39 months, overall survival was worse for P-loop and another point mutation (T315-I), but not for other BCR-ABL mutations. For individuals in chronic phase only, analysis demonstrated a worse overall survival for P-loop and worse progression free survival for T315-I mutations.

Professional Societies/Organizations
National Cancer Institute (NCI): Regarding BCR-ABL mutation analysis in individuals with chronic myeloid leukemia (CML), the NCI states "In case of treatment failure or suboptimal response, patients should undergo BCR::ABL1 kinase domain mutation analysis to help guide therapy with the newer TKIs or with allogeneic transplant" (NCI, 2025b).

Health Equity Considerations

Health equity is the highest level of health for all people; health inequity is the avoidable difference in health status or distribution of health resources due to the social conditions in which people are born, grow, live, work, and age.

Social determinants of health are the conditions in the environment that affect a wide range of health, functioning, and quality of life outcomes and risks. Examples include safe housing, transportation, and neighborhoods; racism, discrimination and violence; education, job opportunities and income; access to nutritious foods and physical activity opportunities; access to clean air and water; and language and literacy skills.

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Revision Details

Type of Revision	Summary of Changes	Date
Focused Review	• Revised not covered or reimbursable section.	5/15/2026
Focused Review	• No clinical policy statement changes.	4/10/2026
Annual Review	• Revised policy statements for tissue-based broad molecular profile panel testing; primary myelofibrosis testing; and not covered or reimbursable tests.	11/9/2025
Focused Review	• Removed policy statements for targeted PIK3CA and NTRK fusions testing; specific gene expression testing for breast cancer; certain prostate cancer tests; occult neoplasms; topographic genotyping; and adhesive patch gene expression assay. • Added policy statement for specific not covered or reimbursable tests.	11/1/2024
Annual Review	• Revised general criteria for somatic pathogenic or likely pathogenic variant genetic testing. • Removed policy statement for VeriStrat.	5/15/2024