MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**Circulating Tumor DNA for Management of Cancer (Liquid Biopsy)**
Policy Number	**2.02.56**
Category	**Technology Assessment**
Original Effective Date	**08/15/19**
Committee Approval Date	**10/22/20, 11/18/21, 01/19/23, 01/18/24**
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Product Disclaimer	• *Services are contract dependent; if a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan or Child Health Plus product), medical policy criteria apply to the benefit.* • *If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.* • *If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.* • *If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.*

POLICY STATEMENT

Colorectal Cancer

I. Based upon our criteria and assessment of the peer-reviewed literature, including the National Comprehensive Cancer Network (NCCN) clinical guidelines**,** cell-free/circulating tumor DNA (ctDNA or liquid biopsy) analysis, as an alternative to additional tumor tissue biopsy, is considered **medically appropriate** as a technique to direct targeted drug therapy for individuals:

A. In the treatment of metastatic colorectal cancer;
AND
B. **Repeat** invasive biopsy is contraindicated or there is not enough tissue for tissue-based molecular and biomarker analysis; and
C. The test has FDA approval for the specific tumor type or disease site; and
D. The results will be used to guide management of the patient for the following targeted gene mutations;
(CPT code examples not all inclusive):
1. Kirsten rat sarcoma viral oncogene (KRAS) (CPT: 81275, 81276);
2. Neuroblastoma RAS viral oncogene (NRAS) (CPT: 81311);
3. B-Raf proto-oncogene (BRAF) (CPT: 81210);
4. HER2 amplification;
5. Neurotrophic tyrosine receptor kinase (NTRK) gene fusions (CPT: 81191-81193, or 81194).

Non-Small Cell Lung Cancer

II. Based upon our criteria and assessment of the peer-reviewed literature, including National Comprehensive Cancer Network (NCCN) clinical guidelines, cell-free/circulating tumor DNA (ctDNA or liquid biopsy) analysis, as an alternative to additional tumor tissue biopsy, is considered **medically appropriate** as a technique to direct targeted drug therapy for individuals:

A. who have previous biopsy-confirmed, newly diagnosed non-small-cell lung cancer (NSCLC) including adenocarcinoma, large cell, squamous cell, and NSCLC not otherwise specified; **OR**
B. who have non-small-cell lung cancer (NSCLC) that is progressing on or after chemotherapy or immunotherapy, and who have never been tested for molecular and biomarker analysis;

AND

C. **Repeat** invasive biopsy is medically contraindicated or there is not enough tissue for tissue-based molecular and biomarker analysis; and
D. The test has received FDA approval for the specific tumor type or disease site; and
E. The results will be used to guide management of the patient for the following targeted gene mutations;

(CPT code examples not all inclusive):

1. Epidermal Growth Factor Receptor (EGFR) gene mutations (CPT: 81235);
2. Anaplastic lymphoma kinase (ALK) gene rearrangement;
3. KRAS (CPT: 81275, 81276);
4. NTRK 1/2/3 gene fusion (CPT: 81191-81193, or 81194);
5. ROS proto-oncogene 1 (ROS-1) gene rearrangement;
6. BRAF point mutations (CPT: 81210);
7. Mesenchymal-epithelial transition MET exon 14 skipping variants;
8. High-level MET amplification;
9. Rearranged during transfection (RET) gene rearrangements;
10. Erb-B2 Receptor Tyrosine Kinase 2 (ERBB2)/(HER2) gene mutation.

Melanoma

III. Based upon our criteria and assessment of the peer-reviewed literature, including National Comprehensive Cancer Network (NCCN) clinical guidelines, cell-free/circulating tumor DNA (ctDNA or liquid biopsy) analysis, as an alternative to additional tumor tissue biopsy, is considered **medically appropriate** for individuals:

A. with Stage III melanoma at high risk for recurrence; **OR**
B. with Stage IV melanoma or clinical recurrence;

AND

C. **Repeat** invasive biopsy is medically contraindicated or there is not enough tissue for tissue-based molecular and biomarker analysis; and
D. The test has received FDA approval for the specific tumor type or disease site; and
E. The results will be used to guide management of the patient for the following targeted gene mutations;

(CPT code examples not all inclusive):

1. BRAF (CPT: 81210);
2. KIT (CPT: 81272).

Pancreatic Cancer

IV. Based upon our criteria and assessment of the peer-reviewed literature, including National Comprehensive Cancer Network (NCCN) clinical guidelines, cell-free/circulating tumor DNA (ctDNA or liquid biopsy) analysis, as an alternative to additional tumor tissue biopsy, is considered **medically appropriate** as a technique to direct targeted drug therapy for individuals:

A. who have previous biopsy-confirmed, newly diagnosed metastatic pancreatic cancer; **OR**
B. who have metastatic pancreatic cancer that is progressing on or after chemotherapy or immunotherapy, and have never been tested for molecular and biomarker analysis;

AND

C. **Repeat** invasive biopsy is medically contraindicated or there is not enough tissue for tissue-based molecular and biomarker analysis; and
D. The test has received FDA approval for the specific tumor type or disease site; **AND**
E. The results will be used to guide management of the patient for the following targeted gene mutations;

(CPT code examples not all inclusive):

1. Anaplastic lymphoma kinase (ALK) gene fusions;

2. NRG1 gene fusions;
3. NTRK 1/2/3 gene fusion (CPT: 81191-81193, or 81194);
4. ROS-1 gene fusion;
5. BRAF gene mutation (CPT: 81210);
6. BRCA 1/2 gene mutation (CPT 81162);
7. KRAS gene mutation (CPT: 81275, 81276);
8. PALB2 gene mutation (CPT: 81307);
9. HER2 amplifications;
10. FGFR2 gene fusion;
11. RET gene fusion.

Ovarian Cancer

V. Based upon our criteria and assessment of the peer-reviewed literature, including National Comprehensive Cancer Network (NCCN) clinical guidelines, cell-free/circulating tumor DNA (ctDNA or liquid biopsy) analysis, as an alternative to additional tumor tissue biopsy, is considered **medically appropriate** as a technique to direct targeted drug therapy for individuals:
   A. With recently diagnosed or recurrent ovarian cancer;
   AND
   B. **Repeat** invasive biopsy is medically contraindicated or there is not enough tissue for tissue-based molecular and biomarker analysis; and
   C. The test has received FDA approval for the specific tumor type or disease site; and
   D. The results will be used to guide management of the patient for the following targeted gene mutations; (CPT code examples not all inclusive):
      1. BRCA 1/2 (CPT 81162);
      2. Homologous recombination deficiency (HRD) status;
      3. TMB;
      4. NTRK (CPT: 81191-81193, or 81194);
      5. BRAF (CPT: 81210);
      6. FRα;
      7. RET;
      8. MSI/MMR.

Prostate Cancer

VI. Based upon our criteria and assessment of the peer-reviewed literature, including National Comprehensive Cancer Network (NCCN) clinical guidelines, cell-free/circulating tumor DNA (ctDNA or liquid biopsy) analysis, as an alternative to additional tumor tissue biopsy, is considered medically appropriate as a technique to direct targeted drug therapy for individuals:
   A. who have metastatic prostate cancer;
   AND
   B. **Repeat** invasive biopsy is medically contraindicated or there is not enough tissue for tissue-based molecular and biomarker analysis; and
   C. The test has received FDA approval for the specific tumor type or disease site; and
   D. The results will be used to guide management of the patient for the following targeted gene mutations; (CPT code examples not all inclusive):
      1. BRCA 1/2 (CPT 81162);
      2. ATM;
      3. PALB2 (CPT 81307);
      4. FANCA;
      5. RAD51D;
      6. CHEK2;
      7. CDK12;

8. MSI/MMR.

Breast Cancer

VII. Based upon our criteria and assessment of the peer-reviewed literature, including National Comprehensive Cancer Network (NCCN) clinical guidelines, cell-free/circulating tumor DNA (ctDNA or liquid biopsy) analysis, as an alternative to additional tumor tissue biopsy, is considered medically appropriate as a technique to direct targeted drug therapy for individuals:
   A. who have HR-positive/HER2-negative breast cancer;
   AND
   B. **Repeat** invasive biopsy is medically contraindicated or there is not enough tissue for tissue-based molecular and biomarker analysis; and
   C. The test has received FDA approval for the specific tumor type or disease site; and
   D. The results will be used to guide management of the patient for the following targeted gene mutations;
   (CPT code example not all inclusive):
      1. PIK3CA mutation (CPT 81309)

Other Cancers

VIII. Based upon our criteria and assessment of the peer-reviewed literature, circulating tumor DNA (ctDNA or liquid biopsy) analysis is considered **investigational** for all other indications.

IX. Based upon our criteria and assessment of the peer-review literature, broad molecular panel testing has not been medically proven to be effective and, therefore, is considered **investigational**.

Refer to Corporate Medical Policy #2.02.51 Molecular Testing of Tumor Tissue to Identify Targeted Therapies for Cancers

Refer to Corporate Medical Policy #2.02.53 JAK2, MPL, and CALR Molecular Testing for Myeloproliferative Neoplasm

Refer to Corporate Medical Policy #2.02.54 Measurable Residual Disease Assessment Testing

Refer to Corporate Medical Policy #11.01.03 Experimental or Investigational Services

POLICY GUIDELINES

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

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

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

IV. Cell-free/circulating tumor DNA testing should not be used in lieu of tissue diagnosis.

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

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

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

VIII. On August 7, 2020, the FDA approved the Guardant 360 CDx assay as a companion diagnostic comprehensive liquid biopsy for advanced solid tumors. The molecular panel includes 73 genes and turnaround time is seven days.

IX. On August 26, 2020, the FDA approved the FoundationOne Liquid CDx. This broad molecular liquid biopsy is a companion diagnostic test that analyzes over 300 genes and biomarkers from a blood draw. It can also report blood tumor mutational burden (TMB), microsatellite instability high (MSI-H), and tumor fraction values but these features have not been approved by the FDA. Turnaround time is 10 days. If the test results are negative for certain mutations, reflexing to routine biopsy and tumor mutation status confirmed, using an FDA-approved tumor test should be performed.

DESCRIPTION

The standard for treatment selection in some cancers is biomarker analysis of tissue samples during biopsy or surgery. Both biopsy and surgery are invasive with slow turnaround time for obtaining results. Tumor tissue may also be heterogeneous which may result in patients receiving chemotherapy rather than targeted therapy. An alternative to tissue-based molecular testing is cell-free DNA from plasma in the blood of patients with cancer. Cell-free DNA in blood is derived from nonmalignant and malignant cell DNA. The small DNA fragments released into the blood by tumor cells are referred to as circulating tumor DNA (ctDNA). Most ctDNA is derived from apoptotic and necrotic cells, either from the primary tumor, metastases or circulating tumor cells. Unlike apoptosis, necrosis is considered a pathologic process, generating larger DNA fragments due to an incomplete and random digestion of genomic DNA. The length or integrity of the circulating DNA can potentially distinguish between apoptotic and necrotic origins. The ctDNA can be used for genomic characterization of the tumor and identification of the biomarkers of interest. Detection of ctDNA is challenging because cell-free DNA is diluted by nonmalignant circulating DNA and usually represents a small fraction (less than 1%) of total cell-free DNA. Therefore, methods up to 500 to 1000 times more sensitive than standard sequencing approaches (e.g., Sanger) are needed. Genetic testing of ctDNA can be targeted at specific genes or at commonly found, acquired, somatic variants (“hotspots”) that occur in specific cancers, which can impact therapy decisions. Panel testing for specific genetic variants that may impact therapy decision in many different cancers can also be performed.

Cell-free DNA tests can identify patients with NSCLC who cannot undergo lung biopsy, for whom there is a net benefit of targeted therapy versus chemotherapy.

Biodesix’s GeneStrat uses droplet-digital polymerase chain reaction (PCR) to analyze cell-free DNA and RNA to identify specific driver variants for which targeted therapy is available for NSCLC.

The Association for Molecular Pathology and College of American Pathologists joint publication (2023) recommend the selection of targeted therapy should be based on genomic analysis data derived from recently biopsied tumor tissue and ctDNA analysis. Although tissue genomic analysis remains the standard practice, identification of targetable alterations using ctDNA analysis should also be considered. Optimization of ctDNA analysis will require the use of NGS gene panels similar to those used for tissue analysis and assessment of tumor mutational burden and other biomarkers associated with response to immunotherapy.

RATIONALE

Randomized controlled trials (RCTs) comparing treatment selection based on tumor biomarkers with plasma biomarkers would potentially support evidence on clinical utility, as well as evidence on the ability of liquid biopsy to predict treatment response similar to, or better than, tissue biopsy. If the two tests are highly correlated, they are likely to stratify treatment response similarly overall. To understand the implications of “false-positive: and false-negative” liquid biopsies for outcomes, patients who have discordant results on liquid biopsy and standard tissue biopsy can be assessed for response to EGFR tyrosine kinase inhibitors (TKIs). A negative liquid biopsy for EGFR-sensitizing or -resistance variants, and a positive tissue-based biopsy responding to EGFR tyrosine kinase inhibitors (TKIs), would suggest that the tissue biopsy was correct, and the liquid biopsy results were truly false-negatives. A positive liquid biopsy, and a negative tissue biopsy for EGFR variants responding to EGFR TKIs, would suggest the positive liquid biopsy was correct, rather than false-positive. Clinical utility might alternatively be established, based on the assumption that tissue biomarkers are the standard by which treatment decisions are made; consequently, agreement between liquid and tissue biopsies would infer that treatment selection based on liquid or tissue biopsies is likely to yield similar outcomes. The use of liquid biopsy

rather than a tissue biopsy would reduce the number of patients undergoing invasive tissue sampling and any accompanying complications.

The National Comprehensive Cancer Network (NCCN) guidelines for Non-Small Cell Lung Cancer (NSCLC) state that cell-free/circulating tumor DNA testing should not be used in lieu of tissue diagnosis. Studies have demonstrated that cell-free tumor DNA testing generally has very high specificity, but significantly compromised sensitivity with up to a 30% false-negative rate. Standards for analytical performance characteristics of cell-free tumor DNA have not been established, and in contrast to tissue-based testing, no guidelines exist regarding the recommended performance characteristics of this type of testing. Cell-free tumor DNA testing can identify alterations that are unrelated to a lesion of interest, for example, clonal hematopoiesis of indeterminate potential (CHIP). Use of cell-free/circulating tumor DNA testing can be considered in specific clinical circumstances, most notably when a patient is medically unfit for invasive tissue sampling, there is insufficient tissue for molecular analysis, and a follow-up tissue-based analysis is planned if an oncogenic driver is not identified. The NCCN NSCLC Panel recommends assessing a minimum of the following potential genetic variants: ALK, BRAF, EGFR, ERBB2 (HER2), KRAS, METex14, NTRK1/2/3 gene fusions, RET, and ROS1 rearrangements.

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

BRAF and KIT mutations appear to be early genetic driver events in melanoma. Thus, repeat molecular testing upon recurrence or metastases is likely to be of low yield. Repeat testing following progression on targeted therapy (BRAF- or KIT-directed therapy) does not appear to have clinical utility, since the mechanisms of resistance are diverse and do not have prognostic or therapeutic relevance.

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

The NCCN guidelines for Colon Cancer have expanded recommendations regarding biomarker testing as the role of targeted therapy for treatment of advanced or metastatic colorectal cancer (mCRC) has become increasingly prominent. Currently, determination of tumor gene status for KRAS/NRAS and BRAF mutations, as well as HER2 amplifications and MSI/MMR status (if not previously done), are recommended for patients with mCRC. The testing can be performed on formalin-fixed paraffin-embedded tissue (preferred) or blood-based assay and may be carried out for individual genes or as part of an NGS panel, although no specific methodology is recommended. NGS panels have the advantage of being able to pick up rare and actionable genetic alterations, such as neurotrophic tyrosine receptor kinase (NTRK) fusions. Based on the limited data in the colorectal cancer population, the NCCN Panel does not currently recommend TMB biomarker testing, unless measured as part of a clinical trial.

The NCCN guidelines for Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer state comprehensive tumor testing may not be necessary for certain patients in the upfront setting, specifically those with a germline mutation in BRCA1/2 or other homologous recombination/DNA repair pathway genes. Initially molecular analysis should include

BRCA1/2 status, loss of heterozygosity, or homologous recombination status, in the absence of a germline BRCA mutation. However, some patients (such as those who lack a BRCA1/2 mutation or experience disease recurrence) may benefit from a more thorough tumor molecular analysis to inform additional targeted therapy options. In the recurrence setting, tumor molecular analysis is recommended to include, at a minimum, tests to identify potential benefit from targeted therapeutics that have tumor-specific or tumor-agnostic benefit including, but not limited to, BRCA1/2, HR status, MSI, MMR, TMB, BRAF, *FRα, RET,* and NTRK if prior testing did not include these markers. Molecular analyses may be performed on circulating tumor DNA (ctDNA or liquid biopsy) when tissue-based analysis is not clinically feasible. Additional somatic tumor testing can be considered at the physician's discretion to identify genetic alterations for which FDA-approved tumor-specific or tumor-agnostic targeted therapy options exist. These additional tests may be particularly useful for patients who recurrence therapy options are limited.

The NCCN guidelines for prostate cancer for somatic tumor testing pre-test considerations include that tumor molecular and biomarker analysis may be used for treatment decision-making, including understanding eligibility for biomarker-directed treatments, genetic counseling, early use of platinum chemotherapy, and eligibility for clinical trials. Clinical trials may include established and/or candidate molecular biomarkers for eligibility. The panel strongly recommends a metastatic biopsy for histologic and molecular evaluation. When unsafe or unfeasible, plasma ctDNA assay is an option, preferably collected during biochemical (PSA) and/or radiographic progression in order to maximize diagnostic yield. Caution is needed when interpreting ctDNA-only evaluation due to potential interference from clonal hematopoiesis of indeterminate potential (CHIP), which can result in a false-positive biomarker signal.

The NCCN guidelines for Breast Cancer state the clinical use of Circulating Tumor Cells (CTC) or circulating DNA (ctDNA) in metastatic breast cancer is not yet included in the NCCN Guidelines for Breast Cancer for disease assessment and monitoring but for HR-positive/HER2-negative breast cancer, assess for PIK3CA mutations with tumor or liquid biopsy to identify candidates for alpelisib plus fulvestrant. PIK3CA mutation testing can be done on tumor tissue or ctDNA in peripheral blood (liquid biopsy). If liquid biopsy is negative, tumor tissue testing is recommended.

In the American Society of Clinical Oncology and College of American Pathologists Joint Review of Circulating Tumor DNA Analysis in Patients with Cancer (2018), the authors concluded that current evidence suggests that the optimal specimen type for analysis of circulating tumor DNA (ctDNA) in blood is plasma. Analytical validity must be established for any clinical ctDNA test and different ctDNA assays may not give the same results because of different assay performance characteristics, such as differing limits of detection. Most assays have insufficient evidence to demonstrate clinical validity, and most have no evidence of clinical utility. Well-designed clinical trials or equivalence studies are needed to demonstrate clinical utility for most assays. Evidence shows discordance in results between ctDNA assays and tumor tissue genotyping and supports the value of tumor tissue genotyping to confirm undetected ctDNA findings. For advanced cancer, the evidence indicates that more reliable test results occur when the ctDNA assay is performed at the time of disease progression and not when responding to prior therapy. There is evidence that positive findings from well-validated ctDNA assays may support initiation of a targeted therapy option where an assay for the relevant genomic marker has demonstrated clinical utility when performed in tissue. For monitoring therapy effectiveness, evidence of clinical validity is still emerging, and there is currently no evidence of clinical utility to suggest that ctDNA assays are useful in this context, outside of a clinical trial. For early-stage cancer, evidence of clinical validity is still emerging, and there is currently no evidence of clinical utility to suggest that ctDNA assays are useful at diagnosis or in the adjuvant setting after completing treatment, outside of a clinical trial. For cancer screening, there is no evidence of clinical validity and clinical utility to suggest that ctDNA assays are useful in this context, outside of a clinical trial. Given the rapid pace of research, re-evaluation of the literature will shortly be required, along with the development of tools and guidance for clinical practice.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*
- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).*

CPT Codes

Code	Description
81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (i.e., detection of large gene rearrangements)
81191	NTRK1 (Neurotrophic Receptor Tyrosine Kinase 1) (e.g., solid tumors) translocation analysis
81192	NTRK2 (Neurotrophic Receptor Tyrosine Kinase 2) (e.g., solid tumors) translocation analysis
81193	NTRK3 (Neurotrophic Receptor Tyrosine Kinase 3) (e.g., solid tumors) translocation analysis
81194	NTRK (neurotrophic receptor tyrosine kinase 1, 2, and 3) (e.g., solid tumors) translocation analysis
81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)
81235	EGFR (epidermal growth factor receptor) (e.g., non-small cell lung cancer) gene analysis, common variants (e.g., exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)
81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; variants in exon 2 (e.g., codons 12 and 13)
81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; additional variant(s) (e.g., codon 61, codon 146)
81277 **(E/I)**	Cytogenomic neoplasia (genome-wide) microarray analysis, interrogation of genomic regions for copy number and loss-of heterozygosity variants for chromosomal abnormalities
81307	PALB2 (partner and localizer of BRCA2) (e.g., breast and pancreatic cancer) gene analysis; full gene sequence
81401	Molecular Pathology Procedure Level 2
81402	Molecular Pathology Procedure Level 3
81403	Molecular Pathology Procedure Level 4
81404	Molecular Pathology Procedure Level 5
81405	Molecular Pathology Procedure Level 6
81406	Molecular Pathology Procedure Level 7
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 *(effective 1/1/2023)*

Code	Description
81455 **(E/I)**	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
81456 **(E/I)**	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis *(effective 1/1/2023)*
81462	Solid organ neoplasm, genomic analysis panel, cell-free nucleic acid; DNA analysis or combined DNA and RNA analysis, copy number variants and rearrangements *(effective 01/01/2024)*
81463	Solid organ neoplasm, genomic analysis panel, cell-free nucleic acid; DNA analysis, copy number variants, and microsatellite instability *(effective 01/01/2024)*
81464	Solid organ neoplasm, genomic analysis panel, cell-free nucleic acid; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements *(effective 01/01/2024)*
81479	Unlisted molecular pathology procedure
86152	Cell enumeration using immunologic selection and identification in fluid specimen (e.g., circulating tumor cells in blood);
86153	Cell enumeration using immunologic selection and identification in fluid specimen (e.g., circulating tumor cells in blood); physician interpretation and report, when required
0177U	Oncology (breast cancer), DNA, PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) gene analysis of 11 gene variants utilizing plasma, reported as PIK3CA gene mutation status (therascreen PIK3CA RGQ PCR Kit, QIAGEN, QIAGEN GmbH) *(effective 07/01/2020)*
0179U **(E/I)**	Oncology (non-small cell lung cancer), cell-free DNA, targeted sequence analysis of 23 genes (single nucleotide variations, insertions and deletions, fusions without prior knowledge of partner/breakpoint, copy number variations), with report of significant mutation(s) (Resolution ctDx Lung™, Resolution Bioscience, Resolution Bioscience, Inc) *(effective 07/01/2020)*
0229U **(E/I)**	BCAT1 (Branched chain amino acid transaminase 1) or IKZF1 (IKAROS family zinc finger 1) (e.g., colorectal cancer) promoter methylation analysis (Colvera, Clinical Genomics Pathology Inc)
0239U **(E/I)**	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations (FoundationOne Liquid CDx, Foundation Medicine)
0242U **(E/I)**	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 55-74 genes, interrogation for sequence variants, gene copy number amplifications, and gene rearrangements (Guardant360 CDx, Guardant Health Inc, Guardant Health Inc)

Code	Description
0326U **(E/I)**	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 (Guardant 360 Guardant Health Inc)
0337U **(E/I)**	Oncology (plasma cell disorders and myeloma), circulating plasma cell immunologic selection, identification, morphological characterization, and enumeration of plasma cells based on differential CD138, CD38, CD19, and CD45 protein biomarker expression, peripheral blood (CELLSEARCH® Circulating Multiple Myeloma Cell (CMMC) Test, Menarini Silicon Biosystems, Inc) *(effective 10/01/2022)*
0338U **(E/I)**	Oncology (solid tumor), circulating tumor cell selection, identification, morphological characterization, detection, and enumeration based on differential EpCAM, cytokeratins 8, 18, and 19, and CD45 protein biomarkers, and quantification of HER2 protein biomarker-expressing cells, peripheral blood (CELLSEARCH® HER2 Circulating Tumor Cell (CTC-HER2) Test, Menarini Silicon Biosystems, Inc) *(effective 10/01/2022)*
0388U **(E/I)**	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 (InVisionFirst®-Lung Liquid Biopsy, Inivata, Inc) *(effective 07/01/2023)*
0409U **(E/I)**	Oncology (solid tumor), DNA (80 genes) and RNA (36 genes), by next generation sequencing from plasma, including single nucleotide variants, insertions/deletions, copy number alterations, microsatellite instability, and fusions, report showing identified mutations with clinical actionability (LiquidHALLMARK®, Lucence Health, Inc) *(effective 10/01/2023)*
0428U **(E/I)**	Oncology (breast), targeted hybrid-capture genomic sequence analysis panel, circulating tumor DNA (ctDNA) analysis of 56 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability, and tumor mutation burden *(effective 01/01/2024)*

HCPCS Codes

Code	Description
No specific code(s)	

ICD10 Codes

Code	Description
C18.0-C21.8	Malignant neoplasm of colon, rectosigmoid junction, rectum, and anus and anal canal (code range)
C25.0-C25.9	Malignant neoplasm of pancreas (code range)
C34.10 - C34.12	Malignant neoplasm of upper lobe, bronchus, or lung (code range)
C34.30-C34.32	Malignant neoplasm of lower lobe, bronchus, or lung (code range)
C34.80-C34.82	Malignant neoplasm of overlapping sites of bronchus and lung (code range)
C34.90-C34.92	Malignant neoplasm of unspecified part of bronchus or lung (code range)

Code	Description
C50.011-C50.929	Malignant neoplasm of breast (code range)
C56.1-C56.9	Malignant neoplasm of ovary (code range)
C61	Malignant neoplasm of prostate
C78.5	Secondary malignant neoplasm of large intestine and rectum
C79.60-C79.62	Secondary malignant neoplasm of ovary (code range)
C79.81	Secondary malignant neoplasm of breast
D05.00-D05.02	Lobular carcinoma in situ of breast (code range)
D05.10-D05.12	Intraductal carcinoma in situ of breast (code range)
D05.80-D05.92	Carcinoma in situ of breast, specified, unspecified (code range)
D07.30-D07.39	Carcinoma in situ of other and unspecified female genital organs (code range)
D40.0	Neoplasm of uncertain behavior of prostate

REFERENCES

Alimirzaie S, et al. Liquid biopsy in breast cancer: a comprehensive review. Clin Genet 2019 Jun;95(6):643-660.

Asante DB, et al. Liquid biopsy in ovarian cancer using circulating tumor DNA and cells: ready for primetime? Cancer Lett 2020 Jan;468:59-71.

Botrus G, et al. Circulating tumor DNA (ctDNA) based testing and actionable findings in patients with advanced and metastatic pancreatic adenocarcinoma. Oncologist 2021 Jul;26(7):569-578.

Grunvald MW, et al. Current status of circulating tumor DNA liquid biopsy in pancreatic cancer. Int J Mol Sci 2020 Oct; 21(20): 7651.

Guven DC, et al. A systematic review and meta-analysis of the association between circulating tumor DNA (ctDNA) and prognosis in pancreatic cancer. Crit Rev Oncol Hematol 2021 Dec;168:103528.

Herbreteau G, et al. Circulating free tumor DNA in non-small cell lung cancer (NSCLC): clinical application and future perspectives. J Thorac Dis 2019; 11(Supp 1):S113-S126.

Lockwood CM, et al. Recommendations for cell-free DNA assay validations: A joint consensus recommendation of the Association for Molecular Pathology and College of American Pathologists. J Mol Diagn 2023 Dec;25(12):876-897.

Mack PC, et al. Spectrum of driver mutations and clinical impact of circulating tumor DNA analysis in non-small cell lung cancer: analysis of over 8000 cases. Cancer 2020 Jul;126(14):3219-3228.

Marchi G, et al. Extensive mutational ctDNA profiles reflect high-grade serous cancer tumors and reveal emerging mutations at recurrence. Transl Oncol 2023 Nov 2;39:101814.

Mathai RA, et al. Potential utility of liquid biopsy as a diagnostic and prognostic tool for the assessment of solid tumor: implications in the precision oncology. J Clin Med 2019;8:373.

*Merker JD, 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 2018:36(16):1631–1641.

*National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Breast Cancer. V.4.2023. March 23, 2023 [https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf] accessed 11/21/23.

*National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Colon Cancer. V.4.2023. November 16, 2023 [https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf] accessed 11/21/23.

*National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Melanoma: Cutaneous. V.3.2023. October 27, 2023 [https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf] accessed 11/22/23.

*National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Non-Small Cell Lung Cancer. V.5.2023. November 8, 2023 [https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf] accessed 11/21/23.

*National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Ovarian Cancer including fallopian tube cancer and primary peritoneal cancer. V.2.2023. June 2, 2023 [https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf] accessed 11/22/23.

*National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Pancreatic Adenocarcinoma. V.2.2023. June 19, 2023 [https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf] accessed 11/21/23.

*National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Prostate Cancer. V.4.2023. September 7, 2023 [https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf] accessed 11/21/23.

Oellerich M, et al. Circulating cell-free DNA- diagnostic and prognostic applications in personalized cancer therapy. Ther Drug Monit 2019 Apr;41(2):115-120.

Petit J, et al. Cell-free DNA as a diagnostic blood-based biomarker for colorectal cancer: a systematic review. J Surg Res 2019 Apr;236:184-197.

Sabari JK, et al. A prospective study of circulating tumor DNA to guide matched targeted therapy in lung cancers. J Natl Cancer Inst 2019;111(6):

Saarenheimo J, et al. The value of liquid biopsies for guiding therapy decisions in non-small cell lung cancer. Front Oncol 2019;9:129.

Sivapalan L, et al. Molecular profiling of ctDNA in pancreatic cancer: Opportunities and challenges for clinical application. Pancreatology 2021 Mar;21(2):363-378.

Tolaney SM, et al. Clinical Significance of PIK3CA and ESR1 Mutations in Circulating Tumor DNA: Analysis from the MONARCH 2 Study of Abemaciclib plus Fulvestrant. Clin Cancer Res. 2022 Apr;28(8):1500-1506. Erratum in: Clin Cancer Res 2022 Oct 14;28(20):4587.

Vidula N, et al. Tumor tissue-versus plasma-based genotyping for selection of match therapy and impact on clinical outcomes in patients with metastatic breast cancer. Clin Cancer Res 2021 Jun;27(12):3404-3413.

*Key Article

KEY WORDS

Circulating tumor cells, CTC, ctDNA, cell-free DNA, cfDNA, Guardant 360, FoundationOne Liquid, liquid biopsy.

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a National Coverage Determination (NCD) for Next Generation Sequencing (NGS) (90.2). Please refer to the following NCD website for Medicare Members: https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=372&ncdver=2&bc=AAAAIAAAAAAA& accessed 12/01/23.

There is currently a Local Coverage Determination (LCD) for Molecular Pathology Procedures (L35000). Please refer to the following LCD website for Medicare Members: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=35000&ver=138&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=All&bc=AAgAAAQBIAAA&= accessed 12/01/23.

There is currently a Local Coverage Article (LCA) for Billing and Coding: Molecular Pathology Procedures (A56199). Please refer to the following LCA website for Medicare Members: https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleId=56199&ver=95 accessed 12/01/23.