Medical Policy
Liquid Biopsy

Policy Number: PG0500
Last Review: 08/21/2023

PARAMOUNT

HMO & PPO
MARKETPLACE
ELITE (MEDICARE ADVANTAGE)

GUIDELINES

- This policy does not certify benefits or authorization of benefits, which is designated by each individual policyholder terms, conditions, exclusions, and limitations contract. It does not constitute a contract or guarantee regarding coverage or reimbursement/payment. Self-Insured group specific policy will supersede this general policy when group supplementary plan document or individual plan decision directs otherwise.
- Paramount applies coding edits to all medical claims through coding logic software to evaluate the accuracy and adherence to accepted national standards.
- This medical policy is solely for guiding medical necessity and explaining correct procedure reporting used to assist in making coverage decisions and administering benefits.

SCOPE

X Professional
_ Facility

DESCRIPTION

A liquid biopsy is a test done on a sample of blood to look for cancer cells from a tumor that are circulating in the blood or for pieces of DNA from tumor cells that are in the blood. This is a noninvasive diagnostic approach that may serve in the future for screening, diagnosis, prognosis, and therapy guidance. A liquid biopsy may be used to help find cancer at an early stage. It may also be used to help plan treatment or to find out how well treatment is working or if cancer has come back. Being able to take multiple samples of blood over time may play a complementary/companion role to medical imaging in understand what kind of molecular changes are taking place in a tumor.

The National Cancer Institute defines a liquid biopsy as “a test done on a sample of blood to look for cancer cells from a tumor that are circulating in the blood or for pieces of DNA from tumor cells that are in the blood. A liquid biopsy may be used to help find cancer at an early stage. It may also be used to help plan treatment or to find out how well treatment is working or if cancer has come back. Being able to take multiple samples of blood over time may also help doctors understand what kind of molecular changes are taking place in a tumor.”

Circulating tumor cells (CTCs) are shed from either primary or secondary tumor sites where they then migrate into the circulatory system and initiate distant metastases. Tumor cells release circulating free DNA (cfDNA), also known as circulation tumor DNA (ctDNA), into the blood. It can be found in various substances, including blood, urine, saliva, etc. A liquid biopsy, or blood sample, can provide the genetic landscape of all cancerous lesions (primary and metastases) as well as offering the opportunity to systematically track genomic evolution for tumor biology analyzing. Liquid biopsy markers including circulating tumor cells (CTCs), circulating free DNA (cfDNA) and extracellular vesicles (EVs) and exosomes, as a source of genomic and proteomic information in patients with cancer.

Liquid biopsies allow for the collection of robust and reproducible data in a simple and noninvasive way using a blood sample, but may be performed on other body fluid samples. Whereas the traditional methods of performing biopsies on tumor tissue pose the following concerns: biopsies are invasive, involve risks, are typically costly and are typically difficult to obtain, along with the treatment decision often relies on one single biopsy. To date, liquid biopsy is not a routine test in clinical practice, but its potential applications are rapidly growing: from diagnostic

genomic profiling to the monitoring of surgical outcomes, from evaluating either response or resistance to systemic treatments, to quantifying minimal residual disease. Serial sampling of a tumor is particularly useful related to somatic mutations and the changing treatment decisions in a tumor progression.

The challenge of CTC detection is related to the requirement for high sensitivity combined with high specificity, but several factors still hinder standardized clinical application, including the relatively low blood CTCs in circulation; the absence of a reliable and efficient marker to distinguish CTCs from other blood-borne cells and the high-cost of downstream molecular and genomic characterization in the case of a low number of detected CTCs.

While CTCs and cfDNA present in blood have already demonstrated potential to present corresponding information on possible therapeutic targets and resistance mechanisms, EVs on the contrary present in several bodily fluids (urine, saliva, breast milk, cerebrospinal fluid *etc.*) including blood are believed to be genetic messengers and present an alternative mode of cancer progression.

Liquid biopsy testing methods are typically analyzed by one of the following methods:

- Standard testing methodologies, such as PCR or sequencing, are used to identify targeted mutations commonly present in tumors of a specific type
- NGS-based sequencing or array-CGH testing used to identify both novel and recurrent mutations. These include whole genome sequencing or whole exome sequencing. These approaches analyze single genes, panels of genes, exomes, or genomes.

On August 7, 2020, the FDA approved the Guardant 360 CDX assay to be used by qualified health care professionals in accordance with professional guidelines in oncology for cancer patients with any solid malignant neoplasms.

On August 26, 2020, the FDA approved the FoundationOne Liquid CDx. The test is a qualitative, next-generation sequencing based, in vitro diagnostic test that uses targeted, high through-put, hybridization-based capture technology to detect and report substitutions, insertions, and deletions (indels) in 311 genes, including rearrangements and copy number losses only BRCA1 and BRCA2. 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.

Foundation Medicine's Foundation Liquid CDx uses hybrid capture-based next-generation sequencing (NGS) to detect variants in over 60 genes for targeted therapy in metastatic cancer.

Guardant Health markets the Guardant360 test. This test uses NGS to identify variants in 73 genes associated with several different cancers.

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 NSCLS.

POLICY

Paramount Commercial Insurance Plans and Medicare Advantage Plans
Effective 01/01/2022

- **Liquid biopsy as a source of genomic and proteomic information is covered when the coverage criteria below is met.**
- **Prior Authorization is required for all product lines.**

Refer to medical policy Genetic Testing, PG0041 for specific procedure-to-product line coverage determination.

Non-participating providers are required to obtain prior authorization BEFORE any services are rendered.

COVERAGE CRITERIA
Medicare Advantage Plans

Prior Authorization Required
Next Generation Sequencing (NGS) as a diagnostic laboratory test is reasonable and necessary and covered nationally, when performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, when ordered by a treating physician, and when all of the following requirements are met:

a. Patient has:
   i. either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; and
   ii. not been previously tested with the same test using NGS for the same cancer genetic content, and
   iii. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).
b. The diagnostic laboratory test using NGS must have:
   i. Food & Drug Administration (FDA) approval or clearance as a companion in vitro diagnostic; and,
   ii. an FDA-approved or -cleared indication for use in that patient's cancer; and
   iii. results provided to the treating physician for management of the patient using a report template to specify treatment options

Guardant360® is covered only when all of the following conditions are met:

- Patient has been diagnosed with a recurrent, relapsed, refractory, metastatic, or advanced solid tumor that did not originate from the central nervous system. Patients who would meet all of the indications on the FDA label for larotrectinib if they are found to have an NTRK mutation may be considered to have advanced cancer, and
- Patient has not previously been tested with the Guardant360® test for the same genetic content. For a patient who has been tested previously using Guardant360® for cancer, that patient may not be tested again unless there is clinical evidence that the cancer has evolved wherein testing would be performed for different genetic content. Specifically, in patients with previously tested cancer, who have evidence of new malignant growth despite response to a prior targeted therapy, that growth may be considered to be sufficiently genetically different to require additional genetic testing, and
- Patient is untreated for the primary cancer being tested, or the patient is not responding to treatment (e.g., progression or new lesions on treatment), and
- The patient has decided to seek further cancer treatment with the following conditions:
- The patient is a candidate for further treatment with a drug that is either FDA-approved for that patient's cancer, or has an NCCN 1 or NCCN 2A recommendation for that patient's cancer, and
- The FDA-approved indication or NCCN recommendation is based upon information about the presence or absence of a genetic biomarker tested for in the Guardant360® assay, and
- Tissue-based, CGP is infeasible (e.g., quantity not sufficient for tissue-based CGP or invasive biopsy is medically contraindicated) or specifically in NSLC Tissue-based CGP has shown no actionable mutations.
- If no alteration is detected by Guardant360® or if ctDNA is insufficient/not detected, tissue-based genotyping should be considered.

Other liquid biopsies will be covered for the same indications if they display similar performance in their intended used applications to Guardant360®".

Paramount Commercial Insurance Plans
Prior Authorization Required
This is a limited coverage policy for next-generation sequencing (NGS) assays performed on solid tumor cell-free DNA in plasma, from here on called "liquid biopsies."

General Coverage Criteria:
Based upon 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) (e.g., Guardant 360, Foundation One Liquid CDx, Cobas, Genestrat, OncoBEAM) analysis, as an alternative to additional tumor tissue biopsy, is considered medically appropriate as a technique, a companion diagnostic assays to direct targeted drug therapy for individuals:

- When the 'liquid biopsy' is not used in lieu of a histological tissue diagnosis; and
- The Member has a diagnosis of cancer; and
- Treatment with a medication for which there is a liquid biopsy-based FDA-approved companion diagnostic is being considered, and

    - Note: not all indications for medications with an FDA-approved companion diagnostic liquid biopsy test require the results of the test prior to prescribing. Testing would not be considered medically necessary when prescribed for indications that do not require the companion diagnostic.
- Whom the result will be used to guide management of the member; and
- The test has received FDA approval for the specific tumor type or disease site; and
- The Member has not had previous somatic and/or germline testing that would have identified the genetic change required to prescribe medication under consideration; and
- Repeat invasive biopsy is medically contraindicated or there is not enough tissue for tissue-based molecular and biomarker analysis

Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

- Coverage Criteria indicated above has been met; and
    - Initial Biomarker Determination
        - FDA approved companion diagnostic tests (i.e., cobas EGFR Mutation Test v2, FoundationOne® Liquid CDx, or Guardant360® CDx) or a targeted multi-gene panel, e.g., ctDx Lung™, are medically necessary when tissue-based testing cannot be performed, e.g., insufficient tissue
    - At time of progression on an EGFR tyrosine kinase inhibitor (TKI) therapy
        - Targeted cell-free testing (i.e., cobas EGFR Mutation Test v2) is medically necessary
        - Targeted cell-free testing is not medically necessary when progression is on osimertinib

Testing for the following gene mutations:

1. EGFR TKI-sensitizing variants (exon 19 deletion or a point mutation in exon 21 (L858R) (CPT 81235);
2. EGFR TKI-sensitizing variants (exon 20 or T790M) (CPT 81235);
3. anaplastic lymphoma kinase (ALK) rearrangement;
4. KRAS G12C (CPT: 81275);
5. NTRK 1/2/3 gene fusion (CPT: 81191-81193);
6. ROS-1 gene rearrangement;
7. BRAFV600E (CPT: 81210);
8. MET ex 14 skipping;
9. High-level MET amplification;
10. RET rearrangements; and
11. ERBBS (HER2).

Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

- Coverage Criteria indicated above has been met; and
- FoundationOne® Liquid CDx is medically necessary if tumor is unavailable in women with ovarian, fallopian tube, or primary peritoneal cancer when the patient meets criteria per the FDA label for treatment(s) for which this test has been approved as a companion diagnostic

Advanced or Metastatic Breast Cancer

- Coverage Criteria indicated above has been met; and
- FoundationOne® Liquid CDx is medically necessary if tumor is unavailable in individuals with breast cancer when the patient meets criteria per the FDA label for treatment(s) for which this test has been approved as a companion diagnostic
    - OR
- therascreen® PIK3CA testing is medically necessary using liquid biopsy if tumor is unavailable for advanced or metastatic breast cancer when the patient meets criteria per the FDA label for treatments for which this test has been approved as a companion diagnostic

Metastatic Castrate-Resistant Prostate Cancer

- Coverage Criteria indicated above has been met; and
- FoundationOne® Liquid CDx is medically necessary in men with metastatic castrate-resistant prostate cancer when the individual meets criteria per the FDA label for treatments for which this test has been approved as a companion diagnostic

Paramount Commercial Insurance Plans and Medicare Advantage Plans
VeriStrat is a serum-based mass spectrometric, eight proteins, including amyloid A, signature proteomic test. It is intended to aid in evaluating prognosis and predicting response to systemic or targeted therapies in individuals with advanced NSCLC. Procedure 81539 - Refer to Medical Policy VeriStrat Testing, PG0111.

Paramount Commercial Insurance Plans and Medicare Advantage Plans
Non-Coverage
Many laboratories are developing liquid biopsy assays. For many of these assays, analytical validity studies have been performed; however, data regarding the clinical validity and clinical utility of these tests is still emerging. Members may not be eligible for the following liquid biopsy as a source of genomic and proteomic information in patients with cancer (ie, including circulating tumor cells (CTCs), circulating tumor DNA (ctDNA) and extracellular vesicles (EVs) and exosomes) including, but not limited to:

- CellSearch
- ColonSentry
- Colvera
- Donor-derived cell-free DNA whole genome next-generation sequencing for transplant medicine (i.e., Viracor TRAC dd-cfDNA)
- FirstSightCRC
- Galleri
- GeneStrat
- GPS Cancer (NantHealth Liquid GPS)
- NavDx
- OncoCEE
- Papgene
- Promoter methylation analysis (BCAT1 or IKZF1)
- Resolution ctDx Lung
- Septin 9 (SEPT9) DNA methylation assay (eg, ColoVantage, Epi proColon)
- Serum proteomic testing (ie, Veristrat)
- Signatera
- Tempus xF
- Trovera BRAF
- Trovera KRAS

These molecular and genomic (MolGen) tests are considered experimental/investigational, as they have not been identified as widely used and generally accepted for the proposed uses as reported in nationally recognized peer-reviewed medical literature. There is insufficient data to determine the net health impact, which typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical management option.

Additional Reference and Medical Policies, not all-inclusive:

- **Medical Policy - Genetic Testing, PG0041**
- **Medical Policy VeriStrat Testing, PG0111**
- **Medical Policy Molecular Profiling (Somatic Testing) Panels for Cancer, PG0438**
- **https://www.paramounthealthcare.com/services/providers/prior-authorization-criteria/**
- **https://www.paramounthealthcare.com/services/providers/prior-authorization-criteria/specialty-drug-prior-authorization-criteria-library**
- **https://www.paramounthealthcare.com/medicare/2021/current-members/prior-authorization**

CODING/BILLING INFORMATION
The inclusion or exclusion of a code in this section does not necessarily indicate coverage. Codes referenced in this clinical policy are for informational purposes only.
Codes that are covered may have selection criteria that must be met.

Payment for supplies may be included in payment for other services rendered.

CPT CODE	
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) [Medical Policy PG0041]
81327	SEPT9 (Septin9) (eg, colorectal cancer) promoter methylation analysis [Medical Policy PG0065 Colorectal Cancer Screening]
81479	Unlisted molecular pathology procedure
81538	Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival [Medical Policy PG0111]
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
0091U	Oncology (colorectal) screening, cell enumeration of circulating tumor cells, utilizing whole blood, algorithm, for the presence of adenoma or cancer, reported as a positive or negative result
0179U	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]
0229U	BCAT1 (Branched chain amino acid transaminase 1) or IKZF1 (IKAROS family zinc finger 1) (eg, colorectal cancer) promoter methylation analysis
0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations [FoundationOne Liquid CDx]
0242U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 55-74 genes, interrogation for sequence variants, gene copy number amplifications, and gene rearrangements [Guardant360 CDx]
0326U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 83 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden [Medical Policy PG0041]
0388U	Oncology (non-small cell lung cancer), next-generation sequencing with identification of single nucleotide variants, copy number variants, insertions and deletions, and structural variants in 37 cancer-related genes, plasma, with report for alteration detection [Effective 07/01/2023]

REVISION HISTORY EXPLANATION
ORIGINAL EFFECTIVE DATE: 12/09/2021

Date	Explanation & Changes
12/09/2021	• Medical Policy created
08/08/2022	• Added procedure 0326U, new procedure code effective 7/1/2022, requires prior authorization for all product lines
03/09/2023	• Medical Policy updated to reflect Medicaid coverage to Anthem as of 02/01/2023
05/02/2023	• Added new 2023 procedure code 0388U, effective 07/01/2023 – covered with a prior authorization for Paramount Commercial Insurance Plans and Medicare Advantage Plans
07/31/2023	• Updated Elite criteria to default to the latest updates from the CMS coverage database • Removed procedure 0326U, not relevant to the medical policy coverage indications
08/21/2023	• Documented specific Medicare Advantage Plan coverage criteria

Paramount reserves the right to review and revise our policies periodically when necessary. When there is an update, we will publish the most current policy to https://www.paramounthealthcare.com/providers/medical-policies/policy-library

REFERENCES/RESOURCES

Centers for Medicare and Medicaid Services, CMS Manual System and other CMS publications and services

American Medical Association, *Current Procedural Terminology (CPT®)* and associated publications and services

Centers for Medicare and Medicaid Services, Healthcare Common Procedure Coding System, HCPCS Release and Code Sets

U.S. Preventive Services Task Force, http://www.uspreventiveservicestaskforce.org/
Industry Standard Review

Hayes, Inc.

Industry Standard Review

MEDICAL POLICY PRIOR TO 07/31/2023:

DESCRIPTION

A liquid biopsy is a test done on a sample of blood to look for cancer cells from a tumor that are circulating in the blood or for pieces of DNA from tumor cells that are in the blood. This is a noninvasive diagnostic approach that may serve in the future for screening, diagnosis, prognosis, and therapy guidance. A liquid biopsy may be used to help find cancer at an early stage. It may also be used to help plan treatment or to find out how well treatment is working or if cancer has come back. Being able to take multiple samples of blood over time may play a complementary/companion role to medical imaging in understand what kind of molecular changes are taking place in a tumor.

The National Cancer Institute defines a liquid biopsy as “a test done on a sample of blood to look for cancer cells from a tumor that are circulating in the blood or for pieces of DNA from tumor cells that are in the blood. A liquid biopsy may be used to help find cancer at an early stage. It may also be used to help plan treatment or to find out how well treatment is working or if cancer has come back. Being able to take multiple samples of blood over time may also help doctors understand what kind of molecular changes are taking place in a tumor.”

Circulating tumor cells (CTCs) are shed from either primary or secondary tumor sites where they then migrate into the circulatory system and initiate distant metastases. Tumor cells release circulating free DNA (cfDNA), also known as circulation tumor DNA (ctDNA), into the blood. It can be found in various substances, including blood, urine, saliva, etc. A liquid biopsy, or blood sample, can provide the genetic landscape of all cancerous lesions (primary and metastases) as well as offering the opportunity to systematically track genomic evolution for tumor biology analyzing. Liquid biopsy markers including circulating tumor cells (CTCs), circulating free DNA (cfDNA) and

extracellular vesicles (EVs) and exosomes, as a source of genomic and proteomic information in patients with cancer.

Liquid biopsies allow for the collection of robust and reproducible data in a simple and noninvasive way using a blood sample, but may be performed on other body fluid samples. Whereas the traditional methods of performing biopsies on tumor tissue pose the following concerns: biopsies are invasive, involve risks, are typically costly and are typically difficult to obtain, along with the treatment decision often relies on one single biopsy. To date, liquid biopsy is not a routine test in clinical practice, but its potential applications are rapidly growing: from diagnostic genomic profiling to the monitoring of surgical outcomes, from evaluating either response or resistance to systemic treatments, to quantifying minimal residual disease. Serial sampling of a tumor is particularly useful related to somatic mutations and the changing treatment decisions in a tumor progression.

The challenge of CTC detection is related to the requirement for high sensitivity combined with high specificity, but several factors still hinder standardized clinical application, including the relatively low blood CTCs in circulation; the absence of a reliable and efficient marker to distinguish CTCs from other blood-borne cells and the high-cost of downstream molecular and genomic characterization in the case of a low number of detected CTCs.

While CTCs and cfDNA present in blood have already demonstrated potential to present corresponding information on possible therapeutic targets and resistance mechanisms, EVs on the contrary present in several bodily fluids (urine, saliva, breast milk, cerebrospinal fluid *etc.*) including blood are believed to be genetic messengers and present an alternative mode of cancer progression.

Liquid biopsy testing methods are typically analyzed by one of the following methods:

- Standard testing methodologies, such as PCR or sequencing, are used to identify targeted mutations commonly present in tumors of a specific type
- NGS-based sequencing or array-CGH testing used to identify both novel or recurrent mutations. These include whole genome sequencing or whole exome sequencing. These approaches analyze single genes, panels of genes, exomes, or genomes.

On August 7, 2020, the FDA approved the Guardant 360 CDX assay to be used by qualified health care professionals in accordance with professional guidelines in oncology for cancer patients with any solid malignant neoplasms.

On August 26, 2020, the FDA approved the FoundationOne Liquid CDx. The test is a qualitative, next-generation sequencing based, in vitro diagnostic test that uses targeted, high through-put, hybridization-based capture technology to detect and report substitutions, insertions, and deletions (indels) in 311 genes, including rearrangements and copy number losses only BRCA1 and BRCA2. 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.

Foundation Medicine's Foundation Liquid CDx uses hybrid capture-based next-generation sequencing (NGS) to detect variants in over 60 genes for targeted therapy in metastatic cancer.

Guardant Health markets the Guardant360 test. This test uses NGS to identify variants in 73 genes associated with several different cancers.

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 NSCLS.

POLICY

Paramount Commercial Insurance Plans, Medicare Advantage Plans, and Paramount Advantage Medicaid

Effective 01/01/2022

- Liquid biopsy as a source of genomic and proteomic information is covered when the coverage criteria below is met.
- **Prior Authorization is required for all product lines**.

Refer to medical policy Genetic Testing, PG0041 for specific procedure-to-product line coverage determination.

Non-participating providers are required to obtain prior authorization BEFORE any services are rendered.

COVERAGE CRITERIA
Medicare Advantage Plans
Prior Authorization Required
This is a limited coverage policy for next-generation sequencing (NGS) assays performed on solid tumor cell-free DNA in plasma, from here on called "liquid biopsies."

Guardant360® is covered for indications that are outside the scope of a companion diagnostic testing, only when all of the following conditions are met:

- Patient has been diagnosed with a recurrent, relapsed, refractory, metastatic, or advanced solid tumor that did not originate from the central nervous system. Patients who would meet all of the indications on the FDA label for larotrectinib if they are found to have an NTRK mutation may be considered to have advanced cancer, and
- Patient has not previously been tested with the Guardant360® test for the same genetic content. For a patient who has been tested previously using Guardant360® for cancer, that patient may not be tested again unless there is clinical evidence that the cancer has evolved wherein testing would be performed for different genetic content. Specifically, in patients with previously tested cancer, who have evidence of new malignant growth despite response to a prior targeted therapy, that growth may be considered to be sufficiently genetically different to require additional genetic testing, and
- Patient is untreated for the primary cancer being tested, or the patient is not responding to treatment (e.g., progression or new lesions on treatment), and
- The patient has decided to seek further cancer treatment with the following conditions:
    - The patient is a candidate for further treatment with a drug that is either FDA-approved for that patient's cancer, or has an NCCN 1 or NCCN 2A recommendation for that patient's cancer, and
    - The FDA-approved indication or NCCN recommendation is based upon information about the presence or absence of a genetic biomarker tested for in the Guardant360® assay, and
- Tissue-based, CGP is infeasible (*e.g.*, quantity not sufficient for tissue-based CGP or invasive biopsy is medically contraindicated) or specifically in NSLC Tissue-based CGP has shown no actionable mutations.

If no alteration is detected by Guardant360® or if ctDNA is insufficient/not detected, tissue-based genotyping should be considered.
Other liquid biopsies will be covered for the same indications if they display similar performance in their intended used applications to Guardant360®" (i.e. FoundationOne Liquid CDx)

This policy provides limited coverage for InvisionFirstTM - Lung (Inivata, Research Triangle Park, NC) (hereafter InVision) a plasma-based, somatic comprehensive genomic profiling test (CGP) for patients with advanced (Stage IIIB/IV) non-small cell lung cancer (NSCLC):

- **At diagnosis-**
    - When results for EGFR single nucleotide variants (SNVs) and insertions and deletions (indels); rearrangements in ALK and ROS1; and SNVs for BRAF are not available AND when tissue-based CGP is infeasible [i.e., quantity not sufficient (QNS) for tissue-based CGP or invasive biopsy is medically contraindicated],

or

- **At progression**
    - For patients progressing on or after chemotherapy or immunotherapy who have not been tested for EGFR SNVs and indels; rearrangements in ALK and ROS1; and SNVs for BRAF, and for whom tissue-based CGP is infeasible;
    - For patients progressing on EGFR tyrosine kinase inhibitors (TKIs).

If no genetic alteration is detected by InVision or if circulating tumor DNA (ctDNA) is insufficient/not detected, tissue-based genotyping should be considered.

Paramount Commercial Insurance Plans and Paramount Advantage Medicaid
Prior Authorization Required
This is a limited coverage policy for next-generation sequencing (NGS) assays performed on solid tumor cell-free DNA in plasma, from here on called "liquid biopsies."

General Coverage Criteria:
Based upon 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) (e.g., Guardant 360, Foundation One Liquid CDx, Cobas, Genestrat, OncoBEAM) analysis, as an alternative to additional tumor tissue biopsy, is considered medically appropriate as a technique, a companion diagnostic assays to direct targeted drug therapy for individuals:

- When the 'liquid biopsy' is not used in lieu of a histological tissue diagnosis; and
- The Member has a diagnosis of cancer; and
- Treatment with a medication for which there is a liquid biopsy-based FDA-approved companion diagnostic is being considered, and
    - Note: not all indications for medications with an FDA-approved companion diagnostic liquid biopsy test require the results of the test prior to prescribing. Testing would not be considered medically necessary when prescribed for indications that do not require the companion diagnostic.
- Whom the result will be used to guide management of the member; and
- The test has received FDA approval for the specific tumor type or disease site; and
- The Member has not had previous somatic and/or germline testing that would have identified the genetic change required to prescribe medication under consideration; and
- Repeat invasive biopsy is medically contraindicated or there is not enough tissue for tissue-based molecular and biomarker analysis

<u>Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)</u>

- Coverage Criteria indicated above has been met; and
    - Initial Biomarker Determination
        - FDA approved companion diagnostic tests (i.e., cobas EGFR Mutation Test v2, FoundationOne® Liquid CDx, or Guardant360® CDx) or a targeted multi-gene panel, e.g., ctDx Lung™, are medically necessary when tissue-based testing cannot be performed, e.g., insufficient tissue
    - At time of progression on an EGFR tyrosine kinase inhibitor (TKI) therapy
        - Targeted cell-free testing (i.e., cobas EGFR Mutation Test v2) is medically necessary
        - Targeted cell-free testing is not medically necessary when progression is on osimertinib

Testing for the following gene mutations:
1. EGFR TKI-sensitizing variants (exon 19 deletion or a point mutation in exon 21 (L858R) (CPT 81235);
2. EGFR TKI-sensitizing variants (exon 20 or T790M) (CPT 81235);
3. anaplastic lymphoma kinase (ALK) rearrangement;
4. KRAS G12C (CPT: 81275);
5. NTRK 1/2/3 gene fusion (CPT: 81191-81193);
6. ROS-1 gene rearrangement;
7. BRAFV600E (CPT: 81210);
8. MET ex 14 skipping;
9. High-level MET amplification;
10. RET rearrangements; and
11. ERBBS (HER2).

<u>Ovarian, Fallopian Tube, or Primary Peritoneal Cancer</u>

- Coverage Criteria indicated above has been met; and

- FoundationOne® Liquid CDx is medically necessary if tumor is unavailable in women with ovarian, fallopian tube, or primary peritoneal cancer when the patient meets criteria per the FDA label for treatment(s) for which this test has been approved as a companion diagnostic

Advanced or Metastatic Breast Cancer

- Coverage Criteria indicated above has been met; and
- FoundationOne® Liquid CDx is medically necessary if tumor is unavailable in individuals with breast cancer when the patient meets criteria per the FDA label for treatment(s) for which this test has been approved as a companion diagnostic
    - OR
- therascreen® PIK3CA testing is medically necessary using liquid biopsy if tumor is unavailable for advanced or metastatic breast cancer when the patient meets criteria per the FDA label for treatments for which this test has been approved as a companion diagnostic

Metastatic Castrate-Resistant Prostate Cancer

- Coverage Criteria indicated above has been met; and
- FoundationOne® Liquid CDx is medically necessary in men with metastatic castrate-resistant prostate cancer when the individual meets criteria per the FDA label for treatments for which this test has been approved as a companion diagnostic

Paramount Commercial Insurance Plans, Medicare Advantage Plans, and Paramount Advantage Medicaid
VeriStrat is a serum-based mass spectrometric, eight proteins, including amyloid A, signature proteomic test. It is intended to aid in evaluating prognosis and predicting response to systemic or targeted therapies in individuals with advanced NSCLC. Procedure 81539 - Refer to Medical Policy VeriStrat Testing, PG0111.

Paramount Commercial Insurance Plans, Medicare Advantage Plans, and Paramount Advantage Medicaid Non-Coverage
Many laboratories are developing liquid biopsy assays. For many of these assays, analytical validity studies have been performed; however, data regarding the clinical validity and clinical utility of these tests is still emerging. Members may not be eligible for the following liquid biopsy as a source of genomic and proteomic information in patients with cancer (ie, including circulating tumor cells (CTCs), circulating tumor DNA (ctDNA) and extracellular vesicles (EVs) and exosomes) including, but not limited to:

- CellSearch
- ColonSentry
- Colvera
- Donor-derived cell-free DNA whole genome next-generation sequencing for transplant medicine (ie, Viracor TRAC dd-cfDNA)
- FirstSightCRC
- Galleri
- GeneStrat
- GPS Cancer (NantHealth Liquid GPS)
- NavDx
- OncoCEE
- Papgene
- Promoter methylation analysis (BCAT1 or IKZF1)
- Resolution ctDx Lung
- Septin 9 (SEPT9) DNA methylation assay (eg, ColoVantage, Epi proColon)
- Serum proteomic testing (ie, Veristrat)
- Signatera
- Tempus xF
- Trovera BRAF
- Trovera KRAS

These molecular and genomic (MolGen) tests are considered experimental/investigational, as they have not been identified as widely used and generally accepted for the proposed uses as reported in nationally recognized peer-reviewed medical literature. There is insufficient data to determine the net health impact, which typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical management option.

Additional Reference and Medical Policies, not all-inclusive:

- **Medical Policy - Genetic Testing, PG0041**
- **Medical Policy VeriStrat Testing, PG0111**
- **Medical Policy Molecular Profiling (Somatic Testing) Panels for Cancer, PG0438**
- **https://www.paramounthealthcare.com/services/providers/prior-authorization-criteria/**
- **https://www.paramounthealthcare.com/services/providers/prior-authorization-criteria/specialty-drug-prior-authorization-criteria-library**
- **https://www.paramounthealthcare.com/medicare/2021/current-members/prior-authorization**