Liquid Biopsy Testing

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Introduction

Liquid biopsy testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
ABL1 mutation analysis	81170
APC sequencing	81201
ASXL1 full gene sequencing	81175
ASXL1 mutation analysis	81176
BRAF V600 targeted mutation analysis	81210
BRCA1/2 sequencing	81163
BRCA1 sequencing	81165
BRCA2 sequencing	81216
CALR exon 9 mutation analysis	81219
Caris Assure	0485U
CCND1/IGH (t(11;14)) translocation analysis, major breakpoint	81168
CEBPA full gene sequencing	81218
EGFR targeted mutation analysis	81235
EZH2 common variant(s) (e.g. codon 646)	81237
EZH2 full gene sequencing	81236

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Procedures addressed by this guideline	Procedure codes
FLT3 mutation analysis (internal tandem duplication variants)	81245
FLT3 mutation analysis (tyrosine kinase domain variants)	81246
FoundationOne Liquid CDx	0239U
Guardant360 CDx	0242U
Guardant360 LDT	0326U
Guardant360 Response	0422U
Hematolymphoid neoplasm molecular profiling; 5-50 genes	81450
IDH1 mutation analysis	81120
IDH2 mutation analysis	81121
IGH@/BCL2 (t(14;18)) translocation analysis, major breakpoint region (MBR) and minor cluster region (mcr) breakpoints	81278
InVisionFirst-Lung Liquid Biopsy, Inivata, Inc.	0388U
JAK2 targeted mutation analysis (e.g exons 12 and 13)	81279
JAK2 V617F targeted mutation analysis	81270
KIT D816 targeted mutation analysis	81273
KIT targeted sequence analysis	81272
KRAS exon 2 targeted mutation analysis	81275
KRAS targeted mutation analysis, additional variants	81276
Labcorp Plasma Complete	0585U

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Procedures addressed by this guideline	Procedure codes
LiquidHALLMARK (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)	0409U
LiquidHALLMARK (oncology (pan-solid tumor), ctDNA, utilizing plasma, next-generation sequencing (NGS) of 77 genes, 8 fusions, microsatellite instability, and tumor mutation burden, interpretative report for single-nucleotide variants, copy number alterations, with therapy association)	0530U
LiquidHALLMARK ctDNA and ctRNA [Oncology (solid tumor), DNA (80 genes) and RNA (10 genes), by next-generation sequencing, plasma, including single-nucleotide variants, insertions/deletions, copy-number alterations, microsatellite instability, and fusions, reported as clinically actionable variants	0571U
MGMT promoter methylation analysis	81287
MLH1 sequencing	81292

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Procedures addressed by this guideline	Procedure codes
Molecular tumor marker test	81400 81401 81402 81403 81405 81406 81407 81408 81479
Molecular tumor marker test	88271
MPL common variants (e.g. W515A, W515K, W515L, W515R)	81338
MPL mutation analysis, exon 10	81339
MSH2 sequencing	81295
MSH6 sequencing	81298
NeoLAB Prostate	0011M
Northstar Select	0487U
NPM1 exon 12 targeted mutation analysis	81310
NRAS exon 2 and exon 3 analysis	81311
NTRK1 translocation analysis	81191
NTRK2 translocation analysis	81192
NTRK3 translocation analysis	81193
NTRK translocation analysis	81194
PDGFRA targeted sequence analysis	81314

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Procedures addressed by this guideline	Procedure codes
PGDx elio plasma focus Dx	0562U
PMS2 sequencing	81317
PredicineCARE Assay	0539U
PTEN sequencing	81321
Resolution ctDx Lung	0179U
RUNX1 mutation analysis	81334
SF3B1 common variants (e.g. A672T, E622D, L833F, R625C, R625L)	81347
Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants and rearrangements	81462
Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis, copy number variants, and microsatellite instability	81463
Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements	81464
SRSF2 common variants (e.g. P95H, P95L)	81348
TERT targeted sequence analysis	81345
therascreen PIK3CA RGQ PCR Kit	0177U
TP53 sequencing	81351
TP53 targeted sequence analysis	81352

Procedures addressed by this guideline	Procedure codes
U2AF1 common variants (e.g. S34F, S34Y, Q157R, Q157P)	81357
ZRSR2 common variants (e.g. E65fs, E122fs, R448fs)	81360

Criteria

Introduction

Requests for liquid biopsy testing are reviewed using the following criteria.

Companion Diagnostic (CDx) Liquid Biopsy Assay

Liquid biopsy-based companion diagnostic assays are considered medically necessary when the member meets ALL of the following criteria:

- 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
- FDA approval for the CDx being requested must include the member's specific cancer type as an approved indication, AND
- FDA label for the drug and indication being considered states companion diagnostic testing is necessary for member selection, AND
- Member has not had previous somatic and/or germline testing that would have identified the genetic change required to prescribe the medication under consideration, AND
- Family history:
  - Member does not have a close (1st or 2nd degree) biological relative with a known germline mutation in a gene that is a target of the requested companion diagnostic test (e.g. known familial mutation in BRCA1/2 and requested test is myChoice CDx), or
  - Member has a close (1st or 2nd degree) biological relative with a known germline mutation in a gene that is a target of the requested companion diagnostic test (e.g. known familial mutation in BRCA1/2 and requested test is myChoice CDx), and the member’s germline test was negative, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Note:

Not all indications for medications with an FDA-approved companion diagnostic liquid biopsy test require the results of that test prior to prescribing. Testing would not be

considered medically necessary when prescribed for indications that do not require the companion diagnostic.

Guardant360 LDT

When Guardant360 LDT (laboratory developed test) is being requested for indications that are outside the scope of a companion diagnostic (i.e.: non-CDx), the panel will be considered medically necessary when the following criteria are met:

- The member has a diagnosis of metastatic or recurrent non-small cell lung cancer (NSCLC), AND
- NSCLC diagnosis has been confirmed based on a histopathologic assessment of tumor tissue, AND
- No previous multi-gene panel testing has been performed for NSCLC, AND
- Insufficient tumor tissue is available for broad molecular profiling and member is unable to undergo an additional standard tissue biopsy due to documented medical reasons (i.e., invasive tissue sampling is contraindicated due to the member's clinical condition)

ESR1 Liquid Biopsy Test

- The member has a diagnosis of metastatic or recurrent hormone receptor positive (ER+ or PR+) and human epidermal growth factor receptor 2 (HER2) negative breast cancer, AND
- The member's cancer has progressed following endocrine therapy, AND
- Breast cancer diagnosis has been confirmed based on a histopathologic assessment of tumor tissue, AND
- No previous testing has identified a somatic ESR1 mutation*, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Note:

Repeat testing may be warranted for individuals with ESR1 wild-type results from prior somatic testing whose cancer has progressed following treatment.

Other Non-CDx Liquid Biopsy Tests and Tests for Other Indications

These tests are considered Experimental, Investigational, or Unproven.

- Experimental, Investigational, or Unproven (E/I/U) refers to tests, or uses of tests, that have insufficient data to demonstrate an overall health benefit. This typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity) and significantly improves patient health outcomes (clinical utility). Such tests are also not generally accepted as the standard of care in the evaluation or management of a particular condition.

- In the case of laboratory testing, FDA approval or clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight. In addition, FDA approval or clearance often does not include an assessment of clinical utility.

Billing and Reimbursement

Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

When otherwise reimbursable, the following will apply:

- When a panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code (e.g., 81462, 81463, 81464*).

Note: *The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

What is liquid biopsy testing?

The use of circulating tumor DNA (ctDNA) to identify genetic mutations present in a tumor is also referred to as a liquid biopsy.

- The National Cancer Institute defines a liquid biopsy as "[a] laboratory test done on a sample of blood, urine, or other body fluid to look for cancer cells from a tumor or small pieces of DNA, RNA, or other molecules released by tumor cells into a person's body fluids. Liquid biopsy allows multiple samples to be taken over time, which may help doctors understand what kind of genetic or molecular changes that are taking place in a tumor."[1]
- Circulating tumor DNA is released into circulation by tumors.[2] It can be found in various substances, including blood, urine, saliva, etc.
- Analysis of ctDNA can be performed to help identify indicators of disease recurrence or disease progression. It can also help to determine if a specific treatment is indicated.

- Liquid biopsies can be used to more easily obtain serial sampling of a tumor. This is particularly useful since somatic mutations that are used in treatment decisions can change as the tumor progresses.[2] ctDNA is also thought to provide a more representative sample of the entire tumor genome as well as any metastases that may be present.[2]
- Traditional methods of performing biopsies on tumor tissue pose the following problems:[2,3]
  - Biopsies are invasive, involve risks, are typically costly, and are typically difficult to obtain.
  - Treatment decisions often rely on one single biopsy, while tumors are usually heterogeneous in nature, tumor characteristics can evolve, and information regarding metastases may not be known.[2]
- The use of liquid biopsies can help overcome some of the above problems with traditional biopsies since they can be completed in a noninvasive manner.
- This guideline will only address the use of ctDNA as a liquid biopsy in solid tumors and hematologic malignancies. Circulating tumor cells (CTCs) can be used to help obtain information about an individual's cancer prognosis and treatment options. CTC assays are not addressed by this guideline.

Test information

Introduction

Liquid biopsy testing is an assay that utilizes ctDNA to assist with monitoring disease status and potentially determining sensitivity to certain treatments.

Liquid biopsy methodology

Testing methodology relies on the presence of ctDNA in circulation, which is typically analyzed by one of the following methods:

- Standard testing methodologies, such as polymerase chain reaction (PCR) or sequencing, are used to identify targeted mutations commonly present in tumors of a specific type.
- Methodologies such as next-generation sequencing (NGS) or array comparative genomic hybridization (aCGH) are 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. Use of these approaches allows testing with no prior knowledge of genetic mutations that are present in the individual's tumor.
- Several liquid biopsy tests have been designated by the Food and Drug Administration (FDA) as companion diagnostic (CDx) assays deemed necessary

for the effective use of a specific medication in the context of a specific clinical indication. Within this guideline, liquid biopsy tests that do not have the designation of companion diagnostics are referred to as non-CDx assays.

Note:

Tests that extract DNA from nucleated cells in the blood or bone marrow for hematologic malignancies are not considered liquid biopsies. For information on these assays, please refer to the guideline *Somatic Mutation Testing*, as this testing is not addressed here.

Guidelines and evidence

American Society of Clinical Oncology

A rapid recommendation on testing to guide therapy for metastatic breast cancer from the American Society of Clinical Oncology (ASCO, 2023) included the following statement:[4]

- "To aid in treatment selection, the Expert Panel recommends routine testing for emergence of ESR1 mutations at recurrence or progression on [endocrine treatment] (given with or without CDK4/6 inhibitor) in patients with ER-positive, HER2-negative MBC. Testing with a Clinical Laboratory Improvement Amendments-certified assay should be performed on blood or tissue obtained at the time of progression, as ESR1 mutations develop in response to selection pressure during treatment and are typically undetectable in the primary tumor. Blood-based ctDNA is preferred owing to greater sensitivity. If not performed earlier, testing for PIK3CA mutations should also be performed to guide further therapy. Patients whose tumor or ctDNA tests remain ESR1 wild-type may warrant retesting at subsequent progression(s) to determine if an ESR1 mutation has arisen (Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong)."

A provisional clinical opinion for somatic genomic testing in individuals with metastatic or advanced cancer (ASCO, 2022) stated:[5]

- "There is a growing body of evidence on the clinical utility of genomic testing on cfDNA [cell-free DNA] in the plasma, so-called liquid biopsies. Studies have shown substantial concordance between cfDNA-based testing and tumor testing, with the caveat that copy-number changes may be more difficult to assess in cfDNA, and fusion testing may be more limited in common cfDNA tests used currently. However, cfDNA has the advantage of being noninvasive and expediting testing because of the lack of need to retrieve archival blocks or arrange for a new biopsy. There are already FDA approvals on the basis of cfDNA-based genomic testing (eg, osimertinib for EGFR T790M mutation in lung cancer). Therefore, in patients without tissue-based

genomic test results, treatment may be based on actionable alterations identified in cfDNA. Genomic testing on cfDNA is most helpful when genomic testing is indicated, archival tissue is unavailable, and new tumor biopsies are not feasible. cfDNA is more commonly reported with mutant allelic fractions of individual mutations, compared with solid tumor panels, thus facilitating assessment of clonality. cfDNA testing has the additional advantage of capturing tumor heterogeneity because of pooling in the blood of DNA from throughout the tumor or from multiple tumors and is a promising tool for assessing genomic mechanisms of acquired resistance. Furthermore, cfDNA levels themselves may be prognostic, and early cfDNA dynamics may serve as an early predictor of therapy response or resistance. Ongoing studies are expected to better delineate the clinical utility of serial liquid biopsies."

American Society of Clinical Oncology and College of American Pathologists

Based on a comprehensive systematic review of 77 scientific studies on ctDNA assays for solid tumors, an expert panel assembled by the American Society of Clinical Oncology (ASCO, 2018) and the College of American Pathologists (CAP, 2018) concluded that there is currently insufficient evidence of clinical validity and clinical utility for most ctDNA assays being used in advanced cancer. [6] There are some ctDNA assays that have demonstrated clinical validity and clinical utility with certain types of cancers, such as non-small cell lung cancer. There is no evidence for use in early stage cancer, treatment monitoring, or residual disease detection. They also stated that there is no evidence of clinical value for cancer screening outside of a clinical trial.

To establish clinical validity and clinical utility of ctDNA analyses, the expert panel recommended the following:

- “Future research studies to establish clinical validity and utility of ctDNA assays should include a patient cohort that matches the intended-use population as closely as possible and samples collected from a prospective study with defined entry criteria. Data will most frequently come from a phase II or phase III study in the patient population where it is anticipated the assay would be used in subsequent clinical practice, with the frequency of the variant under study approximately equal to that in an unselected clinical population. In prospective studies of targeted therapies, the entry criteria should allow inclusion of patients in which the variant under study is observed in the plasma, but not in the tissue analysis, to evaluate the treatment response of this population with discordant genotyping results."

European Society for Medical Oncology

The European Society for Medical Oncology (ESMO, 2022) stated the following regarding liquid biopsies (LBs) for testing in individuals with advanced cancer: [7]

- "LB assays with very high analytical and clinical specificity, and therefore positive predictive values, may be used in routine practice when the results will affect

standard treatment options. The limitations of ctDNA assays, however, must be taken into account."
- "...the clinical utility of ctDNA is very much context-dependent, contingent on disease types and stages, available treatment that could effectively eradicate MRD [minimal residual disease] and intended use..."
- Tissue-based testing is the most appropriate test for the majority of individuals, while clinical scenarios exist where ctDNA assays are recommended. These include certain aggressive tumors or when tumor tissue is insufficient or not appropriate.

The guidelines also stated that insufficient evidence exists for implementing use of ctDNA assays for cancer screening, monitoring of treatment response, or detection of molecular relapse or MRD.

International Association for the Study of Lung Cancer

A consensus statement from the International Association for the Study of Lung Cancer (IASLC, 2021) on usage of liquid biopsy for advanced NSCLC made the following recommendations:[8]
- For treatment-naive individuals with advanced NSCLC, tumor genotyping with a tissue sample should be performed first if available. If the tumor tissue is of uncertain adequacy or there is concern for incomplete tumor genotyping, ctDNA genotyping can be performed concurrently or as reflex testing. When a tissue sample is unavailable for these individuals, plasma ctDNA genotyping is the recommended test.
- Usage of plasma ctDNA is recommended "[a]t the time of acquired resistance after tyrosine kinase inhibitor (TKI) therapy in an oncogene-driven NSCLC."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2025) stated the following regarding liquid biopsies for testing in individuals with non-small cell lung cancer:[9]
- "ctDNA testing should not be used in lieu of a histologic tissue diagnosis."
- "ctDNA is not routinely recommended in settings other than advanced/metastatic disease. For stages I-III, tissue-based testing is preferred. Metastatic disease confined to the thorax may have a higher yield with tissue-based testing."
- "Studies have demonstrated ctDNA and tissue testing to have very high specificity. Both ctDNA and tissue testing have appreciable false-negative rates, supporting the complementarity of these approaches, and data support complementary testing to reduce turnaround time and increase yield of targetable alteration detection."
- "…the panel feels that plasma ctDNA testing should not be used to diagnose NSCLC; tissue should be used to diagnose NSCLC. Standards and guidelines for plasma ctDNA testing for somatic variants/mutations have not been published, there is up to a 30% false-negative rate, and variants can be detected that are not related to the

tumor….careful consideration is required to determine whether ctDNA findings reflect a true oncogenic driver or an unrelated finding."

- "…plasma ctDNA testing can be used in specific circumstances if 1) the patient is not medically fit for invasive tissue sampling; or 2) there is insufficient tissue for molecular analysis and follow-up tissue-based analysis will be done if an oncogenic driver is not identified. Data suggest that plasma ctDNA testing is a useful minimally invasive test that can be used to identify ALK, BRAF, EGFR, HER2, MET exon 14 skipping, RET, ROS1, and other oncogenic biomarkers that would not otherwise be identified in patients with metastatic NSCLC."
- "The NCCN Guidelines for NSCLC provide recommendations for individual biomarkers that should be tested and recommend testing techniques but do not endorse any specific commercially available biomarker assays or commercial laboratories."

The National Comprehensive Cancer Network (NCCN, 2024) guidelines for breast cancer stated that "comprehensive germline and somatic profiling" utilizing tumor tissue or ctDNA assays should be performed in individuals with recurrent or stage IV disease.[10] They also stated that "[t]issue-based assays have greater sensitivity, but ctDNA may reflect tumor heterogeneity more accurately." This guideline does state that liquid biopsy is the preferred methodology for the identification of ESR1 mutations in individuals with hormone receptor positive/HER2 negative recurrent unresectable or stage IV breast cancer.

Selected Relevant Publications

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.[3,11-51]

The TRACERx study (Tracking Non-small cell lung cancer evolution through therapy (Rx)) is a large, prospective clinical trial being conducted to evaluate "the relationship between intra-tumour heterogeneity and clinical outcome following surgery and adjuvant therapy."[52] Researchers plan to analyze the individual's tumors before surgery and multiple times after surgery during their treatment regimen. Tumor tissue and ctDNA in individual's blood will be examined in approximately 840 individuals with NSCLC. This trial is expected to continue until 2026.[52]

Limited evidence suggests that liquid biopsy with Guardant360, in individuals with advanced NSCLC, may be a reasonable non-invasive alternative to tumor biopsy, particularly in individuals unable to undergo standard tissue biopsy or in cases where tumor tissues are lacking or insufficient for proper mutation analysis.[53-68]

Several systematic reviews and meta-analyses have synthesized the findings of multiple studies to evaluate the clinical validity and clinical utility of cell-free circulating tumor DNA (ctDNA) to detect a variety of advanced cancer (excluding non-small cell lung

cancer and hematological malignancies).[6,11-15,19-43,69-72] With the exception of FDA-approved ctDNA assays, the majority of assays have limited evidence of clinical validity and very limited-to-no evidence of clinical utility for use in individuals with advanced cancer.[6] Some studies have also reported relatively high rates of discordance between ctDNA assays and tissue-based testing. There is even less evidence regarding the validity of ctDNA testing in early stage disease, during treatment monitoring, or minimal residual disease (MRD) detection.[6] Additional well-designed prospective studies are needed to establish the clinical validity and clinical utility of ctDNA assays before ctDNA assays (liquid biopsy) can be widely adopted in clinical practice.

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for liquid biopsy testing will ensure that testing will be available to those members most likely to benefit from the information provided by the assays. For those not meeting criteria, it ensures alternate diagnostic/management strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

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physician_gls/pdf/nscl.pdf . Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V1.2025 - December 20, 2024. ©2024 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines®, go online to NCCN.org.

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