Test Specific Guidelines

Liquid Biopsy Testing

MOL.TS.194.A
v1.0.2023

Introduction

Liquid biopsy testing is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
APC Sequencing	81201
ASXL1 Full Gene Sequencing	81175
ASXL1 Mutation Analysis	81176
ABL1 Mutation Analysis	81170
BRAF V600 Targeted Mutation Analysis	81210
BRCA1/2 Sequencing	81163
BRCA1 Sequencing	81165
BRCA2 Sequencing	81216
CALR Exon 9 Mutation Analysis	81219
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
FLT3 Mutation Analysis (internal tandem duplication variants)	81245
FLT3 Mutation Analysis (tyrosine kinase domain variants)	81246

Procedures addressed by this guideline	Procedure codes
FoundationOne Liquid CDx	0239U
Guardant360 CDx	0242U
Guardant360 LDT	0326U
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
JAK2 Targeted Mutation Analysis (e.g exons 12 and 13)	81279
JAK2 V617F Targeted Mutation Analysis	81270
KIT Targeted Sequence Analysis	81272
KIT D816 Targeted Mutation Analysis	81273
KRAS Exon 2 Targeted Mutation Analysis	81275
KRAS Targeted Mutation Analysis, Additional Variants	81276
MGMT Promoter Methylation Analysis	81287
MLH1 Sequencing	81292
Molecular Tumor Marker Test	81400 81401 81402 81403 81405 81406 81407 81408 81479

Procedures addressed by this guideline	Procedure codes
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
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
PMS2 Sequencing	81317
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 Molecular Profiling, 5-50 genes	81445
Solid Organ or Hematolymphoid Neoplasm Molecular Profiling - Expanded, 51 or more genes	81455
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

What Is Liquid Biopsy Testing?

Definition

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 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." [1]

Circulating tumor DNA (ctDNA) 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 not 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 Test

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 PCR or sequencing, are used to identify targeted mutations commonly present in tumors of a specific type.

Methodologies such as NGS-based sequencing or array-CGH 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 FDA-designated 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 - Hematological Malignancies*, as this testing is not addressed here.**

Guidelines and Evidence

Introduction

This section includes relevant guidelines and evidence pertaining to liquid biopsy testing.

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.[4] 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 state 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."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2022) stated the following regarding liquid biopsies for testing in individuals with non-small cell lung cancer:[5]

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

"The use of cell-free/circulating tumor DNA testing can be considered in specific clinical circumstances, most notably:"

"If a patient is medically unfit for invasive tissue sampling"

"In the initial diagnostic setting, if following pathologic confirmation of a NSCLC diagnosis there is insufficient material for molecular analysis, cell-free/circulating tumor DNA should be used only if follow-up tissue-based analysis is planned for all patients in which an oncogenic driver is not identified (see NSCL-18 for oncogenic driver with available targeted therapy options)"

"In the initial diagnostic setting, if tissue-based testing does not completely assess all recommended biomarkers owing to tissue quantity or testing methodologies available, consider repeat biopsy and/or cell-free/circulating tumor DNA testing."

"…the panel feels that plasma cell-free/circulating tumor DNA testing should not be used to diagnose NSCLC; tissue should be used to diagnose NSCLC. Standards and guidelines for cell-free DNA (cfDNA)/circulating tumor DNA testing for genetic variants have not been established, 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 cfDNA findings reflect true oncogenic driver or an unrelated finding."

"Recent data suggest that plasma cell-free/circulating tumor DNA testing can be used to identify EGFR, ALK, and other oncogenic biomarkers that would not otherwise be identified in patients with metastatic NSCLC."

"Although the NCCN Guidelines for NSCLC provide recommendations for individual biomarkers that should be tested and recommend testing techniques, the guidelines do not endorse any specific commercially available biomarker assay."

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.[3,6-39]

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-tumor heterogeneity and clinical outcome following surgery and adjuvant therapy." [40] 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 patients with NSCLC. This trial is expected to continue until 2023.[40]

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.[41-56]

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).[6-10,14-39,57-61] 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.[61] 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.[61] 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.

Criteria

Introduction

Requests for liquid biopsy testing are reviewed using these 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 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)

Billing and Reimbursement

The Guardant360 multi-gene panel will only be considered for reimbursement when billed with an appropriate panel CPT code. When multiple CPT codes are billed for components of the panel, eviCore will redirect to the appropriate panel code.

Other Non-CDx Indications

Liquid biopsy tests for all other indications are considered investigational and/or experimental.

Investigational and experimental (I&E) molecular and genomic (MolGen) tests refer to assays involving chromosomes, DNA, RNA, or gene products that have 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. Such tests are also not generally accepted as standard of care in the evaluation or management of a particular condition.

In the case of MolGen testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight and FDA clearance often does not assess clinical utility.

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