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Approval and implementation dates for specific health plans may vary. Please consult the applicable health plan for more details.

Clinical Appropriateness Guidelines

Genetic Testing

Appropriate Use Criteria: Cell-free DNA Testing (Liquid Biopsy) for the Management of Cancer

Table of Contents

Description and Application of the Guidelines

The Carelon Clinical Appropriateness Guidelines (hereinafter “the Carelon Clinical Appropriateness Guidelines” or the “Guidelines”) are designed to assist providers in making the most appropriate treatment decision for a specific clinical condition for an individual. As used by Carelon, the Guidelines establish objective and evidence-based criteria for medical necessity determinations where possible. In the process, multiple functions are accomplished:

- To establish criteria for when services are medically necessary (i.e., in general, shown to be effective in improving health outcomes and considered the most appropriate level of service)
- To assist the practitioner as an educational tool
- To encourage standardization of medical practice patterns
- To curtail the performance of inappropriate and/or duplicate services
- To advocate for patient safety concerns
- To enhance the quality of health care
- To promote the most efficient and cost-effective use of services

The Carelon guideline development process complies with applicable accreditation standards, including the requirement that the Guidelines be developed with involvement from appropriate providers with current clinical expertise relevant to the Guidelines under review and be based on the most up-to-date clinical principles and best practices. Relevant citations are included in the References section attached to each Guideline. Carelon reviews all of its Guidelines at least annually.

Carelon makes its Guidelines publicly available on its website twenty-four hours a day, seven days a week. Copies of the Carelon Clinical Appropriateness Guidelines are also available upon oral or written request. Although the Guidelines are publicly-available, Carelon considers the Guidelines to be important, proprietary information of Carelon, which cannot be sold, assigned, leased, licensed, reproduced or distributed without the written consent of Carelon.

Carelon applies objective and evidence-based criteria, and takes individual circumstances and the local delivery system into account when determining the medical appropriateness of health care services. The Carelon Guidelines are just guidelines for the provision of specialty health services. These criteria are designed to guide both providers and reviewers to the most appropriate services based on a patient’s unique circumstances. In all cases, clinical judgment consistent with the standards of good medical practice should be used when applying the Guidelines. Guideline determinations are made based on the information provided at the time of the request. It is expected that medical necessity decisions may change as new information is provided or based on unique aspects of the patient’s condition. The treating clinician has final authority and responsibility for treatment decisions regarding the care of the patient and for justifying and demonstrating the existence of medical necessity for the requested service. The Guidelines are not a substitute for the experience and judgment of a physician or other health care professionals. Any clinician seeking to apply or consult the Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment.

The Guidelines do not address coverage, benefit or other plan specific issues. Applicable federal and state coverage mandates take precedence over these clinical guidelines. If requested by a health plan, Carelon will review requests based on health plan medical policy/guidelines in lieu of the Carelon Guidelines. Pharmaceuticals, radiotracers, or medical devices used in any of the diagnostic or therapeutic interventions listed in the Guidelines must be FDA approved or conditionally approved for the intended use. However, use of an FDA approved or conditionally approved product does not constitute medical necessity or guarantee reimbursement by the respective health plan.

The Guidelines may also be used by the health plan or by Carelon for purposes of provider education, or to review the medical necessity of services by any provider who has been notified of the need for medical necessity review, due to billing practices or claims that are not consistent with other providers in terms of frequency or some other manner.

General Clinical Guideline

Clinical Appropriateness Framework

Critical to any finding of clinical appropriateness under the guidelines for a specific diagnostic or therapeutic intervention are the following elements:

- Prior to any intervention, it is essential that the clinician confirm the diagnosis or establish its pretest likelihood based on a complete evaluation of the patient. This includes a history and physical examination and, where applicable, a review of relevant laboratory studies, diagnostic testing, and response to prior therapeutic intervention.
- The anticipated benefit of the recommended intervention should outweigh any potential harms that may result (net benefit).
- Current literature and/or standards of medical practice should support that the recommended intervention offers the greatest net benefit among competing alternatives.
- Based on the clinical evaluation, current literature, and standards of medical practice, there exists a reasonable likelihood that the intervention will change management and/or lead to an improved outcome for the patient.

If these elements are not established with respect to a given request, the determination of appropriateness will most likely require a peer-to-peer conversation to understand the individual and unique facts that would supersede the requirements set forth above. During the peer-to-peer conversation, factors such as patient acuity and setting of service may also be taken into account.

Simultaneous Ordering of Multiple Diagnostic or Therapeutic Interventions

Requests for multiple diagnostic or therapeutic interventions at the same time will often require a peer-to-peer conversation to understand the individual circumstances that support the medical necessity of performing all interventions simultaneously. This is based on the fact that appropriateness of additional intervention is often dependent on the outcome of the initial intervention.

Additionally, either of the following may apply:

- Current literature and/or standards of medical practice support that one of the requested diagnostic or therapeutic interventions is more appropriate in the clinical situation presented; or
- One of the diagnostic or therapeutic interventions requested is more likely to improve patient outcomes based on current literature and/or standards of medical practice.

Repeat Diagnostic Intervention

In general, repeated testing of the same anatomic location for the same indication should be limited to evaluation following an intervention, or when there is a change in clinical status such that additional testing is required to determine next steps in management. At times, it may be necessary to repeat a test using different techniques or protocols to clarify a finding or result of the original study.

Repeated testing for the same indication using the same or similar technology may be subject to additional review or require peer-to-peer conversation in the following scenarios:

- Repeated diagnostic testing at the same facility due to technical issues
- Repeated diagnostic testing requested at a different facility due to provider preference or quality concerns
- Repeated diagnostic testing of the same anatomic area based on persistent symptoms with no clinical change, treatment, or intervention since the previous study

- Repeated diagnostic testing of the same anatomic area by different providers for the same member over a short period of time

Repeat Therapeutic Intervention

In general, repeated therapeutic intervention in the same anatomic area is considered appropriate when the prior intervention proved effective or beneficial and the expected duration of relief has lapsed. A repeat intervention requested prior to the expected duration of relief is not appropriate unless it can be confirmed that the prior intervention was never administered.

Cell-free DNA Testing (Liquid Biopsy) for the Management of Cancer

Clinical Indications

General Requirements

Repeated testing of the same individual for the same indication should be limited to evaluation following an intervention, or when there is a change in clinical status such that additional testing is required to determine next steps in management. At times, it may be necessary to repeat a test using different techniques or protocols to clarify a finding or result of the original study.

Repeated testing for the same indication using the same or similar technology may be subject to additional review or require peer-to-peer conversation in the following scenarios:

- Repeated diagnostic testing of the same tumor site with no clinical change, treatment, or intervention since the previous study
- Repeated diagnostic testing of the same individual and the same tumor by different providers for the same member over a short period of time

Cell-free DNA (ctDNA, Liquid Biopsy) Testing

Individuals with invasive malignancy for whom liquid biopsy is a companion diagnostic test

Liquid (ctDNA) based panel tests are considered **medically necessary** for individuals with invasive malignancy for whom the liquid biopsy test is a companion diagnostic test described by the U.S. Food and Drug Administration (FDA) as necessary for patient selection, and **BOTH** of the following criteria are met:

- Specific cancer treatment is being considered to correspond with the FDA companion diagnostic indication
- Other somatic tumor testing results do not already provide support for the specific cancer therapy being considered that corresponds to the FDA companion diagnostic indication

Individuals with locally advanced (stage IIIb), recurrent, or metastatic non-small cell lung cancer

Liquid (ctDNA) based panel tests are considered **medically necessary** for individuals with pathologically confirmed locally advanced (stage IIIb), recurrent, or metastatic non-small cell lung cancer (NSCLC), and **ALL** of the following criteria are met:

- There is insufficient tumor tissue available for NGS-based somatic profiling or for whom tissue biopsy is considered contraindicated due to the member’s clinical condition
- No prior NGS-based somatic profiling test has previously been performed for this pathological diagnosis of NSCLC
- The test is being used to provide genetic information related to the current set of actionable mutations recognized by ASCO guidelines to inform management at diagnosis or treatment progression on or after chemotherapy or immunotherapy

Individuals with metastatic breast cancer who may benefit from a PIK3CA-targeted agent

Liquid (ctDNA) based panel with PIK3CA somatic tumor testing is considered **medically necessary** to identify individuals who may benefit from the use of alpelisib (or another FDA-approved PIK3CA-targeted agent) when **ALL** of the following criteria are met:

- The individual has ER-positive and HER2-negative metastatic breast cancer
- The individual is a candidate for alpelisib (or another FDA-approved PIK3CA-targeted agent)
- The individual has not had prior testing for PIK3CA in the metastatic setting
- There is insufficient tumor tissue available for NGS-based somatic profiling or tissue biopsy is considered contraindicated due to the member's clinical condition

Individuals with metastatic adenocarcinoma of the prostate who may benefit from a PARP inhibitor or PD-1 inhibitor

Liquid (ctDNA) based panel tests are considered **medically necessary** for individuals with metastatic adenocarcinoma of the prostate to identify those who may benefit from the use of an FDA-approved PARP inhibitor (olaparib or rucaparib) or a PD-1 inhibitor when **ALL** of the following criteria are met:

- The individual has biopsy-proven adenocarcinoma of the prostate
- The individual has not had prior NGS testing in the metastatic setting
- The individual is a candidate for olaparib or pembrolizumab based on FDA indications for these drugs and there is insufficient tumor tissue available for NGS-based somatic profiling or tissue biopsy is considered contraindicated due to the member's clinical condition
- The individual is a candidate for treatment with rucaparib based on FDA indications for this drug

Examples of ctDNA panel tests include, but are not limited to:

- Cancer Intercept®
- CellMax-LBx
- Circulogene Comprehensive Lung, Gastrointestinal and Liver and Pancreatic Cancer Panels; Hereditary Cancer Gene Panel
- ClearID® Solid Tumor Cancer Panel
- FoundationOne® Liquid CDx
- Galleri™ Multi-Cancer Detection Test
- GeneStrat®
- Guardant360® CDx and Guardant360®
- OncoGxOne™ NGS Solid Tumor Panel
- OncoBEAM™ Lung2 Panel and OncoBEAM™ EGFR V2 Assay
- PlasmaSELECT™ 64
- Resolution ctDx Lung™
- Target Selector™ Breast Cancer, Non-Small Cell Lung Cancer, Squamous Cell Lung Cancer and Prostate Cancer Profiles

Rationale

Liquid biopsy refers to diagnostic tests obtained from a blood sample used to inform the management of individuals with cancer. Given that intra-tumoral heterogeneity and tumor evolution contribute to treatment failure in patients with cancer, there has been interest in exploring liquid biopsy for use as an alternative to tissue biopsy in the diagnosis of cancer, for clinical response to targeted agents of cancer treatment, for early cancer detection (i.e., screening) and for cancer surveillance. Cell-free DNA (cfDNA) is defined as DNA that is circulating freely in body fluids, such as blood plasma, and is released from all types of cells. Circulating tumor DNA (ctDNA) refers to fragments of DNA that are released from a tumor and migrate into bodily fluids, such as blood plasma. A liquid biopsy panel is defined as five or more ctDNA genes or gene mutation variants being tested. There are more than a dozen commercially available liquid biopsy panel tests, and the turnaround time varies for this testing but is typically 7-10 days.

For liquid biopsy, preanalytical issues, such as the type of specimen analyzed, procedures of sample collection, handling, processing and storage, and certain patient factors.[1] Use of plasma (rather than serum) is preferred and the type of collection tubes, preservatives in those tubes, and temperature of those tubes for 3-7 days after specimen collection are also important. Moreover, liquid biopsy performance of liquid biopsy varies by patient setting. For example, ctDNA levels are often low or undetectable in patients with a low tumor burden, cancer at specific sites and specific histologies, or tumors that have low levels of proliferation, apoptosis and/or vascularization.[2] Of crucial importance to liquid biopsy is that clonal hematopoiesis of indeterminate potential (CHIP), a phenomenon associated with increasing age, can affect the interpretation of cfDNA results, particularly when low variant-associated fraction (VAF) ctDNAs are identified.[2] Overall, limited data are available regarding the effect of blood draw procedures and potentially confounding patient related factors that may contribute to the release of cell-free DNA.[1] Like other tests for clinical use, the stages of development for liquid biopsy tests include demonstration of analytical validity, clinical validity, and clinical utility. Importantly, clinical utility refers to evidence of clinically meaningful improvements in clinical outcomes (clinical efficacy or reduced toxicity) compared with standard testing methods used to direct patient management.

The most common clinical scenario where use of ctDNA analysis is pursued is for patients with advanced or metastatic non-small cell lung cancer. In the past, ctDNA analysis in advanced/metastatic NSCLC was reserved for the assessment of EGFR mutational status, either in treatment-naïve patients with insufficient tissue for tumor genotyping or after acquired resistance to 1st/2nd generation EGFR tyrosine-kinase inhibitor treatments. However, there is now evidence to support the clinical use of broad-based platform such as NGS in genotyping for multiple other actionable oncogene drivers (such as aberrations in EGFR, ALK, ROS1, RET, MET, HER2, KRAS, NTRK, and/or BRAF) in newly diagnosed patients with tumor tissue available for initial genotyping.[3, 4] Prospective studies have shown that positive finding on plasma NGS testing are highly concordant with tissue-based NGS test findings, although negative findings in plasma requires further testing.[5, 6] Some guidelines suggest that liquid biopsy can be used in certain clinical settings when tissue testing proves inadequate[7], although the ASCO guidelines found that there is currently insufficient evidence to support the use of this test method routinely for the diagnosis of primary lung adenocarcinoma.[3]

Another area of keen interest in the application of ctDNA testing is in colorectal cancer where there is exploration of ctDNA in several potential applications to inform clinical decision-making. Prospective studies such as CIRCULATE, COBRA, Dynamic II/III, and ACT3 are underway in the MRD setting to further understand how ctDNA may be used.[8] Data from the Dynamic study, a non-inferiority study featuring use of circulating tumor DNA (ctDNA) to guide adjuvant therapy for stage II colon cancer, have now been published.[9] This is a phase II biomarker-driven multicenter trial that enrolled 455 patients in Australia and New Zealand who were randomly assigned to either ctDNA-guided chemotherapy or standard management, which was clinician-guided based on conventional criteria. The primary endpoint was recurrence-free survival (RFS) at 2 years with a non-inferiority design that involved a large 8.5% margin to still be considered non-inferior. Predictably, the relapse-free survival rate was low and non-inferior in both study arms. The putative advantage to the ctDNA guided therapy was that the proportion of patients who needed to be treated with adjuvant chemotherapy compared to standard management decreased (15.3% vs 27.9%). But the most striking caveat is that the risk of getting exposed to oxaliplatin-containing adjuvant chemotherapy (with its risk of chemotherapy-related peripheral neuropathy) tripled. There is a 2.7% risk of oxaliplatin exposure in the standard arm vs. 9.5% risk in the ctDNA arm. Thus, this innovation does not produce better cancer treatment outcomes and it increases the exposure to the drug most worthy of avoiding in this setting. The predictable early reaction of oncologists to this data was that ctDNA positive patients should be treated but that also ctDNA negative patients with T4 tumors who mismatch-repair proficient should also still be treated (consistent with ASCO guidelines Accounting for this likely set of actions, the net result of adding ctDNA testing for stage II colon cancer patients will be increased exposure to oxaliplatin-containing chemotherapy and little or no real world decrease in total use of adjuvant chemotherapy. Thus, it remains unclear whether use of ctDNA testing will produce net clinical benefit for this patient population.

Finally, there is also interest in the use of ctDNA testing for cancer screening. For example, use of the Galleri test (a type of circulating cell-free DNA test) has been studied in a prospective interventional trial called the Pathfinder study.[10] The premise is that a methylation assay applied to the cfDNA samples is highly informative as a signal for cancer detection and tissue of origin localization. The Pathfinder study primary objectives are the per participant count of the number and types of diagnostic tests required to achieve diagnostic resolution following a "signal detected" multi-cancer early detection test result, and also

the per participant time required to achieve diagnostic resolution following a "signal detected" multi-cancer early detection test result. Those data have not yet been presented. The primary objectives of the Pathfinder study are intermediate endpoints. Cancer screening studies require data to show that the benefits in terms of deaths avoided outweighs various harms of overdiagnosis and overtreatment that can occur based on the screening.[11]

References

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Codes

The following code list is not meant to be all-inclusive. Authorization requirements will vary by health plan. Please consult the applicable health plan for guidance on specific procedure codes.

Specific CPT codes for services should be used when available. Nonspecific or not otherwise classified codes may be subject to additional documentation requirements and review.

CPT/HCPCS

81327	SEPT9 (Septin9) (eg, colorectal cancer) promoter methylation analysis
81479	Unlisted molecular pathology procedure
0007M	Oncology (gastrointestinal neuroendocrine tumors), real-time PCR expression analysis of 51 genes, utilizing whole peripheral blood, algorithm reported as a nomogram of tumor disease index
0011M	Oncology, prostate cancer, mRNA expression assay of 12 genes (10 content and 2 housekeeping), RT-PCR test utilizing blood plasma and/or urine, algorithms to predict high-grade prostate cancer risk
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)

0229U	BCAT1 (Branched chain amino acid transaminase 1) and 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
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
0285U	Oncology, response to radiation, cell-free DNA, quantitative branched chain DNA amplification, plasma, reported as a radiation toxicity score - RadTox™ cfDNA test
0306U	Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis, cell-free DNA, initial (baseline) assessment to determine a patient-specific panel for future comparisons to evaluate for MRD
0307U	Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis of a patient-specific panel, cell-free DNA, subsequent assessment with comparison to previously analyzed patient specimens to evaluate for MRD
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
0333U	Oncology (liver), surveillance for hepatocellular carcinoma (HCC) in high-risk patients, analysis of methylation patterns on circulating cell-free DNA (cfDNA) plus measurement of serum of AFP/AFP-L3 and oncoprotein des-gammacarboxy-prothrombin (DCP), algorithm reported as normal or abnormal result
0340U	Oncology (pan-cancer), analysis of minimal residual disease (MRD) from plasma, with assays personalized to each patient based on prior next-generation sequencing of the patient's tumor and germline DNA, reported as absence or presence of MRD, with disease-burden correlation, if appropriate
0356U	Oncology (oropharyngeal), evaluation of 17 DNA biomarkers using droplet digital PCR (ddPCR), cell-free DNA, algorithm reported as a prognostic risk score for cancer recurrence
0368U	Oncology (colorectal cancer), evaluation for mutations of APC, BRAF, CTNNB1, KRAS, NRAS, PIK3CA, SMAD4, and TP53, and methylation markers (MYO1G, KCNQ5, C9ORF50, FLI1, CLIP4, ZNF132 and TWIST1), multiplex quantitative polymerase chain reaction (qPCR), circulating cell-free DNA (cfDNA), plasma, report of risk score for advanced adenoma or colorectal cancer. Test evaluates a plasma specimen for eight gene mutations and seven gene methylation markers from circulating cell–free DNA (cfDNA) using quantitative polymerase chain reaction (qPCR) methodology. The test includes an algorithmic analysis of findings to report a risk score for colorectal cancer or advanced adenoma.
0405U	Oncology (pancreatic), 59 methylation haplotype block markers, next-generation sequencing, plasma, reported as cancer signal detected or not detected
0409U	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
0410U	Oncology (pancreatic), DNA, whole genome sequencing with 5-hydroxymethylcytosine enrichment, whole blood or plasma, algorithm reported as cancer detected or not detected

ICD-10 Diagnosis

Refer to the ICD-10 CM manual

History

Status	Review Date	Effective Date	Action
Updated	n/a	10/01/2023	Added new CPT codes 0368U, 0405U, 0409U, and 0410U. Added CPT codes 81327, 0007M, 0011M, 0229U, 0285U, 0333U, 0340U (moved from Somatic Tumor Testing guidelines).
Created	09/21/2022	02/12/2023	Independent Multispecialty Physician Panel (IMPP) review. Original effective date.