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Clinical Appropriateness Guidelines

Genetic Testing

Appropriate Use Criteria: Genetic Liquid Biopsy in the Management of Cancer and Cancer Surveillance

Proprietary

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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. The Guidelines establish objective and evidence-based criteria for medical necessity determinations, where possible, that can be used in support of the following:

- To establish criteria for when services are medically necessary
- 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 address 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 and legal 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. Resources reviewed include widely used treatment guidelines, randomized controlled trials or prospective cohort studies, and large systematic reviews or meta-analyses. Carelon reviews all of its Guidelines at least annually.

Carelon makes its Guidelines publicly available on its website. Copies of the Guidelines are also available upon oral or written request. Additional details, such as summaries of evidence, a list of the sources of evidence, and an explanation of the rationale that supports the adoption of the Guidelines, are included in each guideline document.

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. Use of the Guidelines by any external AI entity without the express written permission of Carelon is prohibited.

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, and in the case of reviews for Medicare Advantage Plans, the Guidelines are only applied where there are not fully established CMS criteria. If requested by a health plan, Carelon will review requests based on health plan medical policy/guidelines in lieu of the Carelon Guidelines. 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 is likely to outweigh any potential harms, including from delay or decreased access to services that may result (net benefit).
- Widely used treatment guidelines and/or current clinical literature and/or standards of medical practice should support that the recommended intervention offers the greatest net benefit among competing alternatives.
- There exists a reasonable likelihood that the intervention will change management and/or lead to an improved outcome for the patient.

Providers may be required to submit clinical documentation in support of a request for services. Such documentation must a) accurately reflect the clinical situation at the time of the requested service, and b) sufficiently document the ordering provider's clinical intent.

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 justify a finding of clinical appropriateness. During the peer-to-peer conversation, factors such as patient acuity and setting of service may also be taken into account to the extent permitted by law.

Genetic tests not specifically mentioned in the guidelines are considered not medically necessary.

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. Requests for ongoing services may depend on completion of previously authorized services in situations where a patient's response to authorized services is relevant to a determination of clinical appropriateness.

Genetic Liquid Biopsy in the Management of Cancer and Cancer Surveillance

Clinical Indications

General Requirements

The genomic testing must have established analytical and clinical validity and be performed in an appropriately certified laboratory.

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 over a short period of time

Liquid Biopsy Testing

Definitions

Genetic liquid biopsy refers to the analysis of genetic material obtained from bodily fluids, primarily blood, to detect and monitor genetic changes associated with cancer. This technique focuses on identifying specific genetic pathogenic variants/likely pathogenic variants, alterations, or aberrations in **circulating tumor DNA (ctDNA) or other genetic components like RNA**.

Key applications of genetic liquid biopsy include:

- **Pathogenic variant/likely pathogenic variant detection** – Identifying specific pathogenic variants/likely pathogenic variants in genes that are associated with certain types of cancer, which can guide targeted therapies
- **Tumor profiling** – Understanding the genetic landscape of a tumor to identify potential treatment strategies and assess prognosis
- **Monitoring treatment response** – Tracking changes in ctDNA levels over time to evaluate how well a cancer is responding to treatment
- **Early detection and recurrence monitoring** – Detecting genetic changes that may indicate the presence of cancer at an early stage or the recurrence of a previously treated cancer

General Criteria for Genetic Liquid Biopsy Testing

If Cancer Site-Specific Criteria (e.g., lung carcinoma, biliary tract carcinoma, breast carcinoma, prostate carcinoma) are described in this guideline, apply those criteria prior to use of the General Criteria for Genetic Liquid Biopsy Testing.

The use of an FDA-approved companion diagnostic test or an appropriately validated lab developed test (LDT) performed in a certified laboratory may be considered **medically necessary** when the following criteria are met.

Liquid (ctDNA) based testing is considered **medically necessary** for individuals with invasive malignancy for whom the liquid biopsy test is necessary for treatment selection, and **ALL** the following criteria are met:

- Specific cancer treatment is currently being considered which corresponds with an FDA companion diagnostic indication
- There is insufficient tumor tissue available for NGS-based somatic profiling or for whom tissue biopsy is unsafe or considered infeasible due to the individual's clinical condition
- The individual has not had prior testing for the targeted gene(s) of interest in the relevant clinical scenario
- Other somatic tumor testing results or clinical criteria do not already provide support for the specific cancer therapy being considered that correspond to the FDA companion diagnostic indication and **ALL** the following criteria are met:
    - Clinical decision making incorporates the known or predicted impact of a specific genomic alteration on protein expression or function and published clinical data on the efficacy of targeting that genomic alteration with a particular agent
    - The genetic test is reasonably targeted in the scope of genetic testing applied
    - The genetic test has established clinical utility such that a positive or negative result will meaningfully impact the clinical management of the individual and will likely result in improvement in net health outcomes, **AND ONE or more** of these additional criteria must also be met:
        - The genomic biomarker-linked therapies are approved by the US Food and Drug Administration (FDA) or recommended by NCCN as a category 2A for the individual's specific cancer scenario and such therapies are being considered in the near term
        - Treatment is being considered for which there are specific genomic biomarker-based contraindications or exclusions related to cancer treatment being considered in the near term aligned with the FDA label or NCCN 2A recommendations
        - Treatment is being considered for which the member's health plan has a drug-specific policy requiring additional, appropriately focused genetic biomarker testing otherwise not specified by the FDA label or NCCN 2A recommendation

Cancer Site-Specific Criteria

Lung carcinoma

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

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

- There is insufficient tumor tissue available for NGS-based somatic profiling or for whom tissue biopsy is unsafe or considered infeasible due to the individual'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 pathogenic variants/likely pathogenic variants (ESMO Scale for Clinical Actionability of Targets category 1A or 1B) to inform management at diagnosis or treatment progression on or after chemotherapy or immunotherapy

Biliary tract carcinoma

Individuals with locally advanced, recurrent, or metastatic biliary tract carcinoma

Liquid (ctDNA) based testing is considered **medically necessary** for individuals with pathologically confirmed locally advanced, recurrent, or metastatic biliary tract carcinomas when **ALL** the following criteria are met:

- There is insufficient tumor tissue available for NGS-based somatic profiling or for whom tissue biopsy is unsafe or considered infeasible due to the individual's clinical condition
- No prior NGS-based somatic profiling test has previously been performed for this pathological diagnosis of biliary tract cancer
- The test is being used to provide genetic information related to the current set of actionable pathogenic variants/likely pathogenic variants (ESMO Scale for Clinical Actionability of Targets category 1A or 1B) to inform management at diagnosis or treatment progression on or after chemotherapy or immunotherapy

Breast carcinoma

Individuals with metastatic breast cancer who may benefit from PIK3CA/AKT1/PTEN or ESR1-targeted therapy

Liquid (ctDNA) based testing, to include PIK3CA, AKT1, PTEN and/or ESR1 somatic tumor testing, is considered **medically necessary** to identify individuals who may benefit from the use of alpelisib, capivasertib plus fulvestrant or elacestrant (or other FDA-approved agents targeting these same pathways) when **ALL** the following criteria are met:

- The individual has ER-positive and HER2-negative metastatic breast cancer
- The individual is a candidate for drug treatment in the near term aligned with the FDA label or NCCN 2A recommendations
- The individual has not had prior testing for the targeted gene(s) of interest in the metastatic setting
- There is insufficient tumor tissue available for NGS-based somatic profiling or tissue biopsy is unsafe or considered infeasible due to the individual's clinical condition

Prostate carcinoma

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

Liquid (ctDNA) based testing is considered **medically necessary** for individuals with metastatic adenocarcinoma when **ALL** 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 **ONE** of the following therapies:
    - FDA-approved PARP inhibitor (olaparib, rucaparib, or other PARP inhibitor with NCCN 2A recommendation)

  - FDA-approved PD-1 inhibitor (pembrolizumab or other checkpoint inhibitor with NCCN 2A recommendation)
- There is insufficient tumor tissue available for NGS-based somatic profiling or tissue biopsy is unsafe or considered infeasible due to the individual's clinical condition

Individuals without malignancy for whom liquid biopsy is used for screening

Liquid (ctDNA) based testing including multi-cancer early detection tests (MCED) is considered **not medically necessary** for individuals without invasive malignancy for whom the liquid biopsy test is being used for early initial cancer diagnosis or cancer screening.

- The following test examples are **not medically necessary**:
  - Guardant Shield™ (Guardant Health)
  - Galleri® (GRAIL)

ctDNA and Minimal Residual Disease (MRD)

Liquid (ctDNA) based testing is considered **not medically necessary** for individuals with invasive solid tumor malignancy for whom the liquid biopsy test is being used to assess for MRD during and after treatment.

- The following test examples are **not medically necessary:**
  - Guardant Response™ (Guardant Health)
  - Guardant Reveal™ (Guardant Health)
  - Signatera™ (Natera)

Rationale

Introduction to Liquid Biopsy in Oncology

Liquid biopsy refers to diagnostic tests obtained from a blood sample used to inform the management of individuals with cancer. Liquid biopsies offer a less invasive alternative to traditional tissue biopsies for cancer diagnosis, treatment response evaluation, early cancer detection, and surveillance.[1]

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 pathogenic/likely pathogenic variants being tested. More than a dozen liquid biopsy panel tests are commercially available, and the turnaround time for this testing varies but is typically 7 to 10 days.

Participants at a September 2023 workshop at the US National Cancer Institute regarding ctDNA in cancer treatment and clinical care have noted that despite progress in recent years, challenges remain in validating and translating ctDNA assays into the clinic. Assay high sensitivity and prognostic ability do not imply a clinically meaningful result or utility in terms of treatment decisions, which depend on the availability of effective treatment options. Proof of biomarker clinical utility requires a prospective clinical trial and cannot be demonstrated using retrospective samples, and not all biomarker clinical study designs (e.g., enrichment, stratified, and strategy designs) are equal from an inference and statistical efficiency standpoint. Moreover, effective communication with patients about the assay and its results can be challenging because patients want information that is meaningful, relevant, and actionable in terms that they can understand.[2]

Technical and Clinical Considerations

While there is typically a great deal of enthusiasm by authors writing about ctDNA testing, authors without conflicts of interest from the National Cancer Institute have outlined technical challenges include limitations in sensitivity due to artifacts such as

PCR and sequencing errors, low yield during next-generation sequencing library preparation, and preanalytical variables impacting measurements.[2] Preanalytical issues are important to note, such as the type of specimen analyzed, procedures of sample collection, handling, processing and storage, and certain patient factors.[3] 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 to 7 days after specimen collection are also important. Moreover, performance of liquid biopsy varies by patient setting. Biological impediments include low levels of DNA shedding in early-stage or post-treatment phases, excess of background healthy DNA, and the presence of cancer-like signals within healthy DNA.[2] 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.[1] 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.[1] 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.[3] 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 European Society of Medical Oncology (ESMO) Precision Medicine Working Group acknowledges that while limitations of ctDNA assays must be taken into account, the practical advantages of liquid biopsy should be accounted for also, such as for aggressive tumor types where time to result is clinically important, such as advanced NSCLC or when tissue biopsy is unavailable or inappropriate. Since ctDNA assays have lower sensitivity for detection fusions and copy number events, these variants should be tested in tissue when this is available. For genotyping of advanced cancer, the choice between RT-PCR, digital PCR, and NGS assays in a clinical practice setting are, per ESMO, defined by availability, reimbursement status, and the number of tier I actionable genetic aberrations in a tumor-specific context.[4]

Applications in Lung Cancer

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 epidermal growth factor receptor (EGFR) pathogenic variants/likely pathogenic variant 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 next-generation sequencing (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.[5, 6] 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.[7, 8] Some guidelines suggest that liquid biopsy can be used in certain clinical settings when tissue testing proves inadequate[9], 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.[5] An update of the ASCO guideline for therapy for stage IV non-small cell lung cancer with driver alterations focused on specific evidence around first and second line treatment choices based on driver alterations but not on approaches to molecular diagnosis.[10] The ASCO statement references a paper published by Li and colleagues in 2022 that describes an observational study conducted mostly at one academic center suggesting that targeted therapy matched by either ctDNA or tissue is associated with survival benefit, an observation that should not be interpreted to suggest that ctDNA guided therapy is superior to tissue-based NGS testing to guide therapy.[11] The updated ESMO clinical practice guideline encompasses diagnosis and treatment and makes it clear that tissue samples are critical for histological diagnosis and that use of ctDNA is recommended when tissue samples are unavailable.[12] Testing of ctDNA lacks sensitivity, especially when disease burden is low, and thus expert guidelines uniformly suggest that tissue testing would still be recommended if ctDNA testing is negative.[12, 13] Thus, ctDNA does not replace tissue testing, it is not used in lieu of histologic diagnosis, and it is not recommended in stages I-III disease or in stage IV disease confined to the thorax, and it is not preferred when sufficient tissue is available. It is noteworthy that testing of lung cancer and other solid tumors for tumor mutational burden (TMB) has considerable technical nuance, and more research is needed to improve the assay and identify optimal cutoffs before blood-based TMB testing should be used to drive treatment decisions in clinical practice.[14-16] With regard to testing for driver pathogenic variants/likely pathogenic variants in earlier stages of non-small cell lung cancer, data indicate that use of osimertinib (a targeted agent used to treat EGFR mutated NSCLC) in the adjuvant setting for patients with resected stage IB-IIIA NSCLC is associated with clinically significant improvements in overall survival.[17] In this scenario, EGFR testing of tissue specimens can be obtained before surgery or at the time of surgery. While neoadjuvant treatment targeted at EGFR pathogenic variants/likely pathogenic variants is being explored, it has not been established as effective with major pathological response rates of 15%, which is below the threshold expected.[18]

Colorectal Cancer and ctDNA

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. Analysis of blood ctDNA has been investigated in multiple

settings including early tumor detection, minimal residual disease evaluation, tumor diagnosis and evaluation of prognostic/predictive biomarkers for targeted treatment selection, longitudinal monitoring of treatment response, and identification of resistance mechanisms. However, the work is ongoing with prospective trials that will be needed to inform consensus about its use.[19] Prospective studies such as CIRCULATE, Dynamic II/III, and ACT3 are underway in the MRD setting to further understand how ctDNA may be used.[20] Notably, the phase II/III COBRA study halted enrollment and the phase II endpoint was not met. The authors reported no improvement in ctDNA clearance after 6 months of chemotherapy in patients with ctDNA detected after resection of stage IIA colon cancer.[21] 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.[22] 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. Therefore, 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.

Another study investigating ctDNA testing to guide adjuvant therapy decision-making is the GALAXY study, a prospective large-scale registry to monitor ctDNA status for patients with clinical stage II-IV CRC who planned curative surgical resection. In this study, patients were screened for assignment to one of the two randomized ctDNA-guided interventional phase III trials within the CIRCULATE-Japan platform: ALTAIR (treatment escalation) and VEGA (treatment de-escalation). Overall, for this retrospective and observational substudy of the patients with colorectal liver metastases, the authors acknowledge that the sample size and duration of follow-up are still insufficient from the aspect of statistical power to draw definitive conclusions.[23, 24] Thus far, no phase III randomized controlled trial has demonstrated the overall survival benefit by use of adjuvant chemotherapy in this setting. Future phase III ctDNA-guided randomized-controlled in the subset of patients with colorectal metastases are warranted.

Breast Cancer and ctDNA

PI3K-AKT-mTOR pathways are activated in about 50% of patients with advanced ER-positive breast cancer. While various targeted therapies are now available, the optimal sequence and combination of these treatments, especially post-CDK4/6 inhibitor progression, remain complex due to toxicity concerns and resistance mechanisms.[25] In the realm of breast cancer when tissue testing is not feasible in the setting of metastatic disease, liquid biopsy (ctDNA testing) is an accepted, evidence-based approach to molecular testing for the purpose of identifying specific biomarker-driven therapeutic choices.[26-29] Expansion of the scope of testing for ER+/HER2- locally advanced or metastatic breast cancer to include not only PIK3CA testing to identify candidate for alpelisib with fulvestrant or inavolisib with palbociclib and fulvestrant and ESR1 testing to identify candidates for elacestrant with fulvestrant, but also AKT1 and PTEN testing in response to the testing associated with the more recent FDA approval of capivasertib with fulvestrant.[27] An ASCO rapid guideline update was published in 2023 and updated in 2024 recommending multiple lines of endocrine therapy, frequently paired with targeted agents for metastatic hormone receptor positive and HER2-negative breast cancer patients, specifying that these choices should be informed by routine testing (using tissue or blood obtained at the time of progression) for activating pathogenic variants/likely pathogenic variants in ESR1, PIK3CA, or AKT1, or inactivation of PTEN.[30, 31] The ASCO 2024 guideline update states for both PIK3CA and ESR1 that testing should be on blood OR tissue. While tissue or blood sampling is considered acceptable for acting on the findings, there is inadequate evidence on which to favor routinely testing from blood prior to testing available tissue in this setting.[32, 33] Likewise, the NCCN guidelines (v6.2024) do not claim that ctDNA testing is preferred over tissue testing. However, these NCCN guidelines recommend that tissue testing be done when initial testing with ctDNA is negative for patients with HR-positive and HER2-negative disease. Thus, there is a disadvantage in efficiency by starting with ctDNA testing when tissue is available in that setting.

Prostate Cancer and ctDNA

Circulating tumor DNA (ctDNA) testing, particularly through liquid biopsy, has emerged as a tool being increasingly explored in metastatic prostate cancer. Current evidence and a recent guideline regarding germline and somatic genomic testing for metastatic prostate cancer supports its use for therapeutic decision-making in order to identify actionable pathogenic variants/likely pathogenic variants such as alterations in DNA damage repair (DDR) genes like BRCA1/2, ATM, and CHEK2,

which predict responsiveness to PARP inhibitors (e.g., olaparib, rucaparib).[34, 35] Furthermore, patients with mismatch repair deficiency (MMRd) identified via ctDNA may benefit from immune checkpoint inhibitors like pembrolizumab. In general, ctDNA levels correlate with tumor burden and disease progression and may enable detection of treatment resistance or disease progression. In contrast, in localized prostate cancer ctDNA detection remains difficult due to low tumor shedding. A significant limitation is that ctDNA sensitivity is lower in prostate cancer in general compared to other malignancies due to the lower molecular diversity and limiting shedding in prostate tumors. Ongoing studies aim to validate the use of ctDNA for MRD detection and treatment stratification in prostate cancer (as with various other solid tumors.[36]

Other Malignancies and ctDNA

The use of ctDNA testing is also being explored in various solid tumor realms for the purposes of detecting and monitoring minimal residual disease (MRD).[37, 38] There is particular interest in the realm of colorectal cancer with exploration of both tumor-informed and tumor-agnostic testing approaches with at least 22 major ongoing studies as of November 2024.[39] Early studies have explored associations between MRD and surrogate outcomes in solid tumor settings such as cervical cancer [40], sarcoma [41], head and neck cancer [42], GI stromal tumors [43], and a variety of other adult solid tumors[36] and hematological malignancies.[44] Overall, further research is needed to demonstrate the clinical utility of MRD testing. Prospective study designs are being proposed to guide further research in this realm.[45] One of the challenges faced in widespread testing of individuals with solid tumors is the challenge of diagnosing and potentially treating subclinical hematological neoplasms based on findings of clonal hematopoiesis.[46] The presence of pathogenic variants/likely pathogenic variants from sites other than a target lesion, most commonly clonal hematopoiesis of indeterminate potential (CHIP) or possibly other post-chemotherapy marrow clones, is considered a limitation of ctDNA testing[13] and requires further study.

Regarding hematological malignancies, although marrow-based response assessment remains the gold standard for most blood neoplasms and appears significantly more sensitive in myeloma using current tools, ctDNA may be preferable in select circumstances including extramedullary AML and CLL with a prominent nodal component.[44]

Liquid (ctDNA) Screening for Colorectal Cancer

The ECLIPSE trial assessed a liquid screening test, characterizes and then integrates three types of information about the person's cfDNA: methylation status, aberrant fragmentation patterns, and the presence or absence of somatic pathogenic variants in the genes APC and KRAS. The performance characteristics of a cell-free DNA (cfDNA) blood-based test in a population eligible for colorectal cancer screening. Eligible persons were 45 to 84 years of age at the time of consent, at average risk for colorectal cancer and undergoing routine screening with colonoscopy. The coprimary outcomes were sensitivity for colorectal cancer and specificity for advanced neoplasia (AN; colorectal cancer or advanced precancerous lesions) relative to screening colonoscopy.[47] The specificity for any advanced neoplasia was 89.6% (95% CI, 88.8 to 90.3). Specificity for negative colonoscopy (no colorectal cancer, advanced precancerous lesions, or nonadvanced precancerous lesions) was 89.9% (95% CI, 89.0 to 90.7). This test only found 13% of large polyps compared to 95% with a colonoscopy. The false positive rate was 10%. Overall, more research is needed, as the ECLIPSE study does not support the clinical utility of this approach to routine colorectal screening.

Liquid (ctDNA) Screening for Multi-cancer Detection

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 the Pathfinder study, a prospective interventional trial.[48] 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 primary objectives (intermediate endpoints) of the Pathfinder study 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.[48] A "cancer signal" was found in 92 (1.4%) of 6621 enrolled people. Half of the 35 cancers diagnosed were early stage. Standard screening, in contrast, identified 29 cancers. Of the 92 positive tests, 57 (62%) were false positives. The positive predictive value was 38%-41% depending on the version of the test. These positive tests led to a higher level of anxiety in patients, and 30% of the false positive tests led to invasive procedures. While this study did show that MCED screening is feasible, the authors make no claims regarding clinical utility.[49] Similarly, SYMPLIFY is a multicenter, prospective, observational study done to evaluate the performance of MCED testing in patients with nonspecific symptoms or symptoms potentially related to gynecological, lung, or upper or lower gastrointestinal tract cancers. In a cohort of 5461 patients, the MCED test detected a cancer signal in 323 cases, of whom 244 received a cancer diagnosis. Again, this study shows that MCED testing on a larger scale (this time in patients with non-specific symptoms) is feasible; however, prospective testing remains necessary to evaluate the clinical utility of MCED testing.[50] Cancer screening studies require data to show that the benefits in terms of deaths avoided outweigh various harms of overdiagnosis and overtreatment that can occur based on the screening.[51, 52] In addition, cell-free DNA based multi-cancer detection tests are being explored for evaluation of individuals who present with symptoms suspicious of cancers. In a prospective, case-controlled Circulating Cell-free Genome Atlas [53] substudy, a total of 2036 cancer and 1472 non-cancer participants were included. These data are consistent with the

SYMPLIFY study conducted in the UK, as the overall sensitivity of cancer signal detection was 64.3% with accuracy of 90.3%. The authors note that "ongoing interventional studies are planned to further investigate clinical utility measures of a multi-cancer detection test."[54]

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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

May Be Medically Necessary When Criteria are Met

Code	May Be Medically Necessary When Criteria are Met
81462	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
81463	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
81464	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
81479	Unlisted molecular pathology procedure
0177U	Oncology (breast cancer), DNA, PIK3CA (phosphatidylinositol-4,5-bisphosphate 3- kinase catalytic subunit alpha) gene analysis of 11 gene variants utilizing plasma, reported as PIK3CA gene mutation status
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)
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
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
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.
0487U	Oncology (solid tumor), cell-free circulating DNA, targeted genomic sequence analysis panel of 84 genes, interrogation for sequence variants, aneuploidy-corrected gene copy number amplifications and losses, gene rearrangements, and microsatellite instability
0539U	Oncology (solid tumor), cell-free circulating tumor DNA (ctDNA), 152 genes, next-generation sequencing, interrogation for single-nucleotide variants, insertions/deletions, gene rearrangements, copy number alterations, and microsatellite instability, using whole-blood samples, mutations with clinical actionability reported as actionable variant
0562U	Oncology (solid tumor), targeted genomic sequence analysis, 33 genes, detection of single-nucleotide variants (SNVs), insertions and deletions, copy-number amplifications, and translocations in human genomic circulating cell-free DNA, plasma, reported as presence of actionable variants

Not Medically Necessary

Code	Not Medically Necessary
81327	SEPT9 (Septin9) (eg, colorectal cancer) promoter methylation analysis; lab test to detect, in free circulating DNA in the blood, methylation of gene promoter regions that affect expression of suppressor gene Septin9 (SEPT9), which serves as a marker for conditions such as colorectal cancer.
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
0013M	Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm reported as a risk score for having recurrent urothelial carcinoma

Code	Not Medically Necessary
0229U	BCAT1 (Branched chain amino acid transaminase 1) and IKZF1 (IKAROS family zinc finger 1) (eg, colorectal cancer) promoter methylation analysis
0285U	Oncology, disease progression and response monitoring to radiation, chemotherapy, or other systematic cancer treatments, cell-free DNA, quantitative branched chain DNA amplification, plasma, reported in ng/mLOncology, 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
0332U	Oncology (pan-tumor), genetic profiling of 8 DNA-regulatory (epigenetic) markers by quantitative polymerase chain reaction (qPCR), whole blood, reported as a high or low probability of responding to immune checkpoint-inhibitor therapy
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-gamma-carboxy 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. NavDx®, Naveris, Inc, Naveris, Inc
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
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
0422U	Oncology (pan-solid tumor), analysis of DNA biomarker response to anti-cancer therapy using cell-free circulating DNA, biomarker comparison to a previous baseline pre-treatment cell-free circulating DNA analysis using next-generation sequencing, algorithm reported as a quantitative change from baseline, including specific alterations, if appropriate
0452U	Oncology (bladder), methylated PENK DNA detection by linear target enrichment-quantitative methylation-specific real-time PCR (LTE-qMSP), urine, reported as likelihood of bladder cancer
0453U	Oncology (colorectal cancer), cell-free DNA (cfDNA), methylation-based quantitative PCR assay (SEPTIN9, IKZF1, BCAT1, Septin9-2, VAV3, BCAN), plasma, reported as presence or absence of circulating tumor DNA (ctDNA)
0467U	Oncology (bladder), DNA, next-generation sequencing (NGS) of 60 genes and whole genome aneuploidy, urine, algorithms reported as minimal residual disease (MRD) status positive or negative and quantitative disease burden
0485U	Oncology (solid tumor), cell-free DNA and RNA by next-generation sequencing, interpretative report for germline mutations, clonal hematopoiesis of indeterminate potential, and tumor-derived single-nucleotide variants, small insertions/deletions, copy number alterations, fusions, microsatellite instability, and tumor mutational burden
0486U	Oncology (pan-solid tumor), next-generation sequencing analysis of tumor methylation markers present in cell-free circulating tumor DNA, algorithm reported as quantitative measurement of methylation as a correlate of tumor fraction
0496U	Oncology (colorectal), cell-free DNA, 8 genes for mutations, 7 genes for methylation by real-time RT-PCR, and 4 proteins by enzyme-linked immunosorbent assay, blood, reported positive or negative for colorectal cancer or advanced adenoma risk
0507U	Oncology (ovarian), DNA, whole-genome sequencing with 5-hydroxymethylcytosine (5hmC) enrichment, using whole blood or plasma, algorithm reported as cancer detected or not detected
0530U	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
0537U	Oncology (colorectal cancer), analysis of cell-free DNA for epigenomic patterns, next-generation sequencing, >2500 differentially methylated regions (DMRs), plasma, algorithm reported as positive or negative
0560U	Oncology (minimal residual disease [MRD]), genomic sequence analysis, cell-free DNA, whole blood and tumor tissue, baseline assessment for design and construction of a personalized variant panel to evaluate current MRD and for comparison to subsequent MRD assessments
0561U	Oncology (minimal residual disease [MRD]), genomic sequence analysis, cell-free DNA, whole blood, subsequent assessment with comparison to initial assessment to evaluate for MRD

Code	Not Medically Necessary
0565U	Oncology (hepatocellular carcinoma), next-generation sequencing methylation pattern assay to detect 6626 epigenetic alterations, cell-free DNA, plasma, algorithm reported as cancer signal detected or not detected
0566U	Oncology (lung), qPCR-based analysis of 13 differentially methylated regions (CCDC181, HOXA7, LRRC8A, MARCHF11, MIR129-2, NCOR2, PANTR1, PRKCB, SLC9A3, TBR1_2, TRAP1, VWC2, ZNF781), pleural fluid, algorithm reported as a qualitative result
0569U	Oncology (solid tumor), next generation sequencing analysis of tumor methylation markers (>20000 differentially methylated regions) present in cell-free circulating tumor DNA (ctDNA), whole blood, algorithm reported as presence or absence of ctDNA with tumor fraction, if appropriate
0571U	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
0585U	Targeted genomic sequence analysis panel, solid organ neoplasm, circulating cell-free DNA (cfDNA) analysis from plasma of 521 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, and microsatellite instability, report shows identified mutations, including variants with clinical actionability
0611U	Oncology (liver), analysis of over 1,000 methylated regions, cell-free DNA from plasma, algorithm reported as a quantitative result (For additional PLA code with identical clinical descriptor, see 0612U. See Appendix O or the most current listing on the AMA CPT website to determine appropriate code assignment)
0612U	Oncology (liver), analysis of over 1,000 methylated regions, cell-free DNA from plasma, algorithm reported as a quantitative result (For additional PLA code with identical clinical descriptor, see 0611U. See Appendix O or the most current listing on the AMA CPT website to determine appropriate code assignment)

ICD-10 Diagnosis

Refer to the ICD-10 CM manual

History

Status	Review Date	Effective Date	Action
Updated codes 01/01/2026	n/a	Unchanged	CPT code update: added 0611U, 0612U (NMN).
Revised	04/21/2025	11/15/2025 except for Anthem BCBS OH Medicaid	Independent Multispecialty Physician Panel (IMPP) review. Renamed guideline to encompass RNA based liquid biopsy tests. Split liquid (ctDNA) based testing into General Criteria and Cancer Site-Specific Criteria. General Requirements – clarified that genomic testing must have established analytical and clinical validity and be performed in an appropriately certified laboratory. General Criteria – added lab developed tests; additional criteria to meet medical necessity. Lung carcinoma – replaced ASCO with comparable ESCAT scale; Biliary tract carcinoma – added new criteria; Breast carcinoma – removed restriction of individual needing to be an adult male or postmenopausal female, added NCCN 2A recommendation as positive criteria; Prostate carcinoma – added NCCN 2A recommendation as positive criteria. Added references. Moved CPT codes 0388U, 0487U, 0539U, 0562U from NMN to MNWCM.
Updated codes 10/01/2025	n/a	Unchanged	CPT code update: added 0585U (NMN).
Updated codes 07/01/2025	n/a	Unchanged	CPT code update: added 0560U, 0561U, 0562U, 0565U, 0566U, 0569U, 0571U (NMN); revised description for 0285U (NMN).
Updated codes 04/01/2025	n/a	Unchanged	CPT code update: added 0013M, 0332U, 0452U, 0467U, 0537U, 0539U (NMN).
Updated codes 01/01/2025	n/a	Unchanged	CPT code update: added 0530U (NMN), remove termed 0428U (NMN). Revised long descriptions for 0486U, 0487U, and 0507U.

Status	Review Date	Effective Date	Action
Revised	04/15/2024	11/17/2024	IMPP review. Expanded the scope of testing for metastatic breast cancer to include AKT1 and PTEN along with PIK3CA and ESR1 testing to help identify individuals who may be treated with targeted therapy. Clarified that liquid screening tests for cancer are not medically necessary. Added references. Moved CPT code 0177U from Somatic Tumor (MNWCM).
Updated codes 10/01/2024	n/a	Unchanged	Added CPT codes 0485U, 0486U, 0487U, 0507U (NMN). Added/ Moved from Polygenic Risk Scores guideline: 81327, 0011M, 0356U, 0368U, 0496U (NMN).
Updated codes 07/01/2024	n/a	Unchanged	Added CPT code 0453U (NMN).
Revised	07/18/2023	03/17/2024	IMPP review. Replaced “contraindicated” with “unsafe or infeasible” for clarification of tissue biopsy. Added references. Removed CPT codes 81327 (NMN) and 0397U (MNWCM). Moved 0326U to MNWCM list. Added required language to General Clinical Guideline per new Medicare regulations.
Updated	n/a	01/01/2024	Annual CPT code update: Added 81462, 81463, and 81464. NMN codes: Added 0422U, 0428U; Removed 0011M, 0356U, 0368U.
Revised	04/12/2023	11/05/2023	IMPP review. Expanded on ESR1 ctDNA testing, per the FDA. Specified FDA approval of PARP and PD-1 inhibitors for treating individuals with metastatic prostate adenocarcinoma. Additional edits for clarity.
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	IMPP review. Original effective date.