Medical Policy

Subject:	Circulating Tumor DNA Panel Testing (Liquid Biopsy)		
Document#:	GENE.00049	**Publish Date:**	12/28/2022
Status:	Reviewed	**Last Review Date:**	11/10/2022

Description/Scope

This document addresses cell-free circulating tumor DNA (ctDNA) panel testing, from a blood sample, in the management of individuals with cancer- for example, 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/or for cancer surveillance. These tests are also known as liquid biopsy panel tests. For the purposes of this document, a panel is defined as five or more ctDNA genes or gene mutation variants tested on the same day on the same member by the same rendering provider. This document also addresses ctDNA tests used for residual disease and recurrence monitoring, such as through combined genomic alterations and methylation analysis. Examples of ctDNA panel tests include, but are not limited to:

- Cancer Intercept® (Pathway Genomics, San Diego, CA)
- CellMax-LBx (CellMax Life, Sunnyvale, CA)
- Circulogene Comprehensive Lung, Gastrointestinal and Liver and Pancreatic Cancer Panels; Hereditary Cancer Gene Panel (Circulogene, Birmingham, AL)
- ClearID® Solid Tumor Cancer Panel (Cynvenio Biosystems, Westlake Village, CA)
- FoundationOne® Liquid CDx (Foundation Medicine, Cambridge, MA)
- Galleri™ Multi-Cancer Detection Test (Grail Inc., Menlo Park, CA)
- GeneStrat® (Biodesix, Boulder, CO)
- Guardant360® CDx, Guardant360® and Guardant Reveal™ (Guardant Health, Redwood, CA)
- NavDx® (Navaris™, Natick, MA)
- OncoGxOne™ NGS Solid Tumor Panel (Admera Health, South Plainfield, NJ)
- OncoBEAM™ Lung2 Panel and OncoBEAM™ EGFR V2 Assay (Sysmex Inostics, Baltimore, MD)
- elio Plasma Complete (Personal Genome Diagnostics, Baltimore, MD)
- Resolution ctDx Lung™ (Resolution Bioscience, Kirkland, WA)
- Target Selector™ Breast Cancer, Non-Small Cell Lung Cancer, Squamous Cell Lung Cancer and Prostate Cancer Profiles (Biocept, San Diego, CA)

Note: This document does not address circulating tumor cell (CTC) testing. Please refer to:

- LAB.00015 Detection of Circulating Tumor Cells

Note: This document does not address ctDNA tests that include 4 or fewer genes or gene mutation variants. Please refer to:

- CG-GENE-14 Gene Mutation Testing for Solid Tumor Cancer Susceptibility and Management

Note: This document does not address gene panel testing using tissue samples. Please refer to:

- GENE.00052 Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling

Note: When another document exists addressing a specific condition or genetic test, that document supersedes this one.

Note: For more information on related topics, please see the following:

- CG-GENE-19 Detection and Quantification of Tumor DNA Using Next Generation Sequencing in Lymphoid Cancers
- CG-GENE-22 Gene Expression Profiling for Managing Breast Cancer Treatment
- GENE.00009 Gene Expression Profiling and Genomic Biomarker Tests for Prostate Cancer
- GENE.00016 Gene Expression Profiling for Colorectal Cancer
- GENE.00023 Gene Expression Profiling of Melanomas and Cutaneous Squamous Cell Carcinoma
- GENE.00025 Proteogenomic Testing for the Evaluation of Malignancies

Position Statement

Investigational and Not Medically Necessary:

The use of a circulating tumor DNA (ctDNA) panel test is considered **investigational and not medically necessary** for all indications.

Rationale

According to the American Society of Clinical Oncology (ASCO), the significance of ctDNA tests are determined by assessing analytical validity (the test can accurately and reliably detect a biomarker), clinical validity (the test can detect the presence or absence of cancer), and clinical utility (the test can improve the outcomes of individuals with cancer). Even though several biomarkers have been shown to be useful for targeting and treating cancer, it cannot be assumed ctDNA tests that look for these biomarkers are automatically valid. Each ctDNA test must demonstrate accuracy, as compared to a tissue biopsy, before it can be used to make clinical decisions.

Furthermore, low shedding of tumor DNA in some individuals may result in false-negative testing findings, when ctDNA is ordered in the absence of a tissue biopsy.

Galleri test

The Galleri test (Grail, Inc., Menlo Park, CA) is a liquid biopsy test designed to detect over 50 types of cancer. The test is intended to be used with existing screening tools to improve cancer detection in individuals at increased risk of cancer. Because its intended use is as a screening test, the developers were primarily interested in creating a test with high specificity and thus a low false-positive rate.

The Galleri test development was informed by findings from the Circulating Cell-Free Atlas (CCGA) study, a prospective observational study to develop and validate a multi-cancer detection test. The CCGA enrolled 15,254 participants, 8584 with cancer and 6670 without cancer. In 2020, Liu and colleagues published results of a sub-study of the CCGA evaluating the sensitivity and specificity of a multi-cancer ctDNA test (the current version of which is known as the Galleri test). The analysis included 6689 participants from the CCGA who did not have cancer (n=4207) or whose cancer was previously untreated (n=2482). The sample was divided into training and validation sets. The test had high specificity in both the training set (99.8%, 95% confidence interval [CI], 99.4 to 99.9) and the validation set (99.3%, 95% CI, 98.3 to 99.8%), indicating a false positive rate of less than 1%. The sensitivity of the test for stage I-III cancers was 44.2% (95% CI, 31.4 to 47.2%) in the training set and 43.9% (95% CI, 39.4 to 48.5%) in the validation set. For the pre-specified group of 12 "high-signal cancers", stage I-III sensitivity was 69.8% (95% CI, 65.6 to 73.7%) in the training set and 67.3% (95% CI, 60.7 to 73.3%) in the validation set. High-signal cancers, identified in preliminary research studies, include the following types of cancer: "anus, bladder, colon/rectum, esophagus, head and neck, liver/bile-duct, lung, lymphoma, ovary, pancreas, plasma cell neoplasm, stomach".

Another sub-analysis of the CCGA was published by Klein and colleagues in 2021 and evaluated the test with an independent validation set of 5309 CCGA participants (n=3237 with cancer and n=2069 without cancer). Specificity was 99.5% (95% CI, 99.0 to 99.8%), indicating a false positive rate of 0.5% and overall sensitivity was 51.5% (95% CI, 49.6% to 53.3%). Sensitivity for the 12 high-signal cancers, discussed above, was 76.3% (95% CI, 74.0 to 78.5%).

Additional clinical trials evaluating the Galleri test are underway, including the PATHFINDER study. As described by Nadauld and colleagues (2021), the PATHFINDER study will evaluate the test in 6200 individuals age 50 years and older who will be stratified into those with and without cancer risk factors other than age. All participants will get the Galleri test and results will be communicated to individuals and their physicians. Individuals who had a cancer signal detected will receive additional testing as determined by their physician. All individuals will be assessed for cancer status at 12 months. The study is not randomized and does not include a comparison group of individuals who are not managed using the Galleri test.

FoundationOne Liquid CDx

In 2020, Woodhouse and colleagues published data on the performance of the FoundationOne Liquid CDX test. The authors retrospectively tested plasma samples from 375 individuals with hormone receptor (HR)-positive, HER2-negative breast cancer to evaluate the clinical validity of the assay as an aid in identifying individuals with PIK3CA alterations. In comparing the FoundationOne Liquid CDx test and the tumor tissue polymerase chain reaction (PCR)-based clinical trial assay (CTA), the positive percent agreement (PPA) was 71.7% and the negative percent agreement (NPA) was 100%. In addition, to evaluate the clinical validity of the assay as an aid in identifying individuals with advanced NSCLC who might be eligible for treatment with an EGFR tyrosine kinase inhibitor, the authors used samples collected for another clinical trial that had been evaluated with a different test (the EGRF Mutation Test v2). They conducted a non-inferiority analysis with 177 samples to evaluate the non-inferiority of the FoundationOne test to two replications of the reference test. The analysis found that the Foundation One Liquid CDx test was non-inferior to the reference test. In the first replication, the PPA between the FoundationOne Liquid CDx test and the reference test was 97.7% and the NPA was 95.6%. In the second replication, the PPA was 97.7% and the NPA was 95.4%.

In 2021, Takeda and colleagues reported on a prospective cohort study to evaluate the feasibility and utility of using the FoundationOne CDx test with individuals who have advanced or recurrent solid tumors. A total of 181 samples were processed and 175 of these yielded gene profiling data, for a success rate of 96.7%. A total of 174 of the 175 tested individuals had at least one known or likely pathogenic gene alteration, and 24 individuals (14%) received targeted therapy. Results of Kaplan-Meier analysis found that the median progression-free survival (PFS) was 12.1 (95% CI, 6.9 to 17.4) months for the individuals who received targeted therapy. The authors did not report PFS in individuals who did not receive targeted therapy.

Yang and colleagues (2022) conducted a multivariate analysis of factors associated with survival in 185 individuals with newly diagnosed glioblastoma who underwent FoundationOne CDx testing. In the full model that controlled for potential confounding variables, the presence of three of nine variants, CDKN2B, EGFR and PTEN were significantly associated with overall survival (OS) (CDKN3B and EGFR with reduced survival and PTEN with higher survival). None of the nine variants assessed were significantly associated with progression-free survival.

The above studies did not compare outcomes in individuals who were or were not managed using the FoundationOne CDx test.

Guardant360 Panel Tests

In a single-center observational study, Thompson and colleagues (2016) examined the concordance between tissue biopsy samples and Guardant360 blood samples for individuals with non-small cell lung cancer (NSCLC). A total

of 102 subjects with a diagnosis of NSCLC or suspected NSCLC were included in the study. Tissue samples (n=50) were processed using the Illumina TruSeq Amplicon 47 gene cancer panel (n=38) or the 20 gene Penn Precision Panel (n=12). For the 50 subjects who had both blood and tissue tests, the overall concordance was 60%. For EGFR mutations, the overall concordance was 79%. The authors concluded that ctDNA testing has potential for real-time molecular monitoring for individuals with advanced cancer. Several studies have also compared Guardant360 to tissue-based broad molecular profile tests with similar or mixed conclusions (Chae, 2016; Hahn, 2017; Pishvaian, 2016; Sandulache, 2017; Schwaederle, 2016; Schwaederle, 2017; Villaflor, 2016; Yang, 2017). These studies were limited by small sample sizes, qualitative methods, or imperfect comparators.

McCoach and colleagues (2018) performed a retrospective cohort study to determine the clinical utility of Guardant360 for detecting anaplastic lymphoma kinase (ALK) fusions in NSCLC during diagnosis or during treatment with ALK inhibitors. The researchers included 88 subjects with 96 plasma-detected ALK fusions from the Guardant360 de-identified database. Subjects were separated into 4 cohorts: cohort 1 (n=42) contained subjects with a newly discovered ALK fusion, cohort 2 (n=31) contained subjects with a known or presumed ALK fusion and whose cell-free DNA (cfDNA) was obtained at progression, cohort 3 (n=13) contained subjects without additional clinical information, and cohort 4 (n=6) contained subjects who had been treated with anti-EGFR targeted therapy and found to have an ALK fusion by cfDNA. In cohort 1, the Guardant360 test found an ALK fusion in 16 subjects who had been reported as tissue-negative or tissue insufficient. Of the 42 subjects in the cohort, 10 had tissue samples available (5 ALK-positive, 5 ALK-negative), 11 had insufficient samples, and 21 did not have ALK information available. For the 5 subjects who were identified by Guardant360 as ALK-positive despite negative tissue biopsies, 3 eventually responded to ALK inhibitor therapy while clinical data was not available for the other 2 subjects. For cohort 2, 16 samples contained 1-3 ALK resistant mutations. For 5 samples, an ALK kinase domain mutation was identified in cfDNA despite the ALK fusion not detected in cfDNA and the prior tissue sample showing an ALK fusion. For cohort 3, the clinical status was unknown and no resistance mutations or bypass pathways were identified. For cohort 4, 6 subjects were found to have ALK fusions. The authors concluded that cfDNA NGS testing is an "additional tool" for detecting alterations, resistance mutations, and bypass pathways. Limitations of the study included the retrospective design and lack of clinical data for some subjects. The authors noted that tissue evaluation was at the providers' discretion and the testing method was not available for all subjects. Furthermore, no sensitivity or specificity information was provided.

Aggarwal and colleagues (2018) conducted a single-center, prospective study to assess mutation detection using Guardant360 for individuals with stage IV NSCLC. A total of 323 participants had Guardant360 plasma testing as part of clinical management. The primary outcomes were targetable alterations detected with plasma and tissue next-generation sequencing, the association between allele fractions of mutations detected in tissue and plasma, and the association of response rate with the plasma allele fractions of the targeted mutations. For 113 individuals, therapeutically targetable mutations were detected in EGFR, ALK, MET, BRCA1, ROS1, RET, ERBB2, or BRAF. Of 94 participants who had plasma testing alone, 31 had a targetable mutation detected and were considered to not need tissue biopsy. For the 229 participants who had concurrent plasma and tissue testing or were not able to have

tissue testing, an additional 35 targetable mutations were detected. For those who received targeted therapy based on the plasma result, 36 out of 42 participants had complete/partial response or stable disease. Of the 128 subjects with concurrent plasma and tissue next generation sequencing results, 8 therapeutically relevant mutations were found in plasma only, 31 were detected in both plasma and tissue, and 16 were detected in tissue only, with an overall concordance of 81.3%. Therapeutically targetable mutation detection was highest for individuals with liver metastases (100% concordance with tissue [n=13]) compared with individuals with M1a disease (46.2% concordance). Based on the level of discordance found in the study, the authors note that "a tissue biopsy remains essential for initial cancer diagnosis"; however, in the setting of inadequate tissue DNA, "plasma NGS can be an adequate surrogate for molecular profiling." The study was limited by a single-center design, potential user bias, and the consideration of plasma testing at a single point. The study was also enriched with individuals who underwent testing after progression to detect resistance mutations, which likely increased the frequency of individuals with EGFR T790M. The long-term outcomes of employing Guardant360 plasma testing in the clinical management of stage IV NSCLC versus, or in conjunction with standard tissue biopsy remains uncertain, as does the potential risk of false-negative results.

Leighl and colleagues (2019) reported on the multicenter, prospective NILE (Non-invasive versus Invasive Lung Evaluation) study, which aimed to assess the clinical utility of Guardant360 for the identification of eight genomic biomarkers (EGFR, ALK, ROS1, BRAF V600E, RET, MET, MET exon 14, ERBB2 [HER2]) in individuals with newly diagnosed metastatic NSCLC. A total of 307 individuals were enrolled with biopsy-confirmed, previously untreated non-squamous NSCLC (stage IIIB/IV) and tissue genotyping (genomic testing and PD-L1 expression analysis using next generation sequencing polymerase chain reaction "hotspot" testing, FISH and/or IHC, or Sanger sequencing). Participants submitted a pre-treatment blood sample for Guardant360 testing. A total of 282 individuals met all inclusion criteria and were included in the final analysis. Tissue genotyping for all eight biomarkers was completed in 51 individuals (18.1%) (the majority of individuals had sequential individual biomarker testing, and did not undergo physician-directed sequencing of all eight genomic biomarkers), and Guardant360 testing for all eight biomarkers was completed in 268 individuals. One of eight biomarkers was identified in tissue samples in 60 individuals compared to 77 individuals with Guardant360 ($p<0.0001$). For 60 individuals with tissue-positive results, one of the eight biomarkers was identified in tissue alone (n=12) but not with Guardant360, a false-negative rate of 20%. In regards to these 12 individuals, the researchers note: "the lack of full genomic assessment obtained by comprehensive cfDNA genomic profiling may have led to the patient being treated with a less efficacious therapy." While the primary objective to demonstrate non-inferiority of Guardant360 compared to tissue-based genotyping was achieved, the study was limited in that only 18% of participants received comprehensive tissue genomic profiling. As with other research on the topic, a substantial number of false-negative results were obtained by cfDNA, which can lead to undertreatment.

Zugazagoitia and colleagues (2019) evaluated the ability of the Guardant360 test to identify individuals with NSCLC in routine clinical practice who have tyrosine-kinase inhibitor (TKI) resistance. This was a prospective study that included 53 individuals with EGFR, ALK or ROS1-altered advanced stage NSCLC who experienced

progression (clinical or radiological) on prior TKI therapy. The sample was divided into 3 subgroups; 1) EGFR-mutant NSCLC with resistance to first/second-generation EGFR TKI (cohort 1, n=31); 2) EGFR T790 + NSCLC with osimertinib resistance (cohort 2, n=15) and ALK/ROS1-rearranged NSCLC with resistance to crizotinib and/or next generation ALK/ROS1 TKI (cohort 3, n=7). Individuals with sufficient tumor DNA shedding such that plasma findings could be adequately interpreted were classified as "shedders". In cohort 1, 20 individuals (65%) were classified as shedders and 9 (29%) were found to have EGFR T790 M mutations with Guardant360 testing. In 2 additional individuals, EGFR T790 M mutations were identified by another method; these 11 individuals received subsequent osimertinib therapy. In cohort 2, Guardant360 testing in 10 individuals were classified as shedders and, in 9 of these, at least 1 pathologic alteration in addition to the EGFR sensitizing and/or T790M mutation was detected. None of the individuals in cohort 2 received subsequent targeted therapies. In cohort 3, which included only 7 individuals, 4 individuals were shedders and were found to have actionable alterations. Two individuals in cohort 3 received subsequent treatment informed by Guardant360 testing. A substantial number of individuals in the study were not considered to be tumor DNA shedders and this study did not compare outcomes in individuals managed with and without the Guardant360 test.

There are several published analyses of the GuardantINFORM™ healthcare claims database reporting on use of the Guardant360 test in clinical practice. Olsen and colleagues (2022) analyzed data on 3084 individuals with NSCLC who underwent genomic profiling with the Guardant360 test within 90 days of starting second-line systemic therapy. ctDNA was detected in samples from 2771 (89.9%) individuals, and 1160 (41.9%) samples had an actionable alteration. Second-line targeted therapy was given to 928 (30.1%) individuals, and, for 433 (14.0%) individuals, therapy was matched to the ctDNA test results. The analysis found that median OS was significantly longer for individuals who received matched targeted therapy for new actionable alterations than in individuals with new actionable alterations who received unmatched therapy. Nakamura and colleagues (2022) reported on 1064 individuals in the GuardantINFORM database with metastatic colorectal cancer (CRC) who underwent Guardant360 testing prior to second- or third-line therapy. ctDNA was detected in samples from 997 (93.7%) individuals, and 507 (47.7%) samples had an actionable alteration. Time to treatment discontinuation (TTD) was longest in individuals with an actionable alteration who received matched therapy, and shorter for those with an actionable alteration who did not get matched therapy and for those without an actionable alteration. The Nakamura study did not report on OS. Limitations of both of these studies were that they were retrospective and did not involve prospective comparison of patient management that did and did not use Guardant360 findings. Moreover, the analyses considered results of only Guardant360 testing because other testing that may have been done to inform therapy choices was not recorded in the GuardantINFORM database.

Guardant Reveal test is a commercially available liquid biopsy test that detects ctDNA for minimal residual disease (MRD) assessment in early-stage colorectal, breast, and lung cancers. In addition, it can be used to monitor cancer recurrence in previously diagnosed individuals. The test interrogates two signals, genomic alterations and DNA methylation. No published studies were identified that evaluate the Guardant Reveal test. Clinical trials using the Guardant Reveal test are underway. The Observation of ResiduAl Cancer With Liquid Biopsy Evaluation

(ORACLE) trial (NCT05059444) is evaluating the ability of the Guardant Reveal test to detect disease recurrence in individuals who were treated for early-stage solid tumors.

NavDx test

Human papillomavirus (HPV) infection is a sexually transmitted virus that is associated with condyloma acuminatum, squamous intraepithelial lesions, as well as malignancy, including anogenital malignancies (cervical, vaginal, vulval, penile, and anal carcinoma) and oropharyngeal squamous cell carcinoma (OPSCC) of the head and neck. HPV-associated head and neck cancers occur primarily in the tonsils, soft palate, or base of tongue.

The NavDx test is a commercially available circulating tumor HPV DNA (ctHPVDNA) test designed to aid in the detection of HPV-related cancer. Chera and colleagues (2020) reported the results of a prospective study that explored if longitudinal monitoring of ctHPVDNA during post-treatment surveillance could accurately detect clinical disease recurrence. A total of 115 participants with nonmetastatic HPV-associated (p16-positive) OPSCC were treated with definitive chemoradiation therapy (CRT). The participants underwent a 3-month post-CRT positron emission tomography (PET)/computed tomography (CT) scan and were thereafter clinically evaluated every 2-4 months (years 1-2), then every 6 months (years 3-5). Chest imaging was carried out every 6 months. Blood specimens were drawn every 6-9 months for analysis of plasma ctHPVDNA using a multianalyte digital polymerase chain reaction assay. The primary endpoint was to estimate the PPV and negative predictive value (NPV) of ctHPVDNA surveillance. After a median follow-up time of 23 months (range, 6.1-54.7 months), 15 subjects (13%) developed disease recurrence. Eighty-seven participants had undetectable ctHPVDNA at all post-treatment time points, and none developed recurrence (NPV, 100%; 95% CI, 96% to 100%). A total of 28 subjects developed a positive ctHPVDNA during post-treatment surveillance, 15 of whom were diagnosed with biopsy-proven recurrence. Sixteen subjects had two consecutively positive ctHPVDNA blood tests, 15 of whom developed biopsy-proven recurrence. The negative predictive value of ctHPVDNA for detecting disease recurrence was 100%; the positive predictive value for recurrence of two consecutive positive tests was 94% (95% CI, 70% to 99%).

In another study O'Boyle and colleagues (2022) conducted a prospective observational study to assess whether the clearance kinetics of ctHPVDNA is associated with postoperative disease status. The study included a total of 33 subjects with HPV+OPSCC undergoing surgery. Blood was collected prior to surgery, on postoperative days 1 (POD 1), 7, and 30 and with follow-up. A subcohort of 12 participants underwent frequent blood collections in the first 24 hours after surgery to define early clearance kinetics. Plasma was analyzed using custom droplet digital polymerase chain reaction (ddPCR) assays for HPV genotypes 16, 18, 33, 35, and 45. In subjects with no pathologic risk factors for recurrence who were observed after surgery, ctHPVDNA rapidly decreased to < 1 copy/mL by POD 1 (n=8/8). In participants with risk factors for macroscopic residual disease, ctHPVDNA was markedly elevated on POD 1 (> 350 copies/mL) and remained elevated until adjuvant treatment (n=3/3). Participants with intermediate POD 1 ctHPVDNA levels (1.2-58.4 copies/mL) all possessed pathologic risk factors for microscopic residual disease (n=9/9). POD 1 ctHPVDNA levels were greater in subjects with known adverse

pathologic risk factors such as extranodal extension > 1 mm (p=0.0481) and with increasing lymph nodes involved (p=0.0453) and were further associated with adjuvant treatment received (p=0.0076). One of 33 subjects had a recurrence that was detected by ctHPVDNA 2 months earlier than clinical detection. These findings are the first to demonstrate that ctHPVDNA could potentially be used as a personalized biomarker for selecting adjuvant treatment in the future.

Early studies of ctHPVDNA as a biomarker for detecting disease recurrence and minimal residual disease have demonstrated promise. Additional studies are needed that demonstrate the clinical validity (the absence and presence of minimal residual disease) of the test and that the results of such testing results in improved measurable outcomes of patient management, compared to decisions independent of test results.

OncoBeam Panel Tests

In a prospective-retrospective cohort study, Grasselli and colleagues (2017) explored the concordance between RAS in tumor tissue and ctDNA for metastatic colorectal cancer to establish eligibility for anti-EGFR therapy. Blood plasma samples and tissue samples were obtained from 146 individuals with a diagnosis of colorectal cancer. RAS status was determined with plasma and tissue samples using BEAMing and real-time PCR as standard of care (SoC) technique. The median time from tissue specimen to ctDNA collection was 1.2 months in therapy-naïve individuals and 20.2 months in previously exposed individuals. The ctDNA BEAMing RAS agreement with SoC was 89.7% compared with 90.0% agreement with SoC for BEAMing in tissue. A total of 15 individuals had discordant tissue-plasma results; there were 9 individuals with low frequency RAS mutations not detected in tissue and 6 individuals with RAS mutations not detected in plasma. Prediction of treatment benefit for individuals receiving anti-EGFR plus irinotecan was equivalent between the two groups. The authors concluded that "ctDNA analysis in plasma can detect RAS mutations to an equivalent level as SoC techniques in tissue." They noted the study was limited by a small cohort size.

In 2018, Garcia-Foncillas and colleagues published a prospective, multicenter study that compared OncoBEAM to tissue analysis for metastatic colorectal cancer. A total of 236 individuals underwent tissue biopsy and blood sample collection at 10 centers between November 2015 and October 2016. RAS mutations were detected in 55.5% of tissue samples and 51.3% of plasma samples. The researchers found that the overall percentage agreement between plasma-based and tissue-based RAS mutation testing was 89%. Performing a re-analysis with BEAMing of tissue from discordant cases, they found 2 false negative and 5 false positive tumor tissue RAS cases, making the final concordance 92%. They concluded that ctDNA analysis by OncoBEAM is comparable to SoC tissue testing techniques for RAS in individuals with colorectal cancer.

In 2021, Garcia and colleagues published a retrospective cohort study on the OncoBEAM EGFR V2 test, which covers 36 EGFR mutations found in NSCLC. Oncobeam results were compared with next-generation sequencing (NGS). The analysis included 540 samples sent by laboratories for EGFR routine screening. Of these, 229 (42.4%)

were for testing at diagnosis of NSCLC and 311 (57.5%) were testing during disease progression. A total of 22 of 229 (11.2%) cases tested at diagnosis were found to have EGFR somatic alterations. Among individuals with progressive disease, 43.7% had EGFR mutations and 40.3% had EFGR resistance mutations after first-line TKI treatment. The cfDNA analysis identified EGFR mutations in 23 of 249 (9%) of samples tested at initial diagnosis and 79 of 366 (21%) of samples with disease progression. The NGS assays test a wider range of variants and, in 13 cases, identified rare alterations not covered by the OncoBEAM test. The study did not show how use of the OncoBEAM EGFR V2 test improved the net health outcome.

Other ctDNA Panel Tests

CancerSEEK (Johns Hopkins Kimmel Cancer Center, Baltimore, MD) is a liquid biopsy test that is in research and development, and not commercially available at this time. Cohen and colleagues (2018) developed CancerSEEK, a genetic alteration and protein biomarker assay, to detect early cancers and reveal the origin of the cancer. The researchers used CancerSEEK to evaluate 1005 subjects already diagnosed with stage I-III cancers of the ovary, liver, stomach, pancreas, esophagus, colorectum, lung, or breast. A control cohort consisted of 812 subjects with no known history of cancer. The researchers found that CancerSEEK had a median sensitivity of 70% and a specificity greater than 99%. In the healthy cohort, 7 subjects tested false-positive with CancerSEEK. The researchers compared CancerSEEK to tissue samples for 153 subjects and found that the mutation in the plasma sample was identical to the mutation in the tumor for 138 subjects (90%). The researchers used supervised machine learning to examine CancerSEEK's ability to find the origin of cancer. The test was able to localize the origin of the cancer to two anatomic sites in a median of 83% of subjects and to a single organ in a median of 63% of subjects. While the results for CancerSEEK are promising, the researchers state that "to actually establish the clinical utility of CancerSEEK and to demonstrate that it can save lives, prospective studies of all incident cancer types in a large population will be required."

There is a paucity of published peer-reviewed literature, especially large-scale, high-quality prospective randomized trials, which determine the validity and utility of these tests compared to traditional pathologic examination. In some cases, studies on plasma-based testing are difficult to compare to each other given that different tissue tests are used for comparison. In addition, there is insufficient evidence that these tests improve health outcomes.

Other Considerations

In a joint-review analysis on circulating tumor DNA (Merker, 2018), ASCO and the College of American Pathologists (CAP) stated:

- Aside from assays that have received regulatory approval, most assays have insufficient evidence to demonstrate clinical validity, and most have no evidence of clinical utility. Well-

designed clinical trials or equivalence studies are needed to demonstrate clinical utility for most assays.
- Evidence shows discordance in results between ctDNA assays and tumor tissue genotyping and supports value of tumor tissue genotyping to confirm undetected ctDNA findings.
- For advanced cancer, the evidence indicates that more reliable test results occur when the ctDNA assay is performed at the time of disease progression and not when responding to prior therapy.
- There is evidence that positive findings from well-validated ctDNA assays may support initiation of a targeted therapy option where an assay for the relevant genomic marker has demonstrated clinical utility when performed in tissue.
- For monitoring therapy effectiveness, evidence of clinical validity is still emerging, and there is currently no evidence of clinical utility to suggest that ctDNA assays are useful in this context, outside of a clinical trial.
- For early-stage cancer, evidence of clinical validity is still emerging, and there is currently no evidence of clinical utility to suggest that ctDNA assays are useful at diagnosis or in the adjuvant setting after completing treatment, outside of a clinical trial.
- For cancer screening, there is no evidence of clinical validity and clinical utility to suggest that ctDNA assays are useful in this context, outside of a clinical trial.

The National Comprehensive Cancer Network (NCCN) guidelines (V4.2022) on non-small cell lung cancer stated:

- Cell-free/circulating tumor DNA testing should not be used in lieu of a histologic tissue diagnosis.
- Some laboratories offer testing for molecular alterations examining nucleic acids in peripheral circulation most commonly I processed plasma (sometimes referred to as “liquid biopsy”).
- Studies have demonstrated cell-free tumor DNA testing to generally have very high specificity, but significantly compromised sensitivity, with up to 30% false-negative rate; however, data support complementary testing to reduce turnaround time and increase yield of targetable alteration detection.
- Published guidelines elaborating standards for analytical performance characteristics of cell-free tumor DNA have not been established, and in contrast to tissue-based testing, no guidelines exist regarding the recommended performance characteristics of this type of testing.
- Cell-free tumor DNA testing can identify alterations that are unrelated to a lesion of interest, for example clonal hematopoiesis of indeterminate potential (CHIP).

- The use of cell-free/circulating tumor DNA testing can be considered in specific 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.
  - In the initial diagnostic setting, if tissue-based testing does not completely access all recommended biomarkers owing to tissue quantity or testing methodologies available, consider repeat biopsy and/or cell-free/circulating tumor DNA testing.

A joint guideline (Lindeman, 2018), *Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment with Targeted Tyrosine Kinase Inhibitors*, from the CAP, International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) stated the following:

- There is currently insufficient evidence to support the use of circulating plasma cfDNA molecular methods for establishing a primary diagnosis of lung adenocarcinoma (no recommendation; insufficient evidence, confidence, or agreement to provide a recommendation).
- In some clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a cfDNA assay to identify EGFR mutations (recommendation; some limitations in quality of evidence).
- Physicians may use plasma cfDNA methods to identify EGFR T790M mutations in lung adenocarcinoma patients with progression or secondary clinical resistance to EGFR-targeted TKIs; testing of the tumor sample is recommended if the plasma result is negative (expert consensus opinion; serious limitations in quality of evidence).

Background/Overview

According to the American Cancer Society (ACS, 2021), in 2021, there will be approximately 1.9 million new cancer diagnoses and 608,570 cancer-related deaths. Cancer develops from genetic alterations in DNA that affect the way cells grow and divide. A tissue biopsy is the gold standard for detecting DNA alterations that can be used to identify cancer, determine treatment options, or evaluate responsiveness to treatment. Tissue biopsies have several disadvantages: the biopsy procedure may be painful, such as the insertion of a long needle or a surgical procedure; the retrieved tissue may be too small for analysis; or an individual may not be able to physically tolerate the procedure. In addition, because tissue biopsies only represent cellular samples from parts of a tumor, important diagnostic data could be missed (Weber, 2014).

Liquid biopsy is proposed as a less-invasive method for cancer identification, surveillance, and treatment guidance. The National Cancer Institute (NIH) defines 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." ctDNA tests detect small fragments of mutated DNA that are released from tumors into blood, presumably by apoptosis and/or necrosis. Some ctDNA liquid biopsy tests are targeted for specific gene mutations. For example, in the instance of non-small cell lung cancer, a targeted liquid biopsy may be used to identify the presence of the EGFR mutation and determine if individuals may benefit from kinase inhibitor medication. Other liquid biopsy tests analyze multiple biomarkers and are purported to detect various cancers or treatments (Perakis, 2017).

There are several limitations of liquid biopsies. In regard to cancer management, many cancers do not have specific DNA mutations that can be identified and, when present, can be different in individuals with the same cancer. The DNA found in the fluid sample may not fully represent the tumor and mislead treatment decisions. The mutations found may not be "driver" mutations and may not provide useful information about the cancer. In regard to cancer detection, liquid biopsies can test positive for cancer when no cancer is present (false-positive) or test negative when cancer is present (false-negative). Because cancer cells release more mutated DNA fragments in later cancer stages, the test may not identify early cancer. Likewise, a liquid biopsy can detect cancerous cells that may never actually cause harm, leading to overtreatment (NIH, 2018). While liquid biopsies are promising, a great deal of research is still needed to determine if these tests improve outcomes for individuals with cancer.

Liquid biopsy tests are regulated by the Clinical Laboratory Improvement Amendments (CLIA) program, which oversees and certifies the laboratories conducting FDA-approved and non-FDA approved tests. In vitro diagnostic liquid biopsies, tests that are manufactured and then commercially sold to multiple labs, are also regulated by the FDA and must meet premarket review requirements. Liquid biopsies that are considered laboratory determined tests (LDTs), tests manufactured and performed in the same CLIA laboratory, have not thought to be subject to FDA regulations. However, in 1976, the FDA was given authority to regulate all in vitro diagnostics as devices. Because LDTs were not complex during that time, the FDA did not enforce premarket review and other requirements. As LDTs have grown more complex, the FDA has taken a renewed interest in overseeing LDTs to ensure public health and safety. On January 13, 2017, the FDA issued a discussion paper on LDTs but has not released an enforceable position at this time (FDA, 2018).

In 2012, the Institute of Medicine released recommendations on genomic-based test development and evaluation. They stated that genomic tests should be designed and properly validated in a CLIA-certified lab, and intended use of the tests, including LDTs, should be discussed with the FDA before validation studies begin. In addition, the authors stated the following:

> Of note, FDA review of a biomarker test has been focused principally on analytical and clinical/biological validity, but not on demonstration of clinical utility…Therefore, FDA approval

or clearance does not necessarily imply that the test improves clinical outcomes or should be used for patient management. LDTs performed in CLIA-certified laboratories also do not require evidence of clinical utility; only analytical and clinical validity of the test must be demonstrated prior to clinical use.

On March 16, 2018, the Centers for Medicare and Medicaid Services (CMS) approved NGS-based in vitro companion diagnostic laboratory tests for national coverage after an FDA-CMS parallel review. In the decision memo they state that "at this time, liquid-based multi-gene sequencing panel tests are left to contractor discretion if certain patient criteria are met."

In August, 2020, the FDA approved the Guardant360 CDx test as a companion diagnostic for individuals with NSCLC considering treatment with osimertinib. The approved indication involves testing for *EGFR* exon 19 deletions, L858R, and T790M. In May 2021, the approved indication was expanded to include companion diagnostic testing for individuals with NSCLC considering treatment with amivantamab. The expanded indication involves identifying individuals with EGFR exon 20 mutations. In August, 2022, the FDA approved another expansion to include companion diagnostic testing to select individuals with unresectable or metastatic HER2-mutant NSCLC whose tumors have activating HER2 (ERBB2) mutations for treatment with fam-trastuzumab deruxtecan-nxki.

In August, 2020, the FDA approved the FoundationOne Liquid CDx test as a companion diagnostic for individuals with NSCLC considering treatment with osimertinib, gefitinib or erlotinib (EGRF exon 19 deletions and EGFR exoin 21 L858R alteration) and for individuals with prostate cancer considering treatment with rucaparib (BRCA1 and BRCA2 alterations). In October 2020, approval was expanded to three additional indications: "1) to identify mutations in BRCA1 and BRCA2 genes in patients with ovarian cancer eligible for treatment with rucaparib (RUBRACA, Clovis Oncology, Inc.), 2) to identify ALK rearrangements in patients with non-small cell lung cancer (NSCLC) eligible for treatment with alectinib (ALECENSA, Genentech USA, Inc). and 3) to identify mutations in the PIK3CA gene in patients with breast cancer eligible for treatment with alpelisib (PIQRAY, Novartis Pharmaceutical Corporation)." And in November, 2020, FDA approval was expanded for us of the test " as a companion diagnostic device to identify mutations in BRCA1, BRCA2 and ATM genes in patients with metastatic castration resistance prostate cancer (mCRPC) eligible for treatment with olaparib (LYNPARZA, AstraZeneca Pharmaceuticals LP)." (FDA, 2020)

Definitions

Cell-free DNA (cfDNA): DNA that is circulating freely in body fluids, such as blood plasma, and is released from all types of cells.

Circulating tumor DNA (ctDNA): Fragments of DNA that are released from a tumor and migrate into bodily fluids, such as blood plasma.

Panel testing: Involves the analysis of multiple genes for multiple mutations simultaneously. For the purposes of this document, a panel is defined by five or more ctDNA targets tested on the same day on the same member by the same rendering provider.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
For the following procedure codes or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT	
81479	Unlisted molecular pathology procedure [when specified as a liquid biopsy panel using plasma specimen]
0179U	Oncology (non-small cell lung cancer), cell-free DNA, targeted sequence analysis of 23 genes (single nucleotide variations, insertions and deletions, fusions without prior knowledge of partner/breakpoint, copy number variations), with report of significant mutation(s) Resolution ctDx Lung™, Resolution Bioscience, Resolution Bioscience, Inc
0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations FoundationOne® Liquid CDx, FOUNDATION MEDICINE, INC, FOUNDATION MEDICINE, INC
0242U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 55-74 genes, interrogation for sequence variants, gene copy number amplifications, and gene rearrangements Guardant360® CDx, Guardant Health Inc, Guardant Health Inc
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

	Invitae PCM Tissue Profiling and MRD Baseline Assay, Invitae Corporation, Invitae Corporation
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 Invitae PCM MRD Monitoring, Invitae Corporation, Invitae Corporation
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 Guardant360, Guardant Health Inc.
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 HelioLiver™ Test, Fulgent Genetics, LLC, Helio Health, Inc
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

ICD-10 Diagnosis

All diagnoses

References

Peer Reviewed Publications:

1. Aggarwal C, Thompson JC, Black TA, et al. Clinical implications of plasma-based genotyping with the delivery of personalized therapy in metastatic non-small cell lung cancer. JAMA Oncol. 2018; 5(2):173-180.
2. Chae YK, Davis AA, Benedito A, et al. Concordance between genomic alterations assessed by next-generation sequencing in tumor tissue or circulating cell-free DNA. Oncotarget. 2016; 7(40):65364–65373.
3. Chera BS, et al. Plasma circulating tumor HPV DNA for the surveillance of cancer recurrence in HPV-associated oropharyngeal cancer. J Clin Oncol. 2020; 38(10):1050-1058.
4. Cohen JD, Li L, Wang Y, et al. Detection and localization of surgically resectable cancers with a multi-analyte blood test. Science. 2018; 359(6378):926-930.
5. Garcia J, Gauthier A, Lescuyer G et al Routine molecular screening of patients with advanced non-smallcell lung cancer in circulating cell-free dNA at diagnosis and during progression using OncoBEAMTM EGFR V2 and NGS technologies. Mol Diagn Ther. 2021 Mar; 25(2):239-250.

6. Garcia-Foncillas J, Tabernero J, Elez E, et al. Prospective multicenter real-world RAS mutation comparison between OncoBEAM-based liquid biopsy and tissue analysis in metastatic colorectal cancer. Br J Cancer. 2018; 119(12):1464-1470.
7. Grasselli J, Elez E, Caratu G, et al. Concordance of blood- and tumor-based detection of RAS mutations to guide anti-EGFR therapyin metastatic colorectal cancer. Ann Oncol. 2017; 28(6):1294-1301.
8. Hahn AW, Gill DM, Maughan B, et al. Correlation of genomic alterations assessed by next-generation sequencing (NGS) of tumor tissue DNA and circulating tumor DNA (ctDNA) in metastatic renal cell carcinoma (mRCC): potential clinical implications. Oncotarget. 2017; 8(20):33614-33620.
9. Klein EA, Richards D, Cohn A et al. Clinical validation of a targeted methylation-based multi-cancer early detection test using an independent validation set. Ann Oncol. 2021; 32(9):1167-1177.
10. Leighl NB, Page RD, Raymond VM, et al. Clinical utility of comprehensive cell-free DNA analysis to identify genomic biomarkers in patients with newly diagnosed metastatic non-small cell lung cancer. Clin Cancer Res. 2019; 25(15):4691-4700.
11. Liu MC, Oxnard GR, Klein EA et al. Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. Ann Oncol. 2020; 31(6):745-759.
12. McCoach CE, Blakely CM, Banks KC, et al. Clinical utility of cell-free DNA for the detection of ALK fusions and genomic mechanisms of ALK inhibitor resistance in non-small cell lung cancer. Clin Cancer Res. 2018; 24(12):2758-2770.
13. Nadauld LD, McDonnell CH 3rd, Beer TM et al., The PATHFINDER Study: Assessment of the implementation of an investigational multi-cancer early detection test into clinical practice. Cancers (Basel). 2021; 13(14):3501.
14. Nakamura Y, Olsen S, Zhang N et al. Comprehensive genomic profiling of circulating tumor DNA in patients with previously treated metastatic colorectal cancer: Analysis of a real-world healthcare claims database. Curr Oncol. 2022 May 9; 29(5):3433-3448.
15. O'Boyle CJ, Siravegna G, Varmeh S, et al. Cell-free human papillomavirus DNA kinetics after surgery for human papillomavirus-associated oropharyngeal cancer. Cancer. 2022; 128(11):2193-2204.
16. Olsen S, Liao J, Hayashi H. Real-world clinical outcomes after genomic profiling of circulating tumor DNA in patients with previously treated advanced non-small cell lung cancer. Curr Oncol. 2022; 29(7):4811-4826.
17. Perakis S and Speicher MR. Emerging concepts in liquid biopsies. BMC Med. 2017; 15(1):75.
18. Pishvaian MJ, Bender RJ, Matrisian LM, et al. A pilot study evaluating concordance between blood-based and patient-matched tumor molecular testing within pancreatic cancer patients participating in the Know Your Tumor (KYT) initiative. Oncotarget. 2017; 8(48):83446–83456.
19. Sandulache VC, Williams MD, Lai SY, et al. Real-time genomic characterization utilizing circulating cell-free DNA in patients with anaplastic thyroid carcinoma. Thyroid. 2017; 27(1):81-87.
20. Schwaederle M, Husain H, Fanta PT, et al. Use of liquid biopsies in clinical oncology: pilot experience in 168 patients. Clin Cancer Res. 2016; 22(22):5497-5505.
21. Schwaederle M, Patel SP, Husain H, et al. Utility of genomic assessment of blood-derived circulating tumor DNA (ctDNA) in patients with advanced lung adenocarcinoma. Clin Cancer Res. 2017; 23(17):5101-5111.

22. Takeda M, Takahama T, Sakai K et al. Clinical application of the FoundationOne CDx assay to therapeutic decision-making for patients with advanced solid tumors. Oncologist.2021; 26(4):e588-e596.
23. Tan G, Chu C, Gui X, et al. The prognostic value of circulating cell-free DNA in breast cancer: A meta-analysis. Medicine. 2018; 97(13):e0197.
24. Thompson JC, Yee SS, Troxel AB et al. Detection of therapeutically targetable driver and resistance mutations in lung cancer patients by next-generation sequencing of cell-free circulating tumor DNA. Clin Cancer Res. 2016; 22(23):5772-5782.
25. Villaflor V, Won B, Nagy R, et al. Biopsy-free circulating tumor DNA assay identifies actionable mutations in lung cancer. Oncotarget. 2016; 7(41):66880–66891.
26. Woodhouse R, Li M, Hughes J et al. Clinical and analytical validation of FoundationOne Liquid CDx, a novel 324-Gene cfDNA-based comprehensive genomic profiling assay for cancers of solid tumor origin. PLoS One. 2020; 15(9):e0237802.
27. Yang PH, Tao Y, Luo J et al. Multivariate analysis of associations between clinical sequencing and outcome in glioblastoma. Neurooncol Adv. 2022; 4(1):vdac002.
28. Yang M, Topaloglu U, Petty WJ, et al. Circulating mutational portrait of cancer: manifestation of aggressive clonal events in both early and late stages. J Hematol Oncol. 2017; 10(1):100.
29. Zugazagoitia J, Gómez-Rueda A, Jantus-Lewintre E et al. Clinical utility of plasma-based digital next-generation sequencing in oncogene-driven non-small-cell lung cancer patients with tyrosine kinase inhibitor resistance. Lung Cancer. 2019; 134:72-78.

Government Agency, Medical Society, and Other Authoritative Publications:

1. American Cancer Society. Cancer Facts and Figures. Available at: https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures.html. Accessed on September 29, 2022.
2. Centers for Medicare and Medicaid Services (CMS). Decision memo for next-generation sequencing (NGS) for Medicare beneficiaries with advanced cancer. CAG-00450N. March 16, 2018. Available at: https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=290&SearchType=Advanced&CoverageSelection. Accessed on September 29, 2022.
3. Food and Drug Administration (FDA). P190032 FoundationOne® Liquid CDx approval order. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf19/P190032A.pdf Accessed on September 29, 2022.
4. Food and Drug Administration (FDA). 2020. FDA approves liquid biopsy NGS companion diagnostic test for multiple cancers and biomarkers. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-liquid-biopsy-ngs-companion-diagnostic-test-multiple-cancers-and-biomarkers. Accessed on September 29, 2022.
5. Food and Drug Administration (FDA). Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf20/P200010A.pdf. P200010 Guardant360® CDx approval order. Accessed on September 29, 2022.

6. Institute of Medicine. Evolution of translational omics: lessons learned and the path forward. Washington (DC): National Academies Press (US). 2012. Available at: https://www.ncbi.nlm.nih.gov/books/NBK202168/. Accessed on September 29, 2022.
7. Lindeman NI, Cagle PT, Aisner DL, et al. Updated molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors: Guideline from the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. Arch Pathol Lab Med. 2018; 142(3):321-346.
8. NCCN Clinical Practice Guidelines in Oncology®. ©2022 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http//www.nccn.org/index.asp. Accessed on September 23, 2022.
    - Non-Small-Cell Lung Cancer (V.4.2022). Revised September 2, 2022.
9. Merker JD, Oxnard GR, Compton C, et al. Circulating tumor DNA analysis in patients with cancer: American Society of Clinical Oncology and College of American Pathologists joint review. J Clin Oncol. 2018; 36(16):1631-1641.
10. U.S. Food and Drug Administration. Laboratory Developed Tests. Rockville, MD: FDA. September 27, 2018. Available at: https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/LaboratoryDevelopedTests/default.htm. Accessed on September 29, 2022.
11. U.S. Food and Drug Administration. P200010 Guardant360® CDx. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf20/P200010A.pdf. Accessed on September 29, 2022.

Websites for Additional Information

1. American Cancer Society. Liquid Biopsies: Past, Present, and Future. February 12, 2018. Available at: https://www.cancer.org/latest-news/liquid-biopsies-past-present-future.html. Accessed on September 29, 2022.
2. National Cancer Institute. Liquid biopsy: using DNA in blood to detect, track, and treat cancer. November 8, 2017. Available at: https://www.cancer.gov/news-events/cancer-currents-blog/2017/liquid-biopsy-detects-treats-cancer. Accessed on September 29, 2022.
3. National Cancer Institute. What is circulating tumor DNA and how is it used to diagnose and manage cancer?Last reviewed July 28, 2021. Available at: https://ghr.nlm.nih.gov/primer/testing/circulatingtumordna. Accessed on September 29, 2022.

Index

Circulogene
ClearID
FoundationOne Liquid CDx
Galleri
GeneStrat
Guardant360
Guardant 360 CDx
Guardant Reveal
Liquid Biopsy
Navaris
NavDx
OncoBEAM
elio Plasma Complete
Target Selector

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	11/10/2022	Medical Policy & Technology Assessment Committee (MPTAC) review. Description/Scope, Rationale, Background/Overview, References and Index sections updated. Updated Coding section with 01/01/2023 CPT changes; added 0356U.
	09/28/2022	Updated Coding section with 10/01/2022 CPT changes; added 0333U.
	06/29/2022	Updated Coding section with 07/01/2022 CPT changes; added 0326U.
	04/11/2022	Corrected typographic errors in Rationale section.
	04/01/2022	Updated Coding section with 04/01/2022 CPT changes; added 0306U, 0307U.
Revised	11/11/2021	MPTAC review. Removed "for cancer" from Title. Removed "for the diagnosis or treatment of cancer" from the INV/NMN statement. Description/Scope, Rationale, Background/Overview, References and Index sections updated.
Revised	02/11/2021	MPTAC review. Added "panel" to title and policy statement. Updated Description, Rationale, References and Index sections. Updated Coding section with 04/01/2021 CPT PLA changes to add 0242U; removed 0229U no longer applicable.

Reviewed	11/05/2020	MPTAC review. Rationale, Background/Overview and References sections updated. Updated Coding section with 01/01/2021 CPT changes; added 0229U, 0239U.
	07/01/2020	Updated Coding section with 07/01/2020 CPT changes; added 0179U.
	04/29/2020	Updated related topics in Description/Scope section.
Reviewed	11/07/2019	MPTAC review. Description/Scope, Rationale, Background, References, Websites and Index sections updated.
Reviewed	06/06/2019	MPTAC review. Description/Scope, Rationale, Background, References and Websites sections updated.
New	07/26/2018	MPTAC review.
New	07/18/2018	Hematology/Oncology Subcommittee review. Initial document development.