HEALTH PLANS
UNIVERSITY OF UTAH

Medical Policy

Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)

Policy MP-038

Origination Date: 07/31/2019

Reviewed/Revised Date: 03/15/2023

Next Review Date: 03/15/2024

Current Effective Date: 03/15/2023

Disclaimer:

1. Policies are subject to change in accordance with State and Federal notice requirements.
2. Policies outline coverage determinations for U of U Health Plans Commercial, Healthy U (Medicaid) and Advantage U (Medicare) plans. Refer to the "Policy" section for more information.
3. This Medical Policy does not guarantee coverage or payment of the service. The service must be a benefit in the member's plan and the member must be eligible for coverage at the time of service. Additional payment guidelines may be applied that are not included in this policy.

Description:

Normal and tumor cells commonly release small fragments of DNA into the blood. This is referred to as cell-free DNA (cfDNA). Tumors, metastases may also release entire cells into the circulation or circulating tumor cells (CTCs). The half-life of a CTC is short (1-2 hours), as they are cleared from the blood stream through extravasation into secondary organs. These cells can generate larger DNA fragments due to incomplete and random digestion of genomic DNA. Circulating tumor DNA (ctDNA) can be used for genomic characterization of the tumor. There are two approaches to detecting ctDNA, the first is targeted, which includes the analysis of known genetic mutations from the primary tumor which can impact therapy decisions (e.g., EGFR and ALK in non-small-cell lung cancer), or the second untargeted which is without knowledge of specific mutations present in the primary tumor. Whether it is targeted or untargeted, the approach to testing includes array comparative genomic hybridization, next-generation sequencing, and whole exome and genome sequencing.

Liquid biopsy refers to the analysis of circulating tumor DNA whether derived from cell free DNA (cfDNA) or circulating tumor cells (CTCs) as a method of noninvasively characterizing tumors and tumor genome from the peripheral blood. This differentiates it from the other common approach to analyzing tumor DNA through assessment of tumor tissue. Liquid biopsy is purported to be helpful in planning or monitoring treatment and determine recurrence though questions related to accuracy of this testing persist.

Policy Statement and Criteria

1. Commercial Plans

U of U Health Plans does NOT cover the use of circulating tumor DNA (ctDNA) and/or circulating tumor cells (CTCs) (liquid biopsy) for cancer management as it is considered investigational for all indications, including but not limited to the following testing examples (not all inclusive):

1. Cancer Intercept® Detect
2. CellMax® Life - (FirstSight$^{CRC™}$, LBx Liquid Biopsy™, PanCa™ Monitoring Test)
3. CellSearch®
4. CirculoGene® Theranostics
5. Colvera™
6. Cynvenio™ - (ClearID™, ClearID™ Solid Tumor Panel, ClearID™ Breast Cancer Test, ClearID® LungLB™ Lung Cancer Detection, ClearID® Biomarker Expression Assays)
7. FoundationACT®/Foundation Liquid® (FoundationOne® Liquid biopsies)
8. Galleri™ Test
9. GeneStrat®
10. Guardant360® *(except for non-small cell lung cancer – see below)*
11. IVDiagnostics (Velox™, Admonitrix™)
12. LiquidGx™
13. Signatera™
14. NeoLAB™ MDS/CMML Profile-Liquid BX
15. OncoBEAM™ for Colorectal Cancer
16. OncoBEAM™ for Lung Cancer
17. OncoBEAM™ for Melanoma
18. Oncotype DX AR-V7 Nucleus Detect
19. PlasmaSELECT®
20. Target Selector™
21. Tempus xF Liquid BX

U of U Health Plans covers Guardant 360 CDx Testing when the following criteria are met (Must meet A & B):

A. The individual has a diagnosis of metastatic (Stage III or IV) non-small cell lung cancer (NSCLC); and

B. One of the following:

   i. There is insufficient tumor tissue available for molecular analysis;

   ii. The individual does not have a biopsy-amendable lesion;

   iii. The individual is unable to undergo a tissue biopsy or an additional tissue biopsy due to documented medical reason (i.e. invasive tissue sampling is contraindicated due to the individual's clinical condition).

2. **Medicaid Plans**
   Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website at:
   http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

   CPT/HCPCS codes covered by Utah State Medicaid may still require further evaluation to determine medical necessity for coverage.

3. **Medicare Plans**
   Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicare policies and coverage, please visit their search website at:
   http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

Clinical Rationale

In another 2017 retrospective study, Rozenblum et. al. reviewed the impact of treatment decisions and clinical outcomes with the influence of hybrid capture (HC)-based next generation sequencing (NGS) testing. A total of 101 patients with advanced lung cancer had HC-based NGS with broad gene panels testing performed between November 2011 and October 2015 in a single cancer center. HC-based NGS was performed off-site on tumor samples with FoundationOne® (n = 82) or on blood samples using a liquid biopsy approach with Guardant360® if the tissue sample had been exhausted (n= 18). The study focused on gene analyses (GAs) with potential clinical relevance. A total of 101 patients were included (median age 63 years [53% females, 45% never-smokers, and 85% with adenocarcinoma]). HC-based NGS was performed upfront and after EGFR/ALK testing yielded negative or inconclusive results in 15% and 85% of patients, respectively. In 51.5% of patients, HC-based NGS was performed before first-line therapy, and in 48.5%, it was performed after treatment failure. HC-based NGS identified clinically actionable genomic alterations in 50% of patients, most frequently in EGFR (18%), Ret proto-oncogene (RET) (9%), ALK (8%), Mesenchymal-epithelial transition factor (MET) receptor tyrosine kinase gene (6%), and erb-b2 receptor tyrosine kinase 2 gene (ERBB2) (5%). In 15 patients, it identified EGFR/ALK aberrations after negative results of prior standard testing. Treatment strategy was changed for 43 patients (42.6%). The overall response rate in these patients was 65% (complete response 14.7%, partial response 50%). Median survival was not reached. Immunotherapy was administered in 33 patients, mostly without an actionable driver, with a presenting disease control rate of 32%, and an association with tumor mutation burden. In conclusion, HC-based NGS has several limitations, despite its strengths, and the efficacy of using it as a tool to aid in therapeutic decision making has not been carefully evaluated. Therefore, further large prospective trials are needed.

In 2016, Villaflor et. al. reviewed a descriptive single institution study of subjects with non-small cell lung cancer (NSCLC) undergoing analysis of circulating tumor DNA (ctDNA) using Guardant360 next-generation sequencing assay. Only 68 of the total 90 patients submitted for ctDNA analysis as part of

clinical care, provided informed consent for inclusion in this study. Thirty-eight samples from the 68 subjects were tested using the 54-gene ctDNA panel, which did not include ALK, RET, or ROS1 fusions, while the remaining 31 samples were analyzed on the 68-gene ctDNA panel. Tissue-based testing was performed on 44 subjects using 9 different testing platforms. The majority of patients had a diagnosis of lung adenocarcinoma (n = 55, 81%), with the remainder lung squamous cell carcinoma (n = 12, 17.7%) and other lung cancers (n = 1, 1.3%). Over 80% of patients had detectable ctDNA. Thirty-one patients had matched tissue and blood samples; there was no documented reason for lack of tissue results for the remaining 37 patients. In cases with detectable ctDNA and completed tissue analysis, an EGFR activating was found in both tissue and blood in 5 paired samples, and in only 2 tissue samples (71% concordance). The time between biopsy and blood draw ranged from 0 days to 7 years, with an average of 8.8 months and median of 1.4 years between biopsy and blood draw. The investigators found no correlation between concordance and timing of blood draw versus tissue biopsy. A total of 9 subjects with paired tissue and blood samples had an EGFR driver mutation identified in plasma and tissue (n = 5), plasma only (n = 1) or tissue only (n = 3). Eight of these individuals were treated with erlotinib or afatinib at first or second line. Two patients were still responding to therapy at the time of data analysis. Of the 6 remaining patients, the median progression-free survival was 11.5 months (range 7.5 months–29 months; 95% CI–5.7–28.7). The investigators concluded, the data suggest that biopsy-free ctDNA analysis is a viable first choice when the diagnostic tissue biopsy is insufficient for genotyping or if a repeated invasive tissue biopsy is not possible and/or preferred at the time of progression. However, they also concluded that the numbers in this series are small and further research in larger prospective cohorts is needed.

CellSearch®

In another systematic review Wang et. al. (2017) aimed to determine the prognostic value of HER2-positive circulating tumor cells (CTCs) in patients with breast cancer. A total of 550 patients within 4 studies with stage I to IV breast cancer were included. Two of the studies used the CellSearch® System to detect CTCs and the other 2 used reverse transcription polymerase chain reaction. HER2-positive CTCs were not associated with worse overall survival (OS [overall survival]; HR [hazard ratio], 1.489, 95% confidence interval [CI], 0.873-2.540, P = .144) or progression-free survival (PFS; HR, 1.543; 95% CI, 0.636-3.744; P = .338). In patients without metastasis, HER2-positive CTCs were associated with worse OS (HR, 2.273; 95% CI, 1.340-3.853; P = .002) and worse PFS (HR, 2.870; 95% CI, 1.298-6.343; P = .009). Subgroups of patients with metastasis had no significant relationship between HER2-positive CTCs and survival. The authors concluded, patients with breast cancer who have HER2-positive CTCs have worse OS and may benefit from more aggressive/targeted therapies. However, further studies are needed with consistent detection methods to evaluate the value of determining HER2-positive CTCs at different tumor stages and sampling times.

Lastly, a large multicenter study (Rack et. al., 2014) evaluated CTCs using the CellSearch® System in 2026 patients with early breast cancer before adjuvant chemotherapy and in 1492 patients after chemotherapy for a median of 35 months (range=0-54). Before chemotherapy, CTCs were detected in 21.5% of patients (n = 435 of 2026), with 19.6% (n = 136 of 692) of node-negative and 22.4% (n = 299 of 1334) of node-positive patients showing CTCs (P < .001). No association was found with tumor size, grading, or hormone receptor status. After chemotherapy, 22.1% of patients (n = 330 of 1493) were CTC positive. The presence of CTCs was associated with poor disease-free survival (DFS; P < .0001), distant DFS (P < .001), breast cancer-specific survival (P = .008), and overall survival (OS; P = .0002). CTCs were confirmed as independent prognostic markers in multivariable analysis for DFS (hazard ratio [HR] = 2.11; 95% confidence interval [CI] = 1.49 to 2.99; P < .0001) and OS (HR = 2.18; 95% CI = 1.32 to 3.59; P = .002). The prognosis was worst in patients with at least five CTCs per 30 mL blood (DFS: HR = 4.51, 95%

CI = 2.59 to 7.86; OS: HR = 3.60, 95% CI = 1.56 to 8.45). The presence of persisting CTCs after chemotherapy showed a negative influence on DFS (HR = 1.12; 95% CI = 1.02 to 1.25; P = .02) and on OS (HR = 1.16; 95% CI = 0.99 to 1.37; P = .06). Some limitations of this study include the short median follow-up (35 months) cells detected by the CellSearch system is limited to cells with expression of Epcam and cytokeratin and those numbers are relatively low. In conclusion, the data suggests that there may be clinical potential of using CTCs to assess the individual risk of patients at the time of primary diagnosis and in the absence of other strong quantitative markers, may be used for tailoring treatment.

OncoBEAM CRC®

A 2017 retrospective-prospective study (Vidal et. al.) analyzed the use of ctDNA during therapy as an alternative to determine baseline status and subsequent monitoring of RAS mutations as a factor of routine clinical practice. The OncoBEAM CRC® colorectal cancer assay was used to detect RAS mutations in plasma (collected before administration of anti-EGFR treatment) and in tissue samples from two Spanish institutions, from June 2009 to August 2016, which included 115 patients with histologically confirmed metastatic colorectal cancer (mCRC) that were anti-EGFR treatment naive. The median time from tumor tissue specimen collection to ctDNA collection was 47.5 days (range 0-1783 days). Of the 115 patients included in the study, 55 (47.8%) and 59 (51.3%) were shown to have RAS mutations in their tumor samples as detected by standard of care RAS tissue testing and as detected in ctDNA by OncoBEAM assay and standard techniques for tissue analysis was 93% (107/115 patients), kappa index 0.844 (95% CI 0.746-0.914). There were several limitations to this study, the fact that it was a retrospective analysis, a limited number of patients received long-term blood extractions, and the conclusions from associations with P-values marginally <0.05% were only from a few patients with specific clinic-pathological characteristics. While this study was encouraging, further trials are needed to determine clinical validity.

Other Commercially Available Tests for ctDNA (Liquid Biopsy):

Additional breast cancer studies included a prospective study by Liu et. al. in 2017 intended to establish the predictive value of the peptide-based nanomagnetic CTC isolation system (Pep@MNPs) as a promising tool in the management of metastatic breast cancer and Xu et. al. in 2018 which used a cross sectional study to examine CTC detection in subjects with newly diagnosed non-metastatic breast cancer. In the Lui study a direct association was not found between CTC status and tumor response at baseline (p=0.822) or at first clinical evaluation (p=0.367). The authors concluded that larger studies are needed to validate the clinical utility of the results found in this study. In the Xu 2018 cross-sectional study, The detection of CTCs was significantly less in benign tumors when compared to subjects with breast cancer (p=0.007). Also, higher triploid CTC counts were significant in subjects with increased tumor size (T1/T3: p=0.048; T2/T3: p=0.006). These authors also concluded, only a few studies have been published in CTC detection for non-metastatic breast cancer, therefore, in order to validate its clinical utility, more stringent and larger studies are needed.

A 2017 study on liquid biopsy for urologic malignancies (Di Meo et. al.) recognized that there is a growing trend towards exploring the use of a minimally invasive "liquid biopsy" to identify biomarkers in a number of cancers. Multiple aspects can be assessed in circulating cell-free DNA, including cell-free DNA levels, integrity, methylation and mutations. Other prospective liquid biopsy markers include circulating tumor cells, circulating RNAs (microRNA [miRNA], long non-coding RNAs [lncRNAs] and messenger RNA [mRNA]), cell-free proteins, peptides and exosomes have also emerged as non-invasive cancer biomarkers. These circulating molecules can be detected in various biological fluids, including blood, urine, saliva and seminal plasma. Conclusions from this study found that although CTCs, circulating RNAs, cell-free proteins, and exomes can be obtained through liquid biopsy, and may provide additional insight into tumor biology, it is still unclear as to whether the molecules are coming from the

tumor or the metastatic lesion. Further studies are warranted to help determine which area the molecules are coming from.

A 2014, randomized controlled trial (Smerage et. al.), reviewed the results of patients with metastatic breast cancer (MBC) that had persistent increase in circulating tumor cells (CTC) levels to test whether changing chemotherapy after one cycle of first-line therapy would improve the primary outcome of overall survival (OS). Patients who did not have increased CTC levels at baseline remained on initial therapy until progression (arm A), patients with initially increased CTC levels that decreased after 21 days of therapy remained on initial therapy (arm B), and patients with persistently increased CTC levels after 21 days of therapy were randomized to continue initial therapy (arm C1) or change to an alternative chemotherapy (arm C2). There were 595 eligible and evaluable patients, 276 (46%) of whom did not have increased CTC levels (arm A). Of patients with initially increased CTC levels, 31 (10%) were not retested, 165 were assigned to arm B, and 123 were randomized to arms C1 or C2. There was no difference in median OS between arms C1 (10.7 months) and C2 12.5 months; p=0.98). CTC levels were strongly prognostic, with a median OS for arms A, B, and C (C1 and C2 combined) of 35 months, 23 months, and 13 months, respectively (p<0.001). The authors concluded that this trial demonstrated the prognostic significance of CTCs in patients with MBC receiving first-line chemotherapy. Patients whose CTC levels persistently increased after 21 days of first-line chemotherapy and were switched early to an alternate cytotoxic therapy did not produce a different effect on OS then those who were not switched. Therefore, a more effective treatment other than standard chemotherapy is needed for this population.

Clinical Practice Guidelines and Recommendations:

Hayes, Inc. performed a Molecular Test Assessment of Guardant360 in August of 2020, their conclusions were “There is evidence to support the analytical validity and clinical validity of the Guardant360 assay; evidence supporting the clinical utility is limited. Available studies do not clearly show that the test results, when used to influence treatment decision-making, result in improved patient outcomes. In addition, most studies use a prior version of the test”. Latest review was in November of 2021, with no changes to their conclusions.

In April of 2022, Hayes updated their molecular test assessment for the FoundationOne CDx (F1CDx) (Foundation Medicine Inc.). No studies were identified in a search for peer-reviewed, published literature, nor was any evidence identified for the analytical validity, clinical validity, and clinical utility of the F1CDx test. Furthermore, the FDA premarket approval (PMA) process does not include an assessment of the analytical validity, clinical validity, and clinical utility for the test. Hayes concluded, “Although the F1CDx has received an FDA PMA, there is no evidence to support the analytical validity, clinical validity, and clinical utility of the test. Studies are needed that demonstrate a clear benefit to patient outcomes with the incorporation of F1CDx into treatment-making decisions”.

In March of 2020, Hayes updated their Molecular Test Assessment for the 70-gene assay FoundationOne Liquid (Foundation Medicine Inc.), it is considered a newer version of FoundationACT which only has a 62-gene assay. One analytical study and four clinical validity studies were found, no findings of clinical utility were found for either test and very low quality of evidence for the 62-gene version. No studies of clinical utility for either test were identified. Hayes found insufficient evidence supporting the use of FoundationOne Liquid to assist physicians in identifying treatment options and providing information about potential targeted therapies and/or clinical trials to better inform treatment decisions. As of 2023, this report was archived due to the technology withdrawn from clinical testing or taken off the market.

In October of 2022 Hayes reported on comprehensive molecular profiling (CMP) of circulating solid tumor DNA (ctDNA) for the intended use as a broad molecular profiling tool for monitoring. The authors concluded that based on a review of included abstracts, there appears to be very minimal support and

based on the professional guidelines there appears to be weak support for genetic testing for CMP of circulating solid tumor DNA as a broad molecular profiling tool to aid in monitoring for indicators of treatment response/failure or tumor progression.

Another October 2022 Hayes report looked at the aid in treatment selection from CMP of ctDNA for the intended use as a broad molecular profiling tool. The authors found that after a review of included abstracts there appears to be minimal support for CMP of circulating solid tumor DNA as a broad molecular profiling tool to aid in decision making regarding biomarker-matched treatment selection (including FDA-approved or off-label use). However, no abstracts reported a randomized trial design and very few studies included comparator study arms. Therefore, a more comprehensive review of full-text articles could alter these conclusions.

The NCCN guidelines for cutaneous melanoma (v.2.2023) reference papers on gene expression profiling (GEP) in the discussion of molecular characteristics of metastatic disease with the statement, "It remains unclear whether available GEP platforms are reliable predictive of outcome across the risk of spectrum melanoma."

NCCN guidelines for non-small cell lung cancer (v.1.2023) states that "T790M can be assessed using a FDA-approved test". "Data suggest that liquid biopsy may be considered at progression instead of at tissue biopsy to detect whether patients have T790M; however, if plasma testing is negative, then tissue biopsy is recommended".

Per the 2018 joint review (Merker et. al.) on the clinical use of circulating tumor DNA in patients with cancer, by the American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP), several proof-of-principle studies demonstrating correlations between changes in ctDNA levels and tumor response or outcomes as well as studies demonstrating that ctDNA can identify the emergence of resistance variants were identified. The review reported a lack of rigorous, prospective validation studies of ctDNA-based monitoring and no trials were identified demonstrating that treatment before relapse based on changes in CTCs improves patient outcomes. In, conclusion the evidence is insufficient to demonstrate test performance for currently available ctDNA and CTC tests for predicting relapse. Further high quality, well designed, large prospective studies are needed to explore and establish whether individualized therapeutic decisions based on ctDNA and CTC assays would improve net health outcomes.

Both the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network have published guidelines on use of CTC or cfDNA testing in certain malignancies. ASCO's clinical practice guideline on appropriate use of breast tumor biomarker assay to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer, last updated in 2016, recommended clinicians not use CTC's to guide decisions on adjuvant systemic therapy. The NCCN guidelines for breast cancer (v.2.2023) state that "In spite of its prognostic ability, CTC count has failed to show a predictive value."

Guardant360 CDx:

Guardant360 CDx is the first liquid biopsy companion diagnostic to be granted FDA approval for selecting NSCLC patients who have EGFR exon 19 deletions, L858R substitution variants, or T790M variants, for treatment with osimertinib. Patients who test negative for the variants detected should be referred for routine biopsy with tissue testing for EGFR variants. Testing for T790M using plasma specimens is most appropriate for consideration in patients for whom a tumor biopsy cannot be obtained, as the efficacy of osimertinib has not been established in T790M plasma-positive, tissue-negative or unknown patient populations.

Evidence for individuals with metastatic non-small cell lung cancer (NSCLC) who receive testing for EGFR TKI-sensitizing variants and other biomarkers/genetic variants/gene fusions in NSCLC using circulating tumor DNA (ctDNA) liquid biopsy testing with the Guardant360 CDx, includes several studies assessing the diagnostic characteristics of liquid biopsy compared with tissue biopsy. The relevant outcomes are overall survival (OS), disease specific survival (DSS), and test validity. Current evidence does not permit determining whether liquid or tissue biopsy is more strongly associated with patient outcomes or treatment response. Currently no randomized controlled trials (RCTs) providing evidence of the clinical utility of this test were identified. The Guardant360 CDx test has adequate evidence of clinical validity. A strategy of liquid biopsy followed by referral (reflex) tissue biopsy of negative liquid biopsies for the tests would result in an overall diagnostic performance similar to tissue biopsy. A chain of evidence demonstrates that the reflex testing strategy with the Guardant360 CDx test should produce outcomes similar to tissue testing. Patients who cannot undergo tissue biopsy would likely otherwise receive chemotherapy. These tests can identify patients for whom there is a net benefit of targeted therapy vs. chemotherapy with high specificity. The studies confirm that this technology determines meaningful improvement in the net health outcomes.

A prospective 2019 clinical utility study (Leighl et.al.) aimed to demonstrate the validity of comprehensive cell-free DNA (cfDNA) analysis (Guardant360) compared to physician discretion standard-of-care (SOC) tissue genotyping to identify guideline-recommended biomarkers in patients with previously untreated malignant non-small cell lung cancer (mNSCLC). The NILE study (Non-invasive versus Invasive Lung Evaluation; ClinicalTrials.gov; NCT03615443) enrolled 307 patients with biopsy proven, previously untreated, nonsquamous mNSCLC (stage IIIB/IV) undergoing physician discretion SOC tissue genotyping at one of 28 North American centers. Eligible patients were prospectively consented to this institutional review board–approved study and enrolled between July 2016 and April 2018. Patients with previously treated localized NSCLC (stage I–IIIA) were eligible if primary surgical resection and/or radiation treatment was completed at least 6 months prior to the development of metastatic disease and adjuvant systemic therapy was completed at least 6 weeks prior to study enrollment. Standard of care tissue genotyping included genomic testing and PD-L1 expression analysis. In accordance with NCCN guidelines, Standard of care tissue genotyping may include NGS, PCR "hotspot" testing, FISH and/or IHC, or Sanger sequencing. The tissue genotyping methodology and spectrum of biomarkers assessed was allowable per physician discretion based on the genotyping they would pursue in a normal and customary SOC setting. Patients submitted a pretreatment blood sample for cfDNA analysis utilizing a CLIA certified, CAP-accredited, New York State Department of Health–approved comprehensive NGS test (Guardant360; Guardant Health). The cfDNA test assesses for single-nucleotide variants (SNV) in 73 genes, insertion–deletion (indel) and fusion alterations, and copy-number amplifications in select genes including all eight guideline-recommended biomarkers and KRAS). The primary analysis for this study was based on results reported to the ordering provider according to study procedures. Among 282 patients, physician discretion SOC tissue genotyping identified a guideline-recommended biomarker in 60 patients versus 77 cfDNA identified patients (21.3% vs. 27.3%; $P < 0.0001$ for noninferiority). In tissue-positive patients, the biomarker was identified alone (12/60) or concordant with cfDNA (48/60), an 80% cfDNA clinical sensitivity for any guideline-recommended biomarker. For FDA-approved targets (EGFR, ALK, ROS1, BRAF) concordance was >98.2% with 100% positive predictive value for cfDNA versus tissue (34/34 EGFR-, ALK-, or BRAF-positive patients). Utilizing cfDNA, in addition to tissue, increased detection by 48%, from 60 to 89 patients, including those with negative, not assessed, or insufficient tissue results. The cfDNA median turnaround time was significantly faster than tissue (9 versus 15 days; $P < 0.0001$). Guideline-complete genotyping was significantly more likely (268 versus 51; $P < 0.0001$). In conclusion, the largest cfDNA study identified guideline-recommended

biomarkers at a rate at least as high as SOC tissue genotyping, with high tissue concordance, more rapidly and completely than tissue-based genotyping.

Schwaederle et. al. conducted a retrospective study in 2017, on the clinicopathologic and outcome data of 88 consecutively tested patients with lung adenocarcinoma followed at UC San Diego Moores Cancer Center, for whom molecular testing (ctDNA test) had been performed on their plasma (August 2014 until October 2015). Data was abstracted from the electronic medical record and performed in accordance with the Declaration of Helsinki. For all patients, this study (PREDICT-UCSD (Profile Related Evidence Determining Individualized Cancer Therapy; NCT02478931) was performed and consents obtained whenever necessary after approval by UCSD Institutional Review Board guidelines. Digital Sequencing of ctDNA (DNA) in all patients was performed by Guardant Health, Inc. (Guardant360, Redwood City, California. Comprehensive plasma ctDNA testing was performed in 88 consecutive patients; 34 also had tissue next generation sequencing; 29, other forms of genotyping; and 25 (28.4%) had no tissue molecular tests because of inadequate tissue or biopsy contraindications. Seventy-two patients (82%) had ≥ 1 ctDNA alteration(s); amongst these, 75% carried alteration(s) potentially actionable by FDA-approved (61.1%) or experimental drug(s) in clinical trials (additional 13.9%). The most frequent alterations were in TP53 (44.3% of patients), EGFR (27.3%), MET (14.8%), KRAS (13.6%), and ALK (6.8%) genes. The concordance rate for EGFR alterations was 80.8% (100% versus 61.5% (≤ 1 versus > 1 month between tests; P = 0.04)) for patients with any detectable ctDNA alterations. Twenty-five patients (28.4%) received therapy matching ≥ 1 ctDNA alteration(s); 72.3% (N=16/22) of the evaluable matched patients achieved stable disease ≥ 6 months (SD) or partial response (PR). Five patients with ctDNA-detected EGFR T790M were subsequently treated with a third generation EGFR inhibitor; all five achieved SD ≥ 6 months/PR. Patients with ≥ 1 alteration with ≥ 5% variant allele fraction (versus < 5%) had a significantly shorter median survival (P = 0.012). In conclusion, the authors found that ctDNA analysis detected alterations in the majority of patients with potentially targetable aberrations found at expected frequencies. Therapy matched to ctDNA alterations demonstrated appreciable therapeutic efficacy, suggesting clinical utility that warrants future prospective studies. However, when ctDNA results in no alterations detected, a tissue biopsy would be recommended as some tumors may not shed sufficient DNA into circulation to be detectable.

Applicable Coding

CPT Codes

0023U Oncology (acute myelogenous leukemia), DNA, genotyping of internal tandem duplication, p.D835, p.I836, using mononuclear cells, reported as detection or non-detection of FLT3 mutation and indication for or against the use of midostaurin

0037U Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden **FoundationACT® (FoundationOne Liquid biopsies)**

0091U Oncology (colorectal) screening, cell enumeration of circulating tumor cells, utilizing whole blood, algorithm, for the presence of adenoma or cancer, reported as a positive or negative result **(CellMax® Life-FirstSight^{CRC})**

0179U Oncology (non-small cell lung cancer), cell-free DNA, targeted sequence analysis of 23 genes (single nucleotide variations, insertions and deletions, fusions

without prior knowledge of partner/breakpoint, copy number variations), with report of significant mutation(s)

0229U BCAT1 (Branched chain amino acid transaminase 1) or IKZF1 (IKAROS family zinc finger 1) (eg, colorectal cancer) promoter methylation analysis **(includes Colvera®)**

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 **(includes FoundationOne® Liquid CDx)**

86152 Cell enumeration using immunologic selection and identification in fluid specimen (e.g., circulating tumor cells in blood) **(CellSearch)**;

86153 Cell enumeration using immunologic selection and identification in fluid specimen (e.g., circulating tumor cells in blood); physician interpretation and report, when required **(CellSearch)**

81479 Unlisted molecular pathology procedure

81599 Unlisted multianalyte assay with algorithmic analysis **(when specified as molecular profiling for malignant tumors, e.g., Molecular Intelligence Service [Target Now], GeneKey or OncInsights)**

HCPCS Codes

No applicable codes

References:

1. Aggarwal, Charu, et al. "Clinical implications of plasma-based genotyping with the delivery of personalized therapy in metastatic non–small cell lung cancer." JAMA oncology 5.2 (2019): 173-180.
2. Di Meo A, Bartlett J, Cheng Y, et al. Liquid biopsy: A step forward towards precision medicine in urologic malignancies. Mol Cancer. 2017;16(1):80.
3. Gupta, Rohan, et al. "Guardant360 Circulating Tumor DNA Assay Is Concordant with FoundationOne Next-Generation Sequencing in Detecting Actionable Driver Mutations in Anti-EGFR Naive Metastatic Colorectal Cancer." The oncologist 25.3 (2020): 235.
4. Gutierrez, Martin E., et al. "Genomic profiling for KRAS, NRAS, BRAF, microsatellite instability, and mismatch repair deficiency among patients with metastatic colon cancer." JCO Precision Oncology 3 (2019): 1-9.
5. Harris, LN, Ismaila, N, McShane, LM, et al. Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology (ASCO) Clinical Practice Guideline. J Clin Oncol. 2016Apr 1;34(10):1134-50. Accessed 3/25/2019. PMID: 26858339
6. Hayes, Inc. (2022). "Comprehensive Molecular Profiling of Circulating Solid Tumor DNA for the Intended Use as a Broad Molecular Profiling Tool for Monitoring". Reviewed October 18, 2022. Accessed: February 15, 2023. Available at: https://evidence.hayesinc.com/report/pmi.monitoring5369
7. Hayes, Inc. (2019) GTE report "FoundationOne Liquid (Foundation Medicine Inc.)" Available at: https://evidence.hayesinc.com/report/gte.foundationact4493 Accessed: July 30, 2019. Archived 04/06/2021.
8. Hayes, Inc. (2022) Molecular Test Assessment. "FoundationOne CDx (Foundation Medicine Inc.) for the Intended Use as a Broad Molecular Profiling Tool". Accessed February 14, 2023. Available at: https://evidence.hayesinc.com/report/gte.foundationone4467
9. Hayes, Inc. Molecular Test Assessment. "Guardant360 (Guardant Health Inc.)" Annual Review: November 19, 2021. Accessed December 31, 2020. Available at: https://evidence.hayesinc.com/report/gte.guardant3767
10. Karlin, Kirill, et al. "Therapy alteration of solid tumors based on FoundationOne comprehensive genome profiling assay." (2019): e14742-e14742.

11. Kim ST, Lee WS, Lanman RB, et al. Prospective blinded study of somatic mutation detection in cell-free DNA utilizing a targeted 54-gene next generation sequencing panel in metastatic solid tumor patients. Oncotarget. 2015;6(37):40360-40369
12. Leighl, Natasha B., 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." Clinical Cancer Research 25.15 (2019): 4691-4700.
13. Lindeman, N. I., et al. (2018). "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 142(3): 321-346.
14. Liu XR, Shao B, Peng JX, et al. Identification of high independent prognostic value of nanotechnology based circulating tumor cell enumeration in first-line chemotherapy for metastatic breast cancer patients. Breast. 2017; 32:119-125.
15. Lokhandwala T, Bittoni MA, Dann RA, et al. Costs of Diagnostic Assessment for Lung Cancer: A Medicare Claims Analysis. Clin Lung Cancer. 2017;18(1):e27-e34.
16. 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 Mar 5:Jco2017768671. PMID: 29504847
17. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology® "Prostate Cancer v.3.2022. [cited 01/18/2022]; Available from:http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
18. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology®: Cutaneous Melanoma. Version 1.2023. Accessed: February 15, 2023. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx
19. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology®: Breast Cancer. Version 2.2023 Accessed: February 15, 2023. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx
20. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology®: Non-Small Cell Lung Cancer. Version 1.2023; Accessed: February 15, 2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
21. Rack B, Schindlbeck C, Juckstock J, et al. Circulating tumor cells predict survival in early average-to-high risk breast cancer patients. J Natl Cancer Inst. May 15 2014;106(5). PMID 24832787
22. Rozenblum AB, Ilouze M, Dudnik E, et al. Clinical Impact of Hybrid Capture-Based Next-Generation Sequencing on Changes in Treatment Decisions in Lung Cancer. J Thorac Oncol. 2017;12(2):258-268.
23. Rubinstein, Jill C., Norman G. Nicolson, and Nita Ahuja. "Next-generation sequencing in the management of gastric and esophageal cancers." Surgical Clinics 99.3 (2019): 511-527.
24. Schwaederle MC, 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. Sep 1 2017;23(17):5101-5111. PMID 28539465
25. Smerage, JB, Barlow, WE, Hortobagyi, GN, et al. Circulating tumor cells and response to chemotherapy in metastatic breast cancer: SWOG S0500. J Clin Oncol. 2014 Nov1;32(31):3483-9. PMID: 24888818
26. Tay, Timothy Kwang Yong, and Puay Hoon Tan. "Liquid Biopsy in Breast Cancer: A Focused Review." Archives of Pathology & Laboratory Medicine (2020).
27. U.S. Food and Drug Administration (FDA). FDA News Release "FDA Approves First Liquid Biopsy Next-Generation Sequencing Companion Diagnostic Test". August 7, 2020. Accessed: December 30, 2020 at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-liquid-biopsy-next-generation-sequencing-companion-diagnostic-test
28. Vidal J, Muinelo L, Dalmases A, et al. Plasma ctDNA RAS mutation analysis for the diagnosis and treatment monitoring of metastatic colorectal cancer patients. Ann Oncol. Jun 1 2017;28(6):1325-1332. PMID 28419195
29. 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. PMID: 27602770
30. Wang CH, Chang CJ, Yeh KY, et al. The prognostic value of HER2-positive circulating tumor cells in breast cancer patients: a systematic review and meta-analysis. Clin Breast Cancer. Aug 2017;17(5):341-349. PMID 28347604
31. Xu L, Jia S, Li H, et al. Characterization of circulating tumor cells in newly diagnosed breast cancer. Oncol Lett. 2018; 15(2):2522-2528.
32. Zugazagoitia, J., et al. "Clinical utility of plasma-based digital next-generation sequencing in patients with advance-stage lung adenocarcinomas with insufficient tumor samples for tissue genotyping." Annals of Oncology 30.2 (2019): 290-296.
33. Zugazagoitia, Jon, 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 134 (2019): 72-78.

The codes for treatments and procedures applicable to this policy are included 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.

U of U Health Plans makes no representations and accepts no liability with respect to the content of any external information cited or relied upon in this policy. U of U Health Plans updates its Coverage Policies regularly, and reserves the right to amend these policies and give notice in accordance with State and Federal requirements.