BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.153 Tumor-Informed Circulating Tumor DNA Testing for Cancer Management

Annual Effective Policy Date: January 1, 2024

Original Policy Date: July 2022

Related Policies:

2.04.141 - Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)
2.04.151 - Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Breast Cancer
2.04.45 - Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Non-Small-Cell Lung Cancer (EGFR, ALK, BRAF, ROS1, RET, MET, KRAS, HER2, PD-L1, TMB)
2.04.53 - Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Metastatic Colorectal Cancer (KRAS, NRAS, BRAF, and HER2)

Tumor-Informed Circulating Tumor DNA Testing for Cancer Management

Description

Description

This evidence review addresses the use of tumor-informed circulating tumor DNA (ctDNA) testing for cancer management. The purpose of tumor-informed ctDNA testing in individuals with cancer is to predict disease course to inform treatment decisions and to monitor for recurrence following treatment.

OBJECTIVE

The objective of this evidence review is to determine whether using tumor-informed circulating tumor DNA (ctDNA) testing improves the net health outcome in individuals with bladder, breast, colorectal, esophageal, or non-small cell lung cancer, or in individuals with solid tumors who are receiving immunotherapy.

POLICY STATEMENT

Tumor-informed circulating tumor DNA testing (e.g., Signatera) is considered **not medically necessary** for all indications.

POLICY GUIDELINES

None

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Some Plans may have contract or benefit exclusions for genetic testing.

FDA REGULATORY STATUS

Signatera is a laboratory developed test regulated under CLIA. Signatera has been developed and its performance characteristics determined by Natera, the CLIA-certified laboratory performing the test. The test has not been cleared or approved by the US Food and Drug Administration (FDA), but has received 3 Breakthrough Device Designations from FDA:

- In May 2019, Signatera was granted a Breakthrough Device Designation (BDD) for the detection of ctDNA in localized or advanced colorectal cancer patients to optimize the use of chemotherapy alone or in combination with durvalumab.
- A March 2021 press release announced that FDA granted 2 additional BDDs covering new intended uses.[1,]

RATIONALE

Summary of Evidence

For individuals with colorectal cancer (CRC) who receive tumor-informed circulating tumor DNA (ctDNA) testing with Signatera to guide treatment decisions and monitor for recurrence, the evidence includes a systematic review, 4 noncomparative studies (N = 1449), and 1 retrospective comparative study (N = 48). Relevant outcomes are overall survival, disease-specific survival, test validity, other test performance measures, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality. The systematic review and nonrandomized studies have reported an association between ctDNA results measured at diagnosis, following surgery, during adjuvant therapy, and during surveillance after curative treatment and prognosis, but these studies are limited by a lack of comparison to tests used for the same purpose, imprecise estimates due to small sample sizes, and clinical heterogeneity of study populations. No study reported management changes made in response to ctDNA test results. A retrospective observational study found no advantage to surveillance with Signatera compared to standard surveillance conducted according to NCCN guidelines (p>.99 for sensitivity and specificity compared to imaging). There is no direct evidence that the use of the test improves health outcomes, and indirect evidence is not sufficient to draw conclusions about clinical validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with breast cancer who receive tumor-informed ctDNA testing with Signatera to guide treatment decisions and monitor for recurrence, the evidence includes 2 noncomparative studies (N = 133). Relevant outcomes are overall survival, disease-specific survival, test validity, other test performance measures, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality. One study evaluated Signatera testing for disease surveillance following primary treatment, and 1 reported the association of test results at different timepoints with response to neoadjuvant chemotherapy. Although the studies found an association of test results with prognosis, the studies are limited by a lack of comparison to tests used for the same purpose, imprecise estimates due to small sample sizes, and clinical heterogeneity of study populations. No study reported management changes made in response to ctDNA test results. There is no direct evidence that the use of the test improves health outcomes, and indirect evidence is not sufficient to draw conclusions about clinical validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with bladder cancer who receive tumor-informed ctDNA testing with Signatera to guide treatment decisions and monitor for recurrence, the evidence includes 1 uncontrolled prospective cohort study (N = 68) and 1 retrospective subgroup analysis from a randomized controlled trial (N = 581). Relevant outcomes are overall survival, disease-specific survival, test validity, other test performance measure, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality. The prospective study reported an association between Signatera test results at diagnosis, during chemotherapy treatment, and during surveillance following cystectomy to prognosis. The retrospective analysis reported an association between test results and response to atezolizumab treatment. Study limitations, including a lack of

comparison to tests used for the same purpose preclude drawing conclusions about clinical validity and usefulness. No study reported management changes made in response to ctDNA test results. There is no direct evidence that the use of the test improves health outcomes, and indirect evidence is not sufficient to draw conclusions about clinical validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with NSCLC who receive tumor-informed ctDNA testing with Signatera to guide treatment decisions and monitor for recurrence, the evidence includes 1 subgroup analysis of participants enrolled in a prospective observational study (N = 24). Relevant outcomes are overall survival, disease-specific survival, test validity, other test performance measures, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality. Of 14 individuals with confirmed relapse, 13 (93%) had a positive ctDNA test (defined as at least 2 single-nucleotide variants detected). Of 10 individuals with no relapse after a median follow up of 775 days, (range 688 to 945 days), 1 had a positive ctDNA test (10%). This study"s small sample size and lack of a comparator preclude drawing conclusions about clinical validity. There is no direct evidence that the use of the test improves health outcomes, and indirect evidence is not sufficient to draw conclusions about clinical validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with esophageal cancer who receive tumor-informed ctDNA testing with Signatera to guide treatment decisions and monitor for recurrence, the evidence includes 1 noncomparative, retrospective study (N = 17). Relevant outcomes are overall survival, disease-specific survival, test validity, other test performance measure, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality. Patients who were ctDNA-positive before surgery had significantly poorer disease-free survival (DFS) (p<.042), with a median DFS of 32.0 months versus 63.0 months in ctDNA-negative preoperative patients. This study was limited by its small number sample size and retrospective design. There is no direct evidence that the use of the test improves health outcomes. Due to the study's limitations and lack of additional supporting studies, the evidence is not sufficient to draw conclusions on clinical validity. Additionally, the management pathway for Signatera testing in esophageal cancer has not been clearly defined. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with solid tumors who receive tumor-informed ctDNA testing with Signatera to monitor response to immunotherapy, the evidence includes a subgroup analysis of individuals enrolled in a nonrandomized trial of pembrolizumab (N = 106). Relevant outcomes are overall survival, disease-specific survival, test validity, other test performance measures, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality. The subgroup analysis evaluated Signatera testing to monitor response to immunotherapy in individuals with advanced solid tumors who were enrolled in a Phase II clinical trial of pembrolizumab. Lower-than-median ctDNA levels at baseline were associated with improved overall survival (adjusted hazard ratio [HR], 0.49; 95% confidence interval [CI], 0.29 to 0.83) and progression-free survival (adjusted HR, 0.54; 95% CI, 0.34 to 0.85). The study was limited by a small sample size, variability in results across different tumor types, and lack of a comparison to standard methods of monitoring response to treatment. There is no direct evidence that the use of the test improves health outcomes, and indirect evidence is not sufficient to draw conclusions about clinical validity. Additionally, the management pathway for Signatera testing for monitoring response to immunotherapy has not been clearly defined. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society of Clinical Oncology

The American Society of Clinical Oncology (ASCO) 2022 guideline update on biomarkers for systemic therapy in metastatic breast cancer (MBC) does not recommend the use of circulating tumor DNA (ctDNA) as a biomarker to monitor the response to therapy (Type of recommendation: informal consensus-based; Quality of evidence: low; Strength of recommendation: moderate). The guidelines also provide the following recommendations:

- "Patients with locally recurrent unresectable or metastatic hormone receptor-positive and human epidermal growth factor receptor 2 (HER2)-negative breast cancer who are candidates for a treatment regimen that includes a phosphatidylinositol 3-kinase inhibitor and hormonal therapy should undergo testing for PIK3CA mutations using next-generation sequencing of tumor tissue or circulating tumor DNA (ctDNA) in plasma to determine their eligibility for treatment with the phosphatidylinositol 3-kinase inhibitor alpelisib plus fulvestrant. If no mutation is found in ctDNA, testing in tumor tissue, if available, should be used as this will detect a small number of additional patients with PIK3CA mutations (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong)."
- "There are insufficient data at present to recommend routine testing for ESR1 mutations to guide therapy for hormone receptor-positive, HER2-negative MBC. Existing data suggest reduced efficacy of aromatase inhibitors (AIs) compared with the selective estrogen receptor degrader fulvestrant in patients who have tumor or ctDNA with ESR1 mutations (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate)."
- "There are insufficient data to recommend routine use of ctDNA to monitor response to therapy among patients with MBC (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate)."

National Comprehensive Cancer Network

National Comprehensive Cancer Network (NCCN) guidelines either do not specifically address tumor-informed ctDNA testing for the cancer types included in this review, or do not provide specific recommendations for use.

The guideline on colon cancer states: "There is currently insufficient evidence to recommend use of circulating tumor DNA (ctDNA) assays outside of a clinical trial. De-escalation of care is not recommended based on ctDNA results. Participation in clinical trials is encouraged."[16,]

The guideline on breast cancer states that for recurrent/stage IV disease: "Tissue or plasma-based circulating tumor DNA (ctDNA) assays may be used. Tissue-based assays have greater sensitivity, but ctDNA may reflect tumor heterogeneity more accurately." Additionally, "For HR-positive/HER2-negative breast cancer, assess for PIK3CA mutations with tumor or liquid biopsy to identify candidates for alpelisib plus fulvestrant. PIK3CA mutation testing can be done on tumor tissue or ctDNA in peripheral blood (liquid biopsy). If liquid biopsy is negative, tumor tissue testing is recommended." The relevant discussion for these recommendations is pending an update.[17,]

The guideline on esophageal and esophagogastric junction cancers states: "The genomic alterations of solid cancers may be identified by evaluating circulating tumor DNA (ctDNA) in the blood, hence a form of "liquid biopsy." Liquid biopsy is being used more frequently in patients with advanced disease, particularly those who are unable to have a clinical biopsy for disease surveillance and management. The detection of mutations/alterations in DNA shed from esophageal and EGJ carcinomas can identify targetable alterations or the evolution of clones with altered treatment response profiles. Therefore, for patients who have metastatic or advanced esophageal/esophagogastric cancers who may be unable to undergo a traditional biopsy or for disease progression monitoring, testing using a validated NGS-based comprehensive genomic profiling assay performed in a CLIA-approved laboratory may be considered. A negative result should be interpreted with caution, as this does not exclude the presence of tumor mutations or amplifications."[18,]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
June 2022	New policy - Add to Pathology/Laboratory section	Policy created with literature review through March 11, 2022. Tumor-informed circulating tumor DNA testing is considered investigational for all indications.
December 2023	Replace policy	Policy updated with literature review through July 20, 2023; references added. Policy statements unchanged.