BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.141 Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)

Effective Policy Date: January 1, 2023

Original Policy Date: October 2016

Related Policies:

2.04.111 - Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management
2.04.115 - Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies
2.04.151 - Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Breast Cancer
2.04.155 - Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Prostate Cancer (BRCA1/2, Homologous Recombination Repair Gene Alterations, Microsatellite Instability/Mismatch Repair, Tumor Mutational Burden)
2.04.33 - Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer
2.04.53 - Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer (KRAS, NRAS, BRAF, MMR/MSI, HER2, and TMB)
2.04.61 - Gene Expression Profile Testing and Circulating Tumor DNA Testing for Predicting Recurrence in Colon Cancer
2.04.77 - Somatic Genetic Testing to Select Individuals with Melanoma or Glioma for Targeted Therapy or Immunotherapy

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

Description

Description

Circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) in peripheral blood, referred to as "liquid biopsy," have several potential uses for guiding therapeutic decisions in patients with cancer or being screened for cancer. This evidence review evaluates uses for liquid biopsies *not addressed in a separate review*. If a separate evidence review exists, then conclusions reached there supersede conclusions here.

OBJECTIVE

The objective of this evidence review is to determine whether circulating tumor DNA or circulating tumor cell testing in patients with cancer or at risk of developing cancer improves the net health outcome compared with standard screening as well as diagnostic and management practices. This evidence review evaluates uses for liquid biopsies *not addressed in a separate review*. If a separate evidence review exists, then conclusions reached there supersede conclusions here. This review does not address the use of blood-based testing for "driver mutations" to select therapy in non-small-cell lung cancer or metastatic colorectal cancer, use of blood-based testing for detection or risk assessment of prostate cancer, use of AR-V7 circulating tumor cells for metastatic prostate cancer, or liquid biopsy to select targeted treatment for breast, ovarian, prostate, or pancreatic cancer.

POLICY STATEMENT

The use of circulating tumor DNA and/or circulating tumor cells is considered **investigational** for all indications reviewed herein (see Policy Guidelines).

POLICY GUIDELINES

This policy does not address the use of blood-based testing for "driver mutations" to select therapy in non-small-cell lung cancer or metastatic colorectal cancer, use of blood-based testing for detection or risk assessment of prostate cancer, the use of AR-V7 circulating tumor cells for metastatic prostate cancer, or liquid biopsy to select treatment for breast, ovarian, prostate, or pancreatic cancer. Refer to the following related policies for indications not covered here:

- 2.04.33 - Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer
- 2.04.53 Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer
- 2.04.61 Multigene Expression Assay for Predicting Recurrence in Colon Cancer
- 2.04.77 Somatic Genetic Testing to Select Individuals with Melanoma or Glioma for Targeted Therapy or Immunotherapy
- 2.04.111 Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management
- 2.04.115 - Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies
- 2.04.151 Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Breast Cancer
- 2.04.155 Biomarker Testing (Including Liquid Biopsy) for Ovarian Cancer Management

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

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

The FDA maintains a list of cleared or approved companion diagnostic tests at https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools.

RATIONALE

Summary of Evidence

For individuals who have advanced cancer who receive testing of circulating tumor DNA (ctDNA) to select targeted treatment, the evidence includes observational studies. Relevant outcomes are overall survival (OS), disease-specific survival, test validity, morbid events, and medication use. Given the breadth of methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently, and these data are lacking for the indications covered in this review. The clinical validity of FoundationOne Liquid compared to tissue biopsy with FoundationOne comprehensive genetic profiling was evaluated in 4 industry-sponsored observational studies. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether variant analysis of ctDNA can replace variant analysis of tissue. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have advanced cancer who receive testing of circulating tumor cells (CTCs) to select targeted treatment, the evidence includes observational studies. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, morbid events, and medication use. Given the breadth of methodologies available to assess CTCs, the clinical validity of each commercially available test must be established independently, and these data are lacking. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of CTCs can replace variant analysis of tissue. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have cancer who receive testing of ctDNA to monitor treatment response, the evidence includes observational studies. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, morbid events, and medication use. Given the breadth of methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently, and these data are lacking. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of ctDNA should be used to monitor treatment response. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have cancer who receive testing of CTCs to monitor treatment response, the evidence includes a single randomized controlled trial (RCT), observational studies, and systematic reviews of observational studies. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, morbid events, and medication use. Given the breadth of methodologies available to assess CTCs, the clinical validity of each commercially available test must be established independently, and these data are lacking. The available RCT found no effect on OS when patients with persistently increased CTC levels after first-line chemotherapy were switched to alternative cytotoxic therapy. Other studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of CTCs should be used to monitor treatment response. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have received curative treatment for cancer who receive testing of ctDNA to predict the risk of relapse, the evidence includes observational studies. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, morbid events, and medication use. Given the breadth of methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently, and these data are lacking. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of ctDNA should be used to predict relapse response. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have received curative treatment for cancer who receive testing of CTCs to predict the risk of relapse, the evidence includes observational studies. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, morbid events, and medication use. Given the breadth of methodologies available to assess CTCs, the clinical validity of each commercially available test must be established independently, and these data are lacking. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of CTCs should be used to predict relapse response. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic and at high-risk for cancer who receive testing of ctDNA to screen for cancer, no evidence was identified. Relevant outcomes are OS, disease-specific survival, test accuracy, and test validity. Published data on clinical validity and clinical utility are lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic and at high-risk for cancer who receive testing of CTCs to screen for cancer, the evidence includes observational studies. Relevant outcomes are OS, disease-specific survival, test accuracy, and test validity. Given the breadth of methodologies available to assess CTCs, the clinical validity of each commercially available test must be established independently, and these data are lacking. Published studies reporting clinical outcomes and/or clinical utility are lacking. 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.

National Comprehensive Cancer Network

There is no general National Comprehensive Cancer Network (NCCN) guideline on the use of liquid biopsy. Refer to treatment recommendations by cancer type for specific recommendations.

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

1. Alix-Panabieres C, Pantel K. Clinical Applications of Circulating Tumor Cells and Circulating Tumor DNA as Liquid Biopsy. Cancer Discov. May 2016; 6(5): 479-91. PMID 26969689
2. 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. Jun 01 2018; 36(16): 1631-1641. PMID 29504847
3. Clark TA, Chung JH, Kennedy M, et al. Analytical Validation of a Hybrid Capture-Based Next-Generation Sequencing Clinical Assay for Genomic Profiling of Cell-Free Circulating Tumor DNA. J Mol Diagn. Sep 2018; 20(5): 686-702. PMID 29936259
4. Zhou C, Yuan Z, Ma W, et al. Clinical utility of tumor genomic profiling in patients with high plasma circulating tumor DNA burden or metabolically active tumors. J Hematol Oncol. Nov 06 2018; 11(1): 129. PMID 30400986
5. Mazel M, Jacot W, Pantel K, et al. Frequent expression of PD-L1 on circulating breast cancer cells. Mol Oncol. Nov 2015; 9(9): 1773-82. PMID 26093818
6. Lv Q, Gong L, Zhang T, et al. Prognostic value of circulating tumor cells in metastatic breast cancer: a systemic review and meta-analysis. Clin Transl Oncol. Mar 2016; 18(3): 322-30. PMID 26260915
7. 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
8. Zhang L, Riethdorf S, Wu G, et al. Meta-analysis of the prognostic value of circulating tumor cells in breast cancer. Clin Cancer Res. Oct 15 2012; 18(20): 5701-10. PMID 22908097
9. Huang X, Gao P, Song Y, et al. Relationship between circulating tumor cells and tumor response in colorectal cancer patients treated with chemotherapy: a meta-analysis. BMC Cancer. Dec 18 2014; 14: 976. PMID 25519477
10. Groot Koerkamp B, Rahbari NN, Buchler MW, et al. Circulating tumor cells and prognosis of patients with resectable colorectal liver metastases or widespread metastatic colorectal cancer: a meta-analysis. Ann Surg Oncol. Jul 2013; 20(7): 2156-65. PMID 23456317
11. Fan JL, Yang YF, Yuan CH, et al. Circulating Tumor Cells for Predicting the Prognostic of Patients with Hepatocellular Carcinoma: A Meta Analysis. Cell Physiol Biochem. 2015; 37(2): 629-40. PMID 26344495
12. Ma X, Xiao Z, Li X, et al. Prognostic role of circulating tumor cells and disseminated tumor cells in patients with prostate cancer: a systematic review and meta-analysis. Tumour Biol. Jun 2014; 35(6): 5551-60. PMID 24563278
13. Wang FB, Yang XQ, Yang S, et al. A higher number of circulating tumor cells (CTC) in peripheral blood indicates poor prognosis in prostate cancer patients--a meta-analysis. Asian Pac J Cancer Prev. 2011; 12(10): 2629-35. PMID 22320965
14. de Bono J., Scher HI, Montgomery RB, et al. Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. Clin Cancer Res. 2008;14(19):6302-6309. PMID
15. Sun T, Zou K, Yuan Z, et al. Clinicopathological and prognostic significance of circulating tumor cells in patients with head and neck cancer: a meta-analysis. Onco Targets Ther. 2017; 10: 3907-3916. PMID 28831265

16. Mocellin S, Hoon D, Ambrosi A, et al. The prognostic value of circulating tumor cells in patients with melanoma: a systematic review and meta-analysis. Clin Cancer Res. Aug 01 2006; 12(15): 4605-13. PMID 16899608
17. Smerage JB, Barlow WE, Hortobagyi GN, et al. Circulating tumor cells and response to chemotherapy in metastatic breast cancer: SWOG S0500. J Clin Oncol. Nov 01 2014; 32(31): 3483-9. PMID 24888818
18. Chidambaram S, Markar SR. Clinical utility and applicability of circulating tumor DNA testing in esophageal cancer: a systematic review and meta-analysis. Dis Esophagus. Feb 11 2022; 35(2). PMID 34286823
19. 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
20. Thalgott M, Rack B, Horn T, et al. Detection of Circulating Tumor Cells in Locally Advanced High-risk Prostate Cancer During Neoadjuvant Chemotherapy and Radical Prostatectomy. Anticancer Res. Oct 2015; 35(10): 5679-85. PMID 26408743
21. Deneve E, Riethdorf S, Ramos J, et al. Capture of viable circulating tumor cells in the liver of colorectal cancer patients. Clin Chem. Sep 2013; 59(9): 1384-92. PMID 23695297
22. Rink M, Chun FK, Dahlem R, et al. Prognostic role and HER2 expression of circulating tumor cells in peripheral blood of patients prior to radical cystectomy: a prospective study. Eur Urol. Apr 2012; 61(4): 810-7. PMID 22277196
23. Gazzaniga P, de Berardinis E, Raimondi C, et al. Circulating tumor cells detection has independent prognostic impact in high-risk non-muscle invasive bladder cancer. Int J Cancer. Oct 15 2014; 135(8): 1978-82. PMID 24599551
24. Schulze K, Gasch C, Staufer K, et al. Presence of EpCAM-positive circulating tumor cells as biomarker for systemic disease strongly correlates to survival in patients with hepatocellular carcinoma. Int J Cancer. Nov 2013; 133(9): 2165-71. PMID 23616258
25. Vashist YK, Effenberger KE, Vettorazzi E, et al. Disseminated tumor cells in bone marrow and the natural course of resected esophageal cancer. Ann Surg. Jun 2012; 255(6): 1105-12. PMID 22580852
26. Msaouel P, Koutsilieris M. Diagnostic value of circulating tumor cell detection in bladder and urothelial cancer: systematic review and meta-analysis. BMC Cancer. Aug 04 2011; 11: 336. PMID 21816094
27. Tang L, Zhao S, Liu W, et al. Diagnostic accuracy of circulating tumor cells detection in gastric cancer: systematic review and meta-analysis. BMC Cancer. Jun 27 2013; 13: 314. PMID 23806209

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

Date	Action	Description
September 2016	New policy	
September 2018	Replace policy	Policy updated with a literature review through March 5, 2018. References 2-14, 16, 18, 22-24, 28-34, and 37 added. Language added to Policy Guidelines that policy does not apply to the use of blood-based testing for EGFR mutations. Clarifying edit to policy statement, add 'or" to the following sentence: "The use of circulating tumor DNA and/or circulating tumor cells...€ Policy Guidelines updated to clarify that this review does not address the use of blood-based testing for epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer or the use of AR-V7 circulating tumor cells for metastatic prostate cancer. Both of these topics are covered in separate reviews. Correct policy number from 2.01.141 to 2.04.141
March 2019	Replace policy	Policy updated with a literature review through October 1, 2018, reference 15 added. Liquid biopsy for metastatic colorectal cancer was removed from 2.04.141 and will be added to 2.04.53 at the next update. Clarifying edit to policy statement, add 'reviewed herein" to stress that other indications are reviewed in separate policies.
September 2019	Replace policy	Policy updated with a literature review through May 29, 2019; references added, references on NCCN updated. Policy statements unchanged.
December 2020	Replace policy	Policy updated with a literature review through June 15, 2020; no references added. Liquid biopsy to select targeted treatment for breast cancer was removed from this policy and will be added to the new policy (to be developed) on Gene Expression Profiling and Circulating Tumor DNA Testing for Breast Cancer Management. Policy statements unchanged.
December 2021	Replace policy	Policy updated with a literature review through July 8, 2021; no references added. Policy statement unchanged.
December 2022	Replace policy	Policy updated with a literature review through July 8, 2022; references added. Policy statement unchanged.