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)

Annual Effective Policy Date: January 1, 2024

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)
2.04.156 - Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Ovarian Cancer (BRCA1, BRCA2, Homologous Recombination Deficiency, Tumor Mutational Burden, Microsatellite Instability/Mismatch Repair)
2.04.33 - Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate 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)
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 (BRAF)

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 individuals 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.

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 (liquid biopsy) to select targeted treatment for breast cancer, non-small cell lung cancer, melanoma/glioma, ovarian cancer, pancreatic cancer, and prostate cancer, the use of liquid biopsy to select immune checkpoint inhibitor therapy, tumor-Informed circulating tumor DNA testing for cancer management, comprehensive genomic profiling for selecting targeted cancer therapies, the use of blood-based testing for detection or risk assessment of prostate cancer; or the use of AR-V7 circulating tumor cells for metastatic prostate 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
- 2.04.45 - 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 and Immunotherapy in Metastatic Colorectal Cancer (KRAS, NRAF, 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 (*BRAF*)
- 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 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)
- 2.04.156 Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Ovarian Cancer (BRCA1, BRCA2, Homologous Recombination Deficiency, Tumor Mutational Burden, Microsatellite Instability/Mismatch Repair)

Plans may need to alter local coverage medical policy to conform to state law regarding coverage of biomarker testing.

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 or have state mandates for biomarker testing coverage.

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.

Certain liquid biopsy-based assays have been cleared or approved by the FDA as companion diagnostic tests (Table 1).[2,] These indication are addressed in other evidence opinions and are listed here for information only. Refer to the associated evidence opinion (Column 5) for details.

Table 1. FDA Cleared or Approved Liquid Biopsy Companion Diagnostic Tests

Diagnostic Name (Manufacturer)	Indication	Biomarker	Drug Trade Name (Generic)	Related Evidence Opinion
Agilent Resolution ctDx FIRST assay	NSCLC	KRAS	Krazati (adagrasib)	2.04.45
cobas EGFR Mutation Test v2 (Roche Molecular Systems, Inc.)	NSCLC	*EGFR* (*HER1*)	Tagrisso (osimertinib)	2.04.45
	NSCLC	*EGFR* (*HER1*)	Iressa (gefitinib)	2.04.45
	NSCLC	*EGFR* (*HER1*)	Tarceva (erlotinib)	2.04.45
	NSCLC	*EGFR* (*HER1*)	Gilotrif (afatinib)	2.04.45
FoundationOne Liquid CDx (Foundation Medicine, Inc.)	NSCLC	*EGFR (HER1)*	Exkivity (mobocertinib)	2.04.45
	NSCLC	*EGFR (HER1)*	Iressa (gefitinib)	2.04.45
	NSCLC	*EGFR (HER1)*	Tagrisso (osimertinib)	2.04.45
	NSCLC	*EGFR (HER1)*	Tarceva (erlotinib)	2.04.45
	NSCLC	*MET*	Tabrecta (capmatinib)	2.04.45
	NSCLC	*ROS1*	Rozlytrek (entrectinib)	2.04.45
	NSCLC	ALK	Alecensa (alectinib)	2.04.45
	Ovarian Cancer	*BRCA1* and *BRCA2*	Rubraca (rucaparib)	2.04.156
	Solid Tumors	*ROS1*	Rozlytrek (entrectinib)	5.01.31
	Breast Cancer	*PIK3CA*	Piqray (alpelisib)	2.04.151
	Metastatic Castrate Resistant Prostate Cancer	*BRCA1,BRCA2* and *ATM*	Lynparza (olaparib)	2.04.155

	Metastatic Castrate Resistant Prostate Cancer	*BRCA1 and BRCA2*	Rubraca (rucaparib)	2.04.155
Guardant360 CDx (Guardant Health, Inc.)	NSCLC	*EGFR* (*HER1*)	Tagrisso (osimertinib)	2.04.45
	NSCLC	*EGFR* (*HER1*)	Rybrevant (amivantamb)	2.04.45
	NSCLC	*KRAS*	Lumakras (sotorasib)	2.04.45
	NSCLC	ERBB2	ENHERTU (fam-trastuzumab deruxtecan-nxki)	2.04.45
	Breast Cancer	*ESR1* *ERB2*	Orserdu (elacestrant) ENHERTU (fam-trastuzumab deruxtecan-nxki)	2.04.151 In development for 2.04.151
therascreen PIK3CA RGQ PCR Kit (QIAGEN GmbH)	Breast Cancer	*PIK3CA*	Piqray (alpelisib)	2.04.151

Source: FDA (2023)[2,]

FDA: US Food and Drug Administration; NSCLC: non-small cell lung cancer

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.

American Society of Clinical Oncology

In 2022, the American Society of Clinical Oncology (ASCO) published a Provisional Clinical Opinion on somatic genetic testing in individuals with metastatic or advanced cancer.[27,] The Opinion addressed circulating tumor DNA (ctDNA) testing under additional topics but did not include a specific statement with a strength of recommendation rating. The panel noted, "There is a growing body of evidence on the clinical utility of genomic testing on cfDNA in the plasma," citing the systematic review conducted by Merker et al (2018)[3,] The panel also noted that ASCO will update that systematic review over the next few years.

The discussion also included the following points:

- "In patients without tissue-based genomic test results, treatment may be based on actionable alterations identified in cfDNA."
- "Testing is most helpful when genomic testing is indicated, archival tissue is unavailable, and new tumor biopsies are not feasible."
- "cfDNA levels themselves may be prognostic and early cfDNA dynamics may serve as an early predictor of therapy response or resistance."
- "Ongoing studies are expected to better delineate the clinical utility of serial liquid biopsies."

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 specifically for liquid biopsy. The national coverage determination on next generation sequencing (NCD 90.2) would apply to liquid biopsy tests meeting the criteria below:[28,]

"Effective for services performed on or after March 16, 2018, the Centers for Medicare & Medicaid Services (CMS) has determined that Next Generation Sequencing (NGS) as a diagnostic laboratory test is reasonable and necessary and covered nationally, when performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, when ordered by a treating physician, and when all of the following requirements are met:

a. Patient has:

i. either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; and

ii. not been previously tested with the same test using NGS for the same cancer genetic content, and

iii. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

b. The diagnostic laboratory test using NGS must have:

i. Food & Drug Administration (FDA) approval or clearance as a companion in vitro diagnostic; and,

ii. an FDA-approved or -cleared indication for use in that patient"s cancer; and,

iii. results provided to the treating physician for management of the patient using a report template to specify treatment options."

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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
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.
December 2023	Replace policy	Policy updated with literature review through July 17, 2023; references added. Policy statement unchanged.