

02.04.16 Circulating Tumor Cells for Cancer Management

Original Effective Date: March 2008

Review Date: December 2025

Revised: October 2023

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This Medical Policy document describes the status of medical technology at the time the document was developed. Since that time, new technology may have emerged, or new medical literature may have been published. This Medical Policy will be reviewed regularly and updated as scientific and medical literature becomes available; therefore, policies are subject to change without notice.

Related Policies:

- [Molecular Testing Utilization Management Program](#)

Summary

Description

Circulating tumor cells (CTCs) are released from a primary tumor and/or a metastatic site into the bloodstream. The half-life of a CTCs in the bloodstream is short (1 to 2 hours), and CTCs are cleared through extravasation into secondary organs. Most assays detect CTCs through the use of surface epithelial markers such as epithelial cell adhesion molecules (EpCAM) and cytokeratins. The primary reason for detecting CTCs is prognostic, through quantification of circulating levels.

The detection and monitoring of circulating tumor cells (CTCs) is being investigated in the screening, prognosis, prediction of response to therapy, or monitoring the clinical course in individuals with primary or metastatic cancer.

Summary of Evidence

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, progression-free survival, recurrence-free survival, 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 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, progression-free survival, recurrence-free survival, 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 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.

Additional Information

Not applicable.

OBJECTIVE

The objective of this evidence review is determine whether circulator tumor cells (CTCs) 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 does not address liquid biopsies using circulating tumor DNA (ctDNA) see [Molecular Testing Utilization Management Program](#)*

PRIOR APPROVAL

Not applicable

Note: For prior approval requirements and Wellmark Lab Management Guidelines related to molecular testing see [Molecular Testing Utilization Management Program](#)

POLICY

The use of circulating tumor cells (CTCs) (e.g., CellSearch®) is considered **investigational** for all indications in the management of cancer (screening, prognosis, prediction of response to therapy, or monitoring the clinical course). The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

POLICY GUIDELINES

NOTE: Iowa House File 2668 (Iowa Code section 514C.36) requires that certain health plans issued or renewed on or after January 1, 2025 “provide coverage for biomarker testing for the purposes of diagnosing, treating, appropriately managing, or monitoring a disease or condition in a covered person when the biomarker testing has demonstrated clinical utility.” Iowa House File 2668 defines clinical utility as “sufficient medical and scientific evidence indicating that the use of a biomarker test will provide meaningful information that affects treatment decisions and guides improvement of net health outcomes, including an improved quality of life or longer survival.” Wellmark has reviewed this Medical Policy in light of Iowa House File 2668.

Coding

See the [Codes](#) table for details.

BACKGROUND

Detecting Circulating Tumor Cells

Circulating tumor cell assays usually start with an enrichment step that increases the concentration of CTCs, either by biologic properties (expression of protein markers) or physical properties (size, density, electric charge). Circulating tumor cells can then be detected using immunologic, molecular, or functional assays.

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.

RATIONALE

This evidence review was created in March 2008 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through November 2025.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Selecting Treatment in Advanced Cancer

Clinical Context and Test Purpose

One purpose of circulating tumor cells (CTCs) of individuals who have advanced cancer is to inform a decision regarding treatment selection (e.g., whether to select a targeted treatment or standard treatment). Treatment selection is informed by tumor type, grade, stage, patient performance status and preference, prior treatments, and the molecular characteristics of the tumor such as the presence of driver mutations.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest are individuals with advanced cancer for whom the selection of treatment depends on the molecular characterization of the tumor(s).

Interventions

The test being considered is CTCs.

Comparators

For individuals who are able to undergo a biopsy, molecular characterization of the tumor is performed using standard tissue biopsy samples. Individuals unable to undergo a biopsy generally receive standard therapy.

Outcomes

CTCs are easier to obtain and less invasive than tissue biopsies. Positive CTC testing results lead to the initiation of appropriate treatment (e.g., targeted therapy) without a tissue biopsy. False-positive CTC test results lead to the initiation of inappropriate therapy, which could shorten progression-free survival.

In individuals able to undergo a tissue biopsy, negative CTCs reflex to tissue testing. In individuals unable to undergo a tissue biopsy, a negative CTC result would not change empirical treatment. Therefore, health outcomes related to negative test results do not differ between CTC testing and tissue biopsy.

The timing of interest for survival outcomes varies by type of cancer.

Review of Evidence

Clinically Valid

The clinical validity of each commercially available CTC test must be established independently, which has not been done to date.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Trials of using CTCs to select treatment are ongoing, see [Ongoing and Unpublished Clinical Trials](#).

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The evidence is insufficient to demonstrate test performance for currently available CTC tests; therefore, no inferences can be made about clinical utility.

Section Summary: Selecting Treatment in Advanced Cancer

For indications reviewed herein, there is no direct evidence that selecting targeted treatment using CTCs improves the net health outcome compared with selecting targeted treatment using tumor tissue testing. Trials are ongoing. 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 evidence is insufficient to demonstrate test performance for currently available CTC tests that are reviewed herein; therefore, no inferences can be made about clinical utility through a chain of evidence.

Monitoring Treatment Response in Cancer

Clinical Context and Test Purpose

Monitoring of treatment response in cancer may be performed using tissue biopsy or imaging methods. Another proposed purpose of CTC testing in individuals who have advanced cancer is to monitor treatment response, which could allow for changing therapy before clinical progression and potentially improve outcomes.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest are individuals who are being treated for cancer.

Interventions

The test being considered is CTCs.

Comparators

Standard monitoring methods for assessing treatment response are tissue biopsy or imaging methods.

Outcomes

The outcome of primary interest are progression-free survival (PFS) and overall survival (OS).

The timing of interest for survival outcomes varies by type of cancer.

Predicting Risk of Relapse

Clinical Context and Test Purpose

Monitoring for relapse after curative therapy in individuals with cancer may be performed using imaging methods and clinical examination. Another proposed purpose of CTC testing in individuals who have cancer is to monitor for residual tumor, which could lead to early treatment that would eradicate residual disease and potentially improve outcomes.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest are individuals who have received curative treatment for cancer.

Interventions

The test being considered is CTCs.

Comparators

Standard monitoring methods for detecting relapse are imaging methods and clinical examination.

Outcomes

The outcome of primary interest are (OS), disease-specific survival, test validity, morbid events, and medication use.

The timing of interest for survival outcomes varies by type of cancer.

Review of Evidence

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic reviews and meta-analyses describing an association between CTCs and poor prognosis have been reported for metastatic breast cancer, colorectal cancer (CRC), hepatocellular cancer, multiple myeloma, prostate cancer, head and neck cancer, and melanoma.

Rack et al (2014) published the results of a large multicenter study in which CTCs were analyzed in 2026 patients with early breast cancer before adjuvant chemotherapy and in 1492 patients after chemotherapy using the CellSearch® System. After chemotherapy, 22% of patients were CTC-positive, and CTC positivity was negatively associated with prognosis.

Smaller studies demonstrating associations between persistent CTCs and relapse have been published in prostate cancer, CRC, bladder cancer, liver cancer, and esophageal cancer.

The clinical validity of each commercially available CTC test must be established independently, which has not been done to date.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Chain of Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

A chain of evidence to demonstrate clinical utility requires an evidence-based management pathway. There is not an explicated, evidence-based management pathway for the use of CTCs to guide early treatment before relapse.

No trials were identified demonstrating that treatment before relapse based on changes in CTCs improves patient outcomes.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs. Smerage et al (2014) reported on the results of an RCT of patients with metastatic breast cancer and persistently increased CTC levels to test whether changing chemotherapy after 1 cycle of first-line therapy could improve overall survival (OS; the primary study outcome). 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; $p=.98$). Circulating tumor cell 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 ($p<.001$). This trial showed the prognostic significance of CTCs in patients, which rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The evidence is insufficient to demonstrate test performance for currently available CTC tests; therefore, no inferences can be made about clinical utility through a chain of evidence.

Section Summary: Monitoring Treatment Response in Cancer

For indications reviewed herein, there is no direct evidence that using CTCs to monitor treatment response improves the net health outcome compared with standard methods. 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 evidence is insufficient to demonstrate test performance for currently available CTC tests that are reviewed herein; therefore, no inferences can be made about clinical utility through a chain of evidence.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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 updated their guideline for biomarkers for systemic therapy in metastatic breast cancer which includes the following recommendation regarding circulating tumor cell testing:

- “There are insufficient data to recommend routine use of circulating tumor cells to monitor response to therapy among patients with MBC (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).”

In 2022, the American Society of Clinical Oncology updated their guideline for biomarkers for adjuvant endocrine and chemotherapy in early-stage breast cancer which includes the following recommendation regarding circulating tumor cell testing:

- “If a patient has node-negative or node-positive ER-positive, HER2-positive, or triple-negative breast cancer (TNBC), the clinician should not use CTC test to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: strong)”

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) is a nonprofit alliance of cancer centers throughout the United States. NCCN develops the Clinical Practice Guidelines in Oncology which are recommendations aimed to help health care professionals diagnose, treat, and manage patients with cancer. These guidelines evolve continuously as new treatments and diagnostics emerge and may be utilized by Wellmark BlueCross BlueShield when determining medical necessity and investigational according to this medical policy.

Treatment by Cancer Type	Current Clinical Practice Guideline
Bladder Cancer	Does not include or indicate the use of circulating tumor cells (CTCs) in the management of bladder cancer.
Breast Cancer	“The clinical use of circulating tumor cells (CTC) or circulating DNA (ctDNA) in metastatic breast cancer for disease assessment and monitoring. Patients with persistently increased CTC after 3 weeks of first-line chemotherapy have a poor PFS and OS. In spite of its prognostic ability, CTC count has failed to show a predictive value. A prospective, randomized, phase 3 trial (SWOG S0500) evaluated the clinical utility of serial enumeration of CTC in patients with metastatic breast cancer. According to the study results, switching to an alternative cytotoxic therapy after 3 weeks of first-line chemotherapy in patients with persistently increased CTC did not affect either PFS or OS”

Treatment by Cancer Type	Current Clinical Practice Guideline
Colorectal Cancer	Does not include or indicate the use of circulating tumor cells (CTCs) in the management of colorectal cancer.
Esophageal and Esophagogastric Junction Cancers	Does not include or indicate the use of circulating tumor cells (CTCs) in the management of esophageal and esophagogastric cancer.
Head and Neck Cancer	Does not include or indicate the use of circulating tumor cells (CTCs) in the management of head and neck cancers.
Hepatocellular Cancer	Does not include or indicate the use of circulating tumor cells (CTCs) in the management of hepatocellular cancer.
Lung Cancer - Non-Small Cell Lung Cancer - Small Cell Lung Cancer	Does not include or indicate the use of circulating tumor cells (CTCs) in the management of non-small cell lung cancer or small cell lung cancer.
Melanoma (Cutaneous)	Does not include or indicate the use of circulating tumor cells (CTCs) in the management of melanoma (cutaneous).
Multiple Myeloma	Does not include or indicate the use of circulating tumor cells (CTCs) in the management of multiple myeloma.
Prostate Cancer	Does not include or indicate the use of circulating tumor cells (CTCs) in the management of prostate cancer.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review can be located at clinicaltrials.gov.

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CODES

To report provider services, use appropriate CPT codes, HCPCS codes, Revenue codes, and/or ICD diagnosis codes.

Codes	Number	Description
CPT		
	86152	Cell enumeration using immunologic selection and identification in fluid specimen (e.g., circulating tumor cells in blood)

	86153	Cell enumeration using immunologic selection and identification in fluid specimen (e.g., circulating tumor cells in blood); physician interpretation and report, when required
	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 FirstSight ^{CRC} , CellMax Life
	0337U	Oncology (plasma cell disorders and myeloma), circulating plasma cell immunologic selection, identification, morphological characterization, and enumeration of plasma cells based on differential CD138, CD38, D19, and CD45 protein biomarker expression, peripheral blood CELLSEARCH [®] Circulating Multiple Myeloma Cell (CMMC) Test, Menarini Silicon Biosystems, Inc, Menarini Silicon Biosystems, Inc
	0338U	Oncology (solid tumor), circulating tumor cell selection, identification, morphological characterization, detection and enumeration based on differential EpCAM, cytokeratins 8, 18, and 19, and CD45 protein biomarkers, and quantification of HER2 protein biomarker-expressing cells, peripheral blood CELLSEARCH [®] HER2 Circulating Tumor Cell (CTC-HER2) Test, Menarini Silicon Biosystems, Inc, Menarini Silicon Biosystems, Inc
	0490U	Oncology (cutaneous or uveal melanoma), circulating tumor cell selection, morphological characterization and enumeration based on differential CD146, high molecular-weight melanoma-associated antigen, CD34 and CD45 protein biomarkers, peripheral blood CELLSEARCH [®] Circulating Melanoma Cell (CMC) Test by Menarini Silicon Biosystems
	0491U	Oncology (solid tumor), circulating tumor cell selection, morphological characterization and enumeration based on differential epithelial cell adhesion molecule (EpCAM), cytokeratins 8, 18, and 19, CD45 protein biomarkers, and quantification of estrogen receptor (ER) protein biomarker-expressing cells, peripheral blood CELLSEARCH [®] ER Circulating Tumor Cell (CTC-ER) Test, Menarini Silicon Biosystems
	0492U	Oncology (solid tumor), circulating tumor cell selection, morphological characterization and enumeration based on differential epithelial cell adhesion molecule (EpCAM), cytokeratins 8, 18, and 19, CD45 protein biomarkers, and quantification of PD-L1 protein biomarker-expressing cells, peripheral blood CELLSEARCH [®] PD-L1 Circulating Tumor Cell (CTC-PDL1) Test, Menarini Silicon Biosystems
HCPCS		

	None	
Type of Service	Laboratory	
Place of Service	Outpatient	

POLICY HISTORY

Date	Action	Action
December 2025	Annual Review	Policy Renewed
October 2024	Annual Review	Policy Renewed
October 2023	Annual Review	Policy Revised
September 2022	Annual Review	Policy Revised
November 2021	Interim Review	Policy Revised
September 2021	Annual Review	Policy Revised
September 2020	Annual Review	Policy Revised
September 2019	Annual Review	Policy Revised
December 2018	Interim Review	Policy Revised
September 2018	Annual Review	Policy Revised
September 2017	Annual Review	Policy Renewed
September 2016	Annual Review	Policy Renewed
October 2015	Annual Review	Policy Renewed
November 2014	Annual Review	Policy Renewed
January 2014	Annual Review	Policy Renewed
January 2013	Annual Review	Policy Renewed
January 2012	Annual Review	Policy Renewed
January 2011	Annual Review	Policy Renewed

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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