



BlueCross BlueShield of Louisiana

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Detection of Circulating Tumor Cells in the Management of Patients with Cancer

Policy # 00147

Original Effective Date: 01/31/2005

Current Effective Date: 01/15/2014

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers detection and quantification of circulating tumor cells (CTCs) in the management of patients with cancer to be **investigational**.*

Background/Overview

The prognosis of cancer patients is often determined by the occurrence of metastatic disease. Studies have suggested that the presence of CTCs in patients with metastatic carcinoma is associated with short survival. The detection of CTCs might be useful for assessing prognosis and guiding cancer therapy.

Circulating tumor cells are malignant cells that are found in the peripheral blood and originate from primary or metastatic tumors. Circulating tumor cells could potentially provide prognostic information that could guide treatment decisions or aid in the monitoring of response to treatment. Circulating tumor cells have been documented in multiple tumor types, such as breast, prostate, lung, and colorectal carcinomas; the largest body of data comes from studies of women with metastatic breast cancer. Circulating tumor cells have also been investigated as an additional prognostic factor in nonmetastatic breast cancer and could be used to determine the need for additional adjuvant chemotherapy.

Detection Methods

Research over the past 10 years has focused on the development of methodologies with improved sensitivity and specificity. Physical techniques such as size filtration, density gradient centrifugation, and microscopic morphology continue to be used. However, biological techniques such as immunomagnetic isolation, flow cytometry, immunofluorescent microscopy, reverse transcriptase-polymerase chain reaction (RT-PCR), polymerase chain reaction (PCR), and fluorescence in situ hybridization (FISH) have been added to provide required specificity.

The CellSearch[™] system (Veridex) is an example of immunofluorescent technology. The technique involves identification of the CTCs in blood, which are tagged using antibody-coated magnetic beads that recognize cell surface antigens. The cells are then labeled with fluorescent dyes, which can then be quantified by a semiautomated fluorescent-based microscopy system.

Note: This policy does not address techniques for the detection of bone marrow disseminated tumor cells (DTCs) or circulating cell-free deoxyribonucleic acid (DNA).



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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

The CellSearch system (Veridex) has received FDA marketing clearance through the 510(k) process for monitoring metastatic breast cancer, for monitoring metastatic colorectal cancer, and for monitoring metastatic prostate cancer. Veridex LLC, a Johnson & Johnson company, markets the CellSearch system. It uses automated instruments manufactured by Immunicon Corp. for sample preparation (Cell Tracks[®] AutoPrep)[‡] and analysis (CellSpotterAnalyzer[®])[‡], together with supplies, reagents, and epithelial cell control kits manufactured by Veridex.

Centers for Medicare and Medicaid Services (CMS)

No Medicare national coverage determination.

Rationale/Source

Numerous studies have reported the association of CTCs with prognosis and/or response to treatment in patients with various types of cancer. However, despite these correlational studies, to complete the causal chain, there must be evidence that patient management decisions based on CTC levels increases the duration or quality of life or decreases adverse events. Literature searches have not identified any published studies that have been published that prospectively evaluate patient treatment decisions and/or health outcomes in patients managed with and without the monitoring of CTCs. Following is a description of the available literature, organized by clinical condition.

Metastatic Breast Cancer

A comprehensive meta-analysis of studies on the association between CTCs and health outcomes in patients with breast cancer was published in 2012 by Zhang and colleagues. The analysis included studies that included more than 30 patients, used RT-PCR, CellSearch or another immunofluorescent technique to detect CTCs and reported survival data stratified by CTC status. A total of 49 studies met eligibility criteria. In a pooled analysis of 12 studies on metastatic breast cancer; CTC positivity was associated with a significantly increased risk of disease progression (hazard ratio [HR]: 1.78, 95% confidence interval [CI]: 1.52-2.09). Circulating tumor cell positivity was associated with a significantly increased risk of death in patients with metastatic breast cancer (HR: 2.23, 95% CI: 2.09 to 2.60, 19 studies). The authors presented a subgroup analysis by detection method; this analysis included studies on non-metastatic and metastatic breast cancer. Pooled analyses of studies using CellSearch found that CTC positivity significantly increased the likelihood of disease progression (HR: 1.85, 95% CI: 1.53 to 2.25, 12 studies) and death (HR: 2.45, 95% CI: 2.10 to 2.85, 18 studies). Studies using RT-PCR also found that CTC positivity was significantly associated with disease progression and death.

A previous 2011 meta-analysis by Zhao and colleagues considered only studies on CTC detected by RT-PCR. A total of 24 studies met inclusion criteria, 5 of which included metastatic breast cancer. The authors did not conduct a separate analysis of studies on metastatic breast cancer. In a pooled analysis of data from 15 studies with 2,894 patients, the presence of CTCs was significantly associated with a lower overall survival (OS) (HR: 3.00, 95% CI: 2.29-3.94) and a lower relapse-free survival (RFS) (HR: 2.67, 95% CI: 2.09-3.42). The authors noted substantial heterogeneity among studies including differences in sampling time, detection methods and demographic or clinical characteristics of the study population.

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Representative prospective studies using CellSearch immunofluorescent technology for identifying CTC in women with metastatic breast cancer are described below:

In 2004, Cristofanilli and colleagues published a multicenter study that included 177 patients with measurable metastatic breast cancer who were followed up for 38.7 weeks or longer. Using the CellSearch System, they measured the number of CTCs before initiating a new line of therapy and at first follow-up (4.5 +/- 2.4 weeks after baseline sample). Also tested were 145 normal subjects and 200 patients with benign breast diseases. The authors report detecting 2 or fewer epithelial cells per 7.5 milliliters (mL) of blood in all normal subjects and patients with benign breast diseases. Using a statistically validated threshold of 5 cells per 7.5 mL of blood, they found that patients below threshold at baseline ($n = 90$; 51%) had longer median progression-free survival (PFS) (7.0 vs. 2.7 months, respectively; $p < 0.001$) and OS greater than 18 months vs. 10.1 months, respectively; $p < 0.001$) than those above threshold ($n = 87$; 49%). Survival duration of a subgroup ($n = 33$) with values above threshold at baseline but below threshold at first follow-up (i.e., after the first cycle of therapy) was similar to that of patients below threshold at baseline. This subgroup's median survival also was significantly longer than survival of those who remained above threshold despite therapy. Multivariate analysis showed that being below threshold for level of CTCs was the most statistically significant independent predictor of longer PFS and OS of all parameters studied, including hormone receptor status, HER-2/neu status, site of metastases, etc.

Nole and colleagues tested 80 patients with metastatic breast cancer for circulating tumor cell levels before starting a new treatment and after 4 weeks, 8 weeks, at the first clinical evaluation, and every 2 months thereafter. Forty-nine patients had 5 or more cells at baseline. At the multivariate analysis, baseline number of CTCs was associated with PFS (HR 2.5; 95% 1.2–5.4). The risk of progression for patients with 5 or more CTCs at the last available follow-up was 5 times the risk of patients with 0–4 CTCs at the same point (HR: 5.3; 95% CI: 2.8–10.4). Patients with rising or persistent counts of 5 or more CTCs at last available follow-up showed a statistically significant higher risk of progression with respect to patients with less than 5 CTCs at both times of blood sampling.

In 2012, Pierga and colleagues in France reported findings from a prospective series that included 267 patients with metastatic breast cancer who were starting first-line chemotherapy. CTCs were analyzed before starting treatment, before the 2nd cycle of treatment, at the first radiologic evaluating before the 3rd or 4th cycle of treatment. At baseline, 44% of patients were positive for CTC (> 5 CTC per 7.5/mL blood). Patients were followed for a median of 14.9 months. During follow-up, there were 57 deaths (21%), and 161 (60%) experienced tumor progression. Baseline CTC count was a strong predictor of PFS ($p < 0.0001$). The median PFS was 19.9 months in patients with 0 CTC and 8.2 months in patients with > 5 CTC per 7.5 mL blood. Baseline CTC was also significantly associated with OS ($p = 0.0002$). In multivariate analysis, baseline CTC positivity was an independent prognostic factor for both PFS and OS.

Metastatic Prostate Cancer

In 2011, Wang and colleagues published a meta-analysis of studies on the association between CTCs and prognosis in patients with metastatic castration-resistant or hormone refractory prostate cancer. The authors searched the literature for studies with at least 30 patients and sufficient data to calculate relative risk (RR) of OS. The authors identified 19 relevant articles, 4 of which met study inclusion criteria. The total



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number of included patients was 486. All studies used the CellSearch system to detect CTCs. In a pooled analysis of the studies, OS was significantly higher in patients with lower levels of CTC compared to those with higher levels (> 5 CTC in 7.5 mL blood); RR: 2.51, 95% CI: 1.96-3.21. In a sensitivity analysis removing the study with the largest sample size, the RR was marginally higher (RR: 3.25, 95% CI: 2.01 to 5.24). The test for study heterogeneity was not statistically significant.

The study by de Bono and colleagues was prospective and included patients with castration-resistant progressive prostate cancer who were initiating a new cytotoxic therapy. Circulating tumor cell levels were measured using the CellSearch system at baseline and before each course of therapy until disease progression or for up to 18 months. A total of 276 patients were enrolled; of these, 33 were subsequently found to not meet eligibility criteria (e.g., did not have an evaluable baseline blood sample or scan or lacked progressive disease) and 2 patients withdrew consent, leaving 231 patients in the analysis. At baseline, 219 patients were evaluable for CTCs; of these, 125 had elevated levels (5 or more cells per 7.5 mL of blood), and 94 had less than 5 cells per mL. The primary study outcome was the association between elevated CTCs 2 to 5 weeks after initiating treatment and OS. An evaluable CTC level was available for 203 patients at the 2- to 5-week follow-up, and CTCs were elevated in 39 (19%). The group of patients with elevated CTCs after initiating treatment had a significantly shorter median survival time (9.5 months) than those without elevated CTC (20.7 months), $p < 0.0001$. Moreover, patients with elevated CTCs at all time points ($n = 71$) had the shortest median OS, 6.8 months. Their OS was significantly shorter than other groups, specifically the group of patients with elevated baseline CTCs who converted to a nonelevated level after treatment ($n = 45$, median OS 21.3 months) and the group of patients with nonelevated CTCs throughout the study ($n = 88$, median OS was greater than 26 months). There were only 26 patients who had non-elevated CTCs at baseline and elevated CTCs after treatment; this group had a mean OS of 9.3 months. A limitation of the study was that only 203 of the 276 enrolled patients (74%) were included in the primary analysis.

Metastatic Colorectal Cancer

A 2013 meta-analysis by Groot Koerkamp and colleagues reviewed studies on the prognostic value of CTCs as well as studies on the detection of DTCs in bone marrow. To be included in the review, studies had to include at least 20 patients with metastatic colorectal cancer and report long-term outcomes. A total of 16 eligible studies were included and 12 had data suitable for meta-analysis. Most studies included detection of CTCs; only 4 included detection of DTCs. Pooled analyses found that detection of CTCs or DTCs in patients with metastatic colorectal cancer was associated with a worse OS (HR: 2.47, 95% CI: 1.74 to 3.51, 11 studies) and a worse PFS (HR: 2.07, 95% CI: 1.44 to 2.98, 9 studies).

One of the larger studies on the association of CTCs to survival in patients with metastatic colorectal cancer was a prospective multicenter industry-sponsored trial by Cohen and colleagues. To be eligible for participation, patients needed to be initiating any first- or second-line systemic therapy, or third-line therapy with an epidermal growth factor receptor (EGFR) inhibitor. CTC cells were assessed at baseline and at regular intervals after starting treatment. In a pre-planned interim analysis, the authors determined that at least 3 CTCs per 7.5 mL blood was the optimal cutoff to use to indicate elevated CTC level. The primary outcome was the agreement between CTC level at the 3-5 week follow-up and response to therapy. Agreement was defined as either a non-elevated level of CTC corresponding to lack of disease progression



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or an elevated level corresponding to progressive disease. A total of 481 patients were enrolled and there were 430 evaluable patients, 320 of whom were assessable for the primary outcome. Thirty-eight of 320 (12%) had elevated levels of CTCs 3-5 weeks after starting treatment. By the end of the study, 20 of these 38 patients (53%) had progressive disease or were unavailable because they had died before receiving a follow-up imaging study. In comparison, 54 of the 282 (19%) patients without elevated CTCs at the 3- to 5-week follow-up had progressive disease or had died (p value not reported). Overall survival and PFS were reported as secondary outcomes. Patients with elevated baseline CTC levels (at least 3 per 7.5 mL blood) had shorter mean PFS and OS than patients with non-elevated baseline CTCs (less than 3 per 7.5 mL blood). Median PFS was 4.5 and 7.9 months, respectively ($p = 0.0002$), and median OS was 9.4 and 18.5 months ($p < 0.001$). A study limitation is that only 320 of 481 enrolled patients (67%) were included in the primary analysis. Additional prospective studies using the same cutoff are needed to confirm the prognostic value of the 3 cells per 7.5 mL blood cutoff, which differs from the 5 cells per 7.5 mL cutoff used in most other studies.

Other Conditions

Studies have also been published evaluating CTC level as a diagnostic and/or prognostic marker for patients with other types of cancer. There are no FDA-cleared tests for these indications, and none of the studies evaluated patient management decisions using levels of CTCs. Conditions include non-metastatic breast cancer, lung, bladder, pancreatic, gastric, melanoma, and head and neck cancer. One meta-analysis was identified; this was published by Ma and colleagues in 2012 and evaluated evidence on the association between CTC level and clinical outcomes in patients with lung cancer. A pooled analyses of study data found that the presence of CTCs before treatment was associated with lower OS (HR: 2.61, 95% CI: 1.82 to 3.74, 9 studies) and lower PFS (HR: 2.37, 95% CI: 1.41 to 3.99, 4 studies). The authors concluded that the presence of CTCs in the peripheral blood indicates a worse prognosis in patients with lung cancer.

Ongoing Clinical Trials

Treatment Decision Making Based on Blood Levels of Tumor Cells in Women With Metastatic Breast Cancer Receiving Chemotherapy (NCT00382018):

This RCT, sponsored by the National Cancer Institute, includes patients with metastatic breast cancer who are beginning first-line chemotherapy. Patients who have elevated levels (5 or more cells per 7.5 mL of blood) of CTCs after their first round of chemotherapy will be randomized to stay on their current treatment or switch to a different treatment regimen. Patients without elevated levels of CTCs will remain on their current treatment. The primary outcomes are PFS and survival. The expected enrollment is 650 patients.

Circulating tumor cells to guide chemotherapy for metastatic breast cancer (NCT01349842):

The trial, known as the CirCé01 study, is an RCT comparing patients managed with and without determination of CTC using CellSearch technology. In the experimental group, CTC levels will be measured before each chemotherapy injection, and chemotherapy will not continue in patients with a low CTC level. Patients will be followed for 4 years; the primary outcome is OS. The study, conducted in France and sponsored by the Institut Curie, aims to include 568 patients with metastatic breast cancer. The estimated study completion date is January 2014.



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Medico-economic Interest of Taking Into Account Circulating Tumor Cells (CTC) to Determine the Kind of First Line Treatment for Metastatic, Hormone-receptors Positive, Breast Cancers (NCT01710605):

This trial, known as the STIC CTC study, is an RCT that aims to evaluate outcomes with and without using CTC count as a criterion for selecting first-line therapy. CTC level will be measured using the CellSearch technique. Patients assigned to the CTC arm will receive hormone therapy if their CTC count is less than 5 per 7.5 mL and chemotherapy if the CTC count is 5 or more per 7.5 mL. Treatment decisions in the other arm will be according to usual criteria. The study is including patients with metastatic hormone-receptor positive breast cancer. The primary outcome is PFS over 2 years. The estimated primary completion date is March 2016; the study aims to recruit 1,000 participants.

Summary

While case series have shown that the level of CTCs (generally using the cutoff > 5 CTC per 7.5 mL blood) is associated with the presence of metastatic disease and prognosis, the prospective use of this information to impact care has not been demonstrated. Several trials are underway evaluating patient management decisions based on CTC level. Given the insufficient evidence to evaluate the impact on patient management or health outcomes, the assessment of CTCs is investigational for the management of cancer.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	86152, 86153
HCPCS	No codes
ICD-9 Diagnosis	All relative diagnoses
ICD-9 Procedure	No codes



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12/07/2004	Medical Director review
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01/31/2005	Managed Care Advisory Council approval
07/07/2006	Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
01/10/2007	Medical Director review
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01/09/2014	Medical Policy Committee review
01/15/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date:	01/2015

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- B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
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