NOTE: This policy has been revised. The revised policy will be effective December 1, 2018. To view the revised policy, click here.

Medical Policy Manual

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

Effective: August 1, 2017

Next Review: May 2018
Last Review: June 2017

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

In CTC testing, blood is examined for the presence of cells from existing tumors. The number of these cells is thought to reflect the patient’s prognosis.

MEDICAL POLICY CRITERIA

Detection and quantification of circulating tumor cells is considered investigative in the management of patients with cancer.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
2. Analysis of Proteomic Patterns for Early Detection or Assessing Risk of Cancer, Laboratory, Policy No. 41
3. Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients With Breast Cancer, Genetic Testing, Policy No. 42

BACKGROUND

CTCs are malignant cells that are found in the peripheral blood and originate from primary or
metastatic tumors. Detection and quantification of CTCs is being investigated to determine whether this testing 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. CTCs 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® Circulating Tumor Cell Kit (Janssen Diagnostics, LLC) is an example of immunofluorescent technology. The technique involves identification of the circulating tumor cells 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.

REGULATORY STATUS

The CellSearch® Circulating Tumor Cell Kit (K103502, Janssen Diagnostics, LLC, a Johnson & Johnson company; formally K073338) received U.S. Food and Drug Administration (FDA) 510(k) approval for monitoring metastatic breast, colorectal, and prostate cancer.

Note: This policy does not address techniques for the detection of disseminated tumor cells, e.g., in bone marrow, or circulating cell-free DNA.

EVIDENCE SUMMARY

Validation of the clinical use of any diagnostic test focuses on three main principles:

1. Analytic validity of the test;
2. Clinical validity of the test (i.e., sensitivity, specificity, and positive and negative predictive values in relevant populations of patients and compared to the gold standard); and
3. Clinical utility of the test (i.e., how the results of the diagnostic test will be used to improve the management of the patient).

Most of the literature on the use of CTCs consists of studies that correlate the quantification of CTCs with survival. Studies on the validation of the use of CTCs for diagnosis or screening are limited. Below are studies that correlate survival and risk of disease progression with quantification of CTCs.

ANALYTIC VALIDITY
There are a variety of methods used to analyzed circulating tumor cells (CTCs), most marginally validated. More assay validation studies are needed to standardize reproducibility before methodology protocols can be put into clinical use.

**METASTATIC BREAST CANCER**

A comprehensive meta-analysis of studies on the association between circulating tumor cells and health outcomes in patients with breast cancer was published in 2012 by Zhang and colleagues.[1] The analysis included studies that evaluated more than 30 patients, used reverse transcriptase-polymerase chain reaction (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 were positively associated with a significantly increased risk of disease progression (hazard ratio [HR]: 1.78, 95% confidence interval [CI]: 1.52-2.09). CTC 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.

Zhao and colleagues published a meta-analysis of studies addressing the association between circulating tumor cells detected by reverse transcriptase-polymerase chain reaction (RT-PCR) and breast cancer prognosis.[2] To be included in their analysis, studies needed to include at least 20 patients and to use some form of RT-PCR. A total of 24 studies with 4,013 patients met inclusion criteria. Five of the studies included 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 OS (hazard ratio [HR]=3.00, 95% confidence interval [CI]=2.29-3.94) and a lower 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. The authors did not conduct a separate analysis of studies on metastatic breast cancer. They did, however, find that CTC-positive breast cancers were significantly associated with high histological grade (HR=1.21, 95% CI=1.09-1.35), tumor size >2cm (HR=1.12, 95% CI=1.02-1.22) and nodal status (at least 1 positive node) (HR=1.10, 95% CI=1.00-1.21).

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

In 2004, Cristofanilli et al published a multicenter study that included 177 patients with measurable metastatic breast cancer who were followed for 38.7 weeks or longer.[3] Using the CellSearch System, investigators measured the number of circulating tumor cells before initiating a new line of therapy and at first follow-up (mean [SD], 4.5 [2.4] weeks after baseline sample). Also tested were 145 normal subjects and 200 patients with benign breast diseases. The authors detected 2 or fewer epithelial cells per 7.5 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 (7.0 months vs 2.7 months, respectively; p<0.001) and OS (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 (ie, after the first cycle of therapy) was similar to that for 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, HER2/neu status, and site of metastases.

Nole et al (2008) tested 80 patients with metastatic breast cancer for CTC levels before starting a new treatment, after 4 and 8 weeks and every 2 months thereafter.[4] Forty-nine patients had 5 or more cells at baseline. In multivariate analysis, baseline number of CTCs was associated with PFS (HR=2.5; 95% CI, 1.2 to 5.4). The risk of progression for patients with 5 or more circulating tumor cells at the last available follow-up was 5 times the risk of patients with 0 to 4 CTCs at the same point (HR=5.3; 95% CI, 2.8 to 10.4). Patients with rising or persistent counts of 5 or more CTCs at last available follow-up showed a statistically higher risk of progression than patients who had fewer than 5 CTCs at both times of blood sampling.

In 2012, Pierga et al in France reported on a prospective series of 267 patients with metastatic breast cancer who were starting first-line chemotherapy.[5] CTCs were analyzed before starting treatment, before the second cycle of treatment, and at the first radiologic evaluation before the third or fourth 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 (21%) deaths, and 161 (60%) experienced tumor progression. Baseline CTC count was a strong predictor of PFS (p<0.001). Median PFS was 19.9 months in patients with 0 CTCs and 8.2 months in patients with more than 5 CTCs per 7.5 mL blood. Baseline CTC was also significantly associated with OS (p<0.001). In multivariate analysis, baseline CTC positivity was an independent prognostic factor for both PFS and OS.

METASTATIC PROSTATE CANCER

A 2014 systematic review and meta-analysis by Ma et al examined studies on the relation between CTCs and disseminated tumor cells (DTCs) on the prognosis of prostate cancer (localized and metastatic).[6] To be included in the review, studies had to report the correlation of CTCs or DTCs with 1 or more survival outcomes. The authors assessed 54 studies for eligibility. Thirty-three studies (27 on CTCs 6 on DTCs) met the inclusion criteria. A pooled analysis of all studies found significantly lower OS in patients with circulating tumor cells (HR=2.43; 95% CI, 2.07 to 2.86). Eight studies (total N=946 patients) used CellSearch technology to detect CTCs. A pooled analysis limited to these studies also found a significant association between CTCs and OS (HR=2.36; 95% CI, 1.95 to 2.85).

Previously, in 2011, Wang et al published a meta-analysis of studies on the association between CTCs and prognosis in patients with metastatic castration-resistant or hormone-refractory prostate cancer.[7] 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 (total N= 486 patients). All studies used the CellSearch System to detect CTCs. A pooled analysis of the studies also found a significant association between CTCs and OS (HR=2.36; 95% CI, 1.95 to 2.85).
The test for study heterogeneity was not statistically significant.

The study by de Bono et al (2008) was prospective and included patients with castration-resistant progressive prostate cancer who were initiating a new cytotoxic therapy.\[8\] CTC levels were measured using the CellSearch System at baseline and before each course of therapy until disease progression or up to 18 months. A total of 276 patients were enrolled; of these, 33 were subsequently found to not meet eligibility criteria (eg, 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 cells per 7.5 mL of blood) and 94 did not (<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<0.001). Moreover, patients with elevated CTCs at all time points (n=71) had the shortest median OS (6.8 months). OS in this group was significantly shorter compared with 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, >26 months). Only 26 patients had nonelevated 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 (74%) of the 276 enrolled patients were included in the primary analysis.

METASTATIC COLORECTAL CANCER

In 2015, Huang et al published a meta-analysis of studies on the association between CTCs detected with the CellSearch System and CRC prognosis.\[9\] Eleven studies with a total of 1847 patients met eligibility criteria. Pooled data analyses found that detection of CTCs in patients with CRC was associated with a significantly worse OS (HR for death, 2.00; 95% CI, 1.49 to 2.69; 9 studies) and PFS (HR for progression or death, 1.80; 95% CI, 1.52 to 2.13; 8 studies). In addition, a pooled analysis of 3 studies found that the response to adjuvant chemotherapy was significantly lower in patients with detectable CTCs than those without CTCs (risk ratio, 0.79; 95% CI, 0.63 to 0.99).

Previously, a 2013 meta-analysis by Groot Koerkamp et al reviewed studies on the prognostic value of CTCs and on the detection of DTCs in bone marrow.\[10\] To be selected, studies had to include at least 20 patients with metastatic CRC and report long-term outcomes. Sixteen 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 CRC was associated with a worse OS (HR for death, 2.47; 95% CI, 1.74 to 3.51; 11 studies) and a worse PFS (HR for progression or death, 2.07; 95% CI, 1.44 to 2.98; 9 studies).

CIRCULATING TUMOR CELL CUTOFFS FOR COLORECTAL CANCER

Studies have used different cutoffs of CTCs. CellSearch materials recommend using a cutoff of at least 3 CTCs in CRC.\[11\] That cutoff used in the 2008 multicenter industry-sponsored study by Cohen et al.\[12\] Eligible participants needed to be initiating any first- or second-line systemic therapy, or third-line therapy with an EGFR inhibitor. CTC were assessed at baseline and at
regular intervals after starting treatment. In a preplanned interim analysis, the authors determined that at least 3 CTCs per 7.5 mL blood was the optimal cutoff to indicate elevated CTC level. The primary outcome was the agreement between CTC level at the 3- to 5-week follow-up and response to therapy. Agreement was defined as either a nonelevated level of CTC corresponding to lack of disease progression or an elevated level corresponding to progressive disease. A total of 481 patients were enrolled; 430 were evaluable patients, 320 of whom were assessable for the primary outcome. Thirty-eight (12%) of 320 patients had elevated levels of CTCs 3 to 5 weeks after starting treatment. By the end of the study, 20 (53%) of these 38 patients had progressive disease or died before receiving a follow-up imaging study. By comparison, 54 (19%) of the 282 patients without elevated CTCs at the 3- to 5-week follow-up had progressive disease or had died (p value not reported). OS and PFS were reported as secondary outcomes. Patients with elevated baseline CTC levels (≥3 per 7.5 mL blood) had shorter mean PFS and OS than patients with nonelevated baseline CTCs (<3 per 7.5 mL blood). Median PFS was 4.5 months and 7.9 months, respectively (p<0.001), and median OS was 9.4 months and 18.5 months, respectively (p<0.001). A study limitation is that only 320 (67%) of 481 enrolled patients were included in the primary analysis.

More recent studies have used other cutoffs. For example, a 2014 prospective study by Seeberg et al used a cutoff of 2 or more CTCs per 7.5 mL blood. The study included 194 patients with colorectal liver metastases. The presence of more than 2 CTCs was associated with significantly shorter survival time in the whole group of patients (p<0.001) and in patients with resectable disease (p=0.037) compared with patients with fewer than 2 CTCs. Moreover, the presence of 2 or more CTCs was associated with significantly shorter RFS in the total patient population (p=0.002) and in resectable patients (p<0.001). A 2015 prospective study by Bork et al used a cutoff of at least 1 cell per 7.5 mL blood. The study included 287 patients with potentially curable CRC. CTC detection was significantly associated with worse OS in the entire cohort (48.4 months for CTC-positive patients vs 33.6 months for CTC-negative patients, p<0.001). Additional prospective studies are needed to confirm the prognostic value of the 1 or 2 cells per 7.5 mL blood cutoff.

OTHER TUMORS

Additional studies and meta-analysis have also been published evaluating circulating tumor cell levels as a diagnostic and/or prognostic marker for patients with nonmetastatic breast as well as other types of cancer including: bladder, gastric, head and neck, liver, lung, melanoma, pancreatic, and ovarian cancer. Although the majority of these studies concluded that the presence of CTCs in the peripheral blood indicates a worse prognosis in cancer patients; there are no FDA-cleared tests for these indications, and none of the studies evaluated patient management decisions using levels of circulating tumor cells.

CLINICAL UTILITY

Published literature on the clinical utility of CTC levels and patient outcomes are lacking. A number of the situations where clinical utility might be demonstrated are listed below. However, because of the uncertainties in analytic and clinical validity, it is not currently possible to establish whether clinical utility is present. These situations are provided as examples of how clinical utility could be demonstrated if analytic and clinical validity were considered adequate.
• For diagnosis or molecular characterization of tumors as an alternative to tissue biopsy, clinical utility can be demonstrated if the test is as accurate as tissue biopsy and avoids the need for an invasive procedure.

• For diagnosis or molecular characterization of tumors in circumstances when tumor tissue is in a location where it cannot be easily accessed or tumor tissue is not available, clinical utility can be demonstrated if the test is able to make a diagnosis or characterization when other methods cannot, and the information from the test leads to management changes that improve outcomes.

• For assessment of the evolution of targeted therapy resistance in real time to allow adaptive treatment strategies, clinical utility can be demonstrated if a management strategy using results from liquid biopsy is superior to a standard management strategy.

• For prognosis including correlation with survival, disease progression, and risk of metastatic relapse, based primarily on quantification of circulating tumor in the blood, clinical utility can be demonstrated if the test provides incremental prognostic information and if this information leads to management changes that improve outcomes.

• For early detection of cancer or as an alternative to current screening methods, possibly before the development of clinically or radiologically detectable cancer in order to treat at an early stage, clinical utility can be demonstrated if a screening strategy using results from liquid biopsy is superior to a screening strategy using standard methods.

**PRACTICE GUIDELINE SUMMARY**

**AMERICAN SOCIETY OF CLINICAL ONCOLOGY**

Based on a review of the recent evidence, the American Society of Clinical Oncology (2016) recommends clinicians not use circulating tumor cells to guide decisions on adjuvant systemic therapy in the clinical practice guideline on appropriate use of breast tumor biomarker assay to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer.[43]

**NATIONAL COMPREHENSIVE CARE NETWORK**

The National Comprehensive Care Network (NCCN) Clinical Practice Guidelines do not include recommendations regarding detection of circulating tumor cells used in the management of patients with breast, colon or prostate cancer.[44-46]

**NATIONAL ACADEMY OF CLINICAL BIOCHEMISTRY**

In 2008, the National Academy of Clinical Biochemistry (NACB) issued a guideline on the use of tumor markers in testicular, prostate, colorectal, breast, and ovarian cancer.[47] Circulating tumor cells were discussed in the future developments section related to prostate cancer. The panel concluded that the measurement of circulating prostate cancer cells was not sufficiently validated to recommend testing for CTCs in routine clinical practice.

**SUMMARY**

There is not enough research to know if measurement for levels of circulating tumor cells (CTCs) improves overall health outcomes for people with cancer. Levels may be associated with the presence of metastatic disease and prognosis, however, the prospective use of this
information to impact care (i.e., clinical utility) has not been demonstrated. In addition, no clinical practice guidelines based on research recommended the use of CTCs in patient management. Therefore, detection and quantification of circulating tumor cells is considered investigational in the management of patients with cancer.

REFERENCES


### CODES

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