Anthem

Medical Policy

Subject: Detection of Circulating Tumor Cells
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Description/Scope

This document addresses the management of individuals with cancer using immunological techniques designed to detect epithelial cells circulating in the blood to quantify circulating tumor cells. The CellSearch® System (Janssen Diagnostics, LLC, Raritan, New Jersey) is an example of the technology. This document does not address circulating tumor DNA testing for cancer (liquid biopsy).

Position Statement

Investigational and Not Medically Necessary:

Detection of circulating tumor cells in the blood is considered **investigational and not medically necessary** in the management of individuals with cancer.

Rationale

Circulating tumor cells (CTCs) are malignant cells found in peripheral blood originating from primary or metastatic tumors. Detection of CTCs has been associated with prognosis or response to treatment in individuals with certain types of cancer, primarily breast, colorectal and prostate cancer. However, evidence is insufficient to demonstrate that clinical decisions based on CTC levels increases quality or duration of life or decreases adverse events.

Breast Cancer

Cristofanilli and colleagues (2004) reported on a prospective multi-center study of 177 subjects with metastatic breast cancer who were tested for levels of CTCs both at the time a new line of therapy was initiated and at the first follow-up visit. Of all the variables studied (that is, hormone receptor status, HER2/*neu* status, site of metastasis), the levels of CTCs at baseline and at the first follow-up visit were the most significant predictors of progression-free survival (PFS) and overall survival (OS). In a follow-up analysis, Cristofanilli and colleagues (2005) focused on a subset of the initial study, consisting of 83 subjects with newly diagnosed measurable metastatic breast cancer about to start first-line systemic therapy. Subjects with five CTCs in 7.5 ml blood at baseline or first follow-up (4 weeks) were found to have a worse prognosis than those with less than five CTCs at baseline (baseline: median PFS, 4.9 versus 9.5 months, respectively; median OS, 14.2 versus 18 months, respectively; first follow-up: median PFS, 2.1 versus 8.9 months, respectively; median OS, 11.1 versus 18 months, respectively). In an analysis of longer-term data (Hayes, 2006), median PFS times for those with less than five CTCs from each of the five follow-up points were 7.0, 6.1, 5.6, 7.0, and 6.0 months, respectively. For those with greater than or equal to five CTCs, median PFS from these same time points was significantly shorter: 2.7, 1.3, 1.4, 3.0, and 3.6 months, respectively. Median OS for individuals with less than five CTCs from the five blood draw time points was greater than 18.5 months. For those with greater than or equal to five CTCs, median OS from these same time points was significantly shorter: 10.9, 6.3, 6.3, 6.6, and 6.7 months, respectively.

The prognostic significance of CTCs was compared with measures of tumor burden and phenotypic subtype of disease in a retrospective analysis of 151 individuals with metastatic breast cancer (Cristofanilli, 2007). CTCs were isolated and counted in whole blood using the CellSearch System. The median age of subjects was 53 years, and 44% had greater than five CTCs. The median OS rates for negative versus positive CTCs were 29.3 months and 13.5 months respectively. The authors noted that the prognostic value was independent of measure of tumor burden and type and line of therapy, and phenotypic subtype of the disease.

Bidard and colleagues (2010), in a prospective study, investigated whether CTC detection had a prognostic impact on nonmetastatic breast cancer. A total of 115 women diagnosed with large operable or locally advanced nonmetastatic breast cancer participated in this trial. Baseline CTC detection rates were low, with 23% and 10% of the women having at least one and two CTC/7.5 ml prior to chemotherapy, respectively. After a median follow-up of 36 months clinical outcomes were reanalyzed. Of the 115 women, 14 (12%) had metastatic relapses and 9 (8%) died. CTC detection before chemotherapy was found to be an independent prognostic factor for both distant metastasis-free survival (DMFS) [DMFS; p=0.01, relative risk (RR)=5.0, 95% confidence interval (CI), 1.4-17] and OS (OS; p=0.007, RR=9, 95% CI, 1.8-45). CTC detection after chemotherapy was of less significance (p=0.07 and 0.09, respectively).

Galardi and colleagues (2021) analyzed the prognostic role of CTC counts in participants enrolled in the cTREnd study, a pre-planned translational sub-study of TREnd, that randomized participants with advanced breast cancer (ABC) to palbociclib therapy alone or palbociclib plus endocrine therapy received in a prior line of treatment. The primary aim of the study was to test the use of CTCs as a biomarker of resistance to palbociclib. The study involved 46 participants with ER-positive, HER2-negative ABC. Blood samples were collected before starting palbociclib treatment (timepoint T0), after the first cycle of treatment (T1), and at disease progression (T2). CTCs were isolated and counted using the CellSearch System. CTC count at T0 did not show significant prognostic value in term of PFS or clinical benefit (defined as the percentage sum of complete responses, partial responses, and stable disease for at least 24 weeks according to RECIST 1.1 criteria). Participants with at least 1 detectable CTC at T1 (n=26) had a worse PFS than those with 0 CTCs (n=16, p=0.02). At T1, participants with an increase of at least 3 CTCs showed reduced PFS compared to those with no increase (median PFS = 3 months versus 9 months, respectively; p=0.004). Participants with ≥ 5 CTCs at T2 (n=6/23) who received chemotherapy as post-study treatment had a shorter time to treatment failure (p=0.02). However, the investigators were unable to analyze participants that received other types of treatments due to limited sample size. Therefore, they were unable to determine if the relationship with elevated post-treatment CTC count is specific to chemotherapy or if it also relates to other groups. The results indicate a potential relationship between CTC counts and response to treatment with palbociclib monotherapy or combined with endocrine therapy. The findings are limited by the sample size, the exploratory nature of the analyses, and the use of an arbitrary cutoff to determine the increase in CTC number during treatment.

Riethdorf and colleagues (2010), in the GeparQuattro clinical trial, studied the detection and characterization of CTCs in the peripheral blood before and after neoadjuvant therapy (NT) for nonmetastatic breast cancer. The trial incorporated NT approaches (epirubicin/cyclophosphamide prior to randomization to docetaxel alone, docetaxel in combination with capecitabine, or docetaxel followed by capecitabine) and additional trastuzumab treatment for those with HER2-positive tumors. The CellSearch system was

used for CTC detection and further evaluation of HER2 expression. Blood samples of 213 subjects with nonmetastatic breast cancer before NT and 207 subjects after NT prior to surgery were examined. Study results included the detection of greater than or equal to one CTC/7.5 ml in 46 of 213 subjects (21.6%) before NT and in 22 of 207 subjects (10.6%) after NT (p=0.002). Twenty (15.0%) cases which were initially CTC-positive were CTC-negative after NT and 11 (8.3%) cases were CTC-positive after NT, even though no CTCs were detected before NT. The detection of CTCs did not correlate with characteristics of primary tumors. In addition, there was no association between tumor response to NT and CTC detection. HER2-overexpressing CTCs were observed in 14 of 58 CTC-positive subjects (24.1%), including 8 with HER2-negative primary tumors and 3 after treatment with trastuzumab. CTCs which were scored as HER2-negative or weakly HER2-positive before or after NT were present in 11 of 21 subjects with HER2-positive primary tumors. HER2 overexpression on CTC appeared to be restricted to ductal carcinomas and associated with high tumor stage (p=0.002).

Fehm and colleagues (2010) assessed HER2 CTC testing in 254 individuals with metastatic breast cancer from nine German university breast cancer centers in a prospective, open label study. Both the CellSearch assay and AdnaTest BreastCancer™ (Adnagen AG, Langenhagen, Germany) were used to assess the HER2 status of CTCs. Using the CellSearch assay, it was determined that 122 of 245 (50%) subjects had greater than or equal to five CTCs, and HER2-positive CTCs were observed in 50 (41%). Using the AdnaTest BreastCancer, it was demonstrated that 90 of 229 (39%) subjects were CTC positive and the HER2 positivity rate was 47% (42 of 90). The percentage of breast cancer cases with HER2-negative primary tumors but HER2-positive CTCs was 32% (25 of 78) and 49% (28 of 57) using the CellSearch assay and AdnaTest BreastCancer, respectively. Concordance between the HER2 status shown by either the CellSearch assay or AdnaTest BreastCancer could only be evaluated in 62 subjects who were CTC positive with both tests. In considering only those individuals who had CTCs on both tests (n=62), concordant results regarding HER2 positivity were obtained in 50% of the cases (31/62). The authors noted that the overall agreement between the tests was low at 64% and both assays should have been able to detect HER2-positive CTCs. In addition, a “potential drawback” of the study was that biopsy of the metastatic tissue was optional and only performed on 30 of 252 subjects; since most of these subjects were CTC negative, “no meaningful comparison could be performed.”

Rack and colleagues (2014) investigated CTCs in early breast cancer. CTCs were analyzed using the CellSearch system in 2026 subjects with early breast cancer before adjuvant chemotherapy and in 1492 subjects after chemotherapy. Follow-up was for a median of 35 months. Prior to chemotherapy, CTCs were detected in 21.5% (n=435 of 2026), with 19.6% (n=136 of 692) of node-negative and 22.4% (n=299 of 1334) of node-positive breast cancers showing CTCs (p<0.001). No association was noted with grading, tumor size, or hormone receptor status. Post-chemotherapy, 22.1% of subjects (n=330 of 1493) were positive for CTCs. The presence of CTCs was associated with poor disease-free survival (DFS). The prognosis was worse in subjects with at least five CTCs per 30 mL blood and the presence of persisting CTCs after chemotherapy showed a negative influence on DFS and on OS. Study limitations as reported by the authors include the short median follow-up of 35 months.

In 2014, Smerage and colleagues reported on OS of women enrolled in SWOG S0500. Arm A included subjects who did not have increased CTCs at baseline and remained on initial therapy until progression (n=276, 46%). Arm B included subjects with initially elevated CTCs that decreased 21 days after initial therapy (n=165, 28%). Arm C included subjects with CTCs lowered from baseline (n=123, 21%) with half of the subjects randomly assigned to arm C1, continuing initial therapy, and half of the subjects assigned to C2, changing to alternative chemotherapy. Of those with initially increased CTCs, 31 (10%) were not retested. No difference in median OS was observed between arm C1 and C2. Median OS for arms A, B, and C (C1 and C2 combined) were 35 months, 23 months, and 13 months, respectively. The authors concluded their data demonstrated that a failure to reduce CTCs within the first 3 to 4 weeks of starting first-line chemotherapy in women with metastatic breast cancer indicated a poor prognosis and general chemotherapy resistance. However, early switching to an alternate chemotherapy regimen had no effect on longer OS.

In 2017, Liu and colleagues conducted a prospective study with the aim to determine the predictive value of the peptide-based nanomagnetic CTC isolation system (Pep@MNPs), which is not FDA approved, in the management of metastatic breast cancer. There were 102 subjects with breast cancer enrolled in the study and each subject had a baseline blood sample taken for CTC detection; 72 of these subjects had blood taken for CTC detection after starting first line chemotherapy. CTCs were detected in 69.6% of subjects at baseline, which was similar to the FDA approved CellSearch (40-80%). Subjects with < 2 CTC/2 ml at baseline had a longer median PFS than did those with > 2 CTC/2 ml (17.0 months vs. 8.0 months; p=0.002). Subjects with < 2 CTC/2 ml both at baseline and first clinical evaluation had the longest PFS (18.2 months) among all subject groups (p=0.004). In subjects with stable disease per imaging, the Pep@MNPs was able to identify those with longer PFS (p<0.001). A direct association was not found between CTC status and tumor response at baseline (p=0.822) or at first clinical evaluation (p=0.367). The investigators note that the results of this study need to be validated by larger studies to prove clinical utility.

A 2012 meta-analysis by Zhang and colleagues investigated the association between CTCs and health outcomes in persons with breast cancer. All studies included more than 30 subjects; 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 positivity was associated with a significantly increased risk of disease progression (hazard ratio [HR]: 1.78, 95% CI: 1.52-2.09). CTC positivity was associated with a significantly increased risk of death in subjects with metastatic breast cancer (HR: 2.23, 95% CI: 2.09 to 2.60, 19 studies). A subgroup analysis by detection method was presented which 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. However, the authors reported that further study is needed to assess the clinical utility of CTCs in breast cancer.

In 2020, Bidard and colleagues published results of a non-inferiority randomized controlled trial (RCT) evaluating the impact of using CTC count to manage first-line treatment decisions in individuals with hormone-receptor positive, ERBB2-negative metastatic breast cancer. A total of 778 individuals were randomized to a clinician-driven treatment choice (n=387) or a CTC-driven treatment choice (n=391). Prior to randomization, clinicians had to declare their treatment recommendation, endocrine therapy (for clinically low-risk individuals) or chemotherapy (for clinically high-risk individuals). Individuals received this treatment in the clinician-driven treatment choice arm. In the CTC-driven treatment choice arm, individuals with low CTC count per CellSearch (< 5 CTCs per 7.5ml) received endocrine therapy and those with high CTC count received chemotherapy. The primary endpoint was PFS, defined as the time to disease progression or death within 2 years of randomization; individuals without events were censored. The non-inferiority margin, upper limit of the CI of the HR for PFS, was set at 1.25. The investigators also assumed that there would be fewer individuals treated with chemotherapy in the CTC-driven treatment arm and that, accordingly, the rate of chemotherapy-related adverse events would be lower.

In the clinician-driven treatment arm 387 individuals were included in the analysis, 103 of whom (27.2%) received chemotherapy. In the CTC-driven arm, 377 individuals were included in the analysis; 138 (36.6%) received chemotherapy. Median PFS was 13.9 months (95% CI, 12.2 to 16.3) in the clinician-driven treatment arm and 15.5 months (95% CI, 12.7 to 17.3) in the CTC-driven treatment arm. The HR for progression for the CTC-driven versus the clinician-driven treatment arm was 0.94 (90% CI, 0.81 to 1.09). This met the non-inferiority criteria since the upper limit of the CI of the HR was less than 1.25. The preplanned secondary analysis for superiority did not find that PFS was significantly better in the CTC-driven arm. There were not fewer individuals in the CTC-decision

arm treated with chemotherapy and the rate of chemotherapy-related adverse events was higher in the CTC-driven treatment arm, not lower. Comparing the CTC-driven treatment arm to the clinician-driven treatment arm, vomiting was reported in 8.2% and 4.8%, anemia in 20.4% and 14.6%, and alopecia in 15.1 versus 10.6%, respectively. Thus, the investigators hypothesis that chemotherapy-related adverse events would be lower in the CTC-driven treatment arm was not met.

The American Society of Clinical Oncology (ASCO) (Henry, 2022) published updated recommendations for the use of biomarkers to guide decisions on systemic therapy for women with metastatic breast cancer. The following recommendation for circulating tumor markers was included: “There are insufficient data to recommend routine use of CTCs to monitor response to therapy among patients with MBC (Type: informal consensus; Evidence quality: intermediate; Strength of recommendation: moderate)”.

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline for breast cancer (V4.2023) cites the SWOG-S0500 randomized trial (Smerage, 2014) and concluded, “in spite of its prognostic ability, CTC count failed to show a predictive value”.

Colorectal Cancer

Sastre and colleagues (2008) attempted to correlate the presence of CTCs with common clinical and morphological variables. Blood samples were collected from 97 subjects with colorectal cancer and 30 healthy volunteers. Quantification of CTCs was performed using the CellSearch System. Three of the 97 subjects with colorectal cancer were excluded from this analysis due to spoiled blood samples. Positive CTCs were detected in 34 of the remaining 94 individuals (36.2%). Correlation was not found among positive CTCs and location of primary tumor, increased carcinoembryonic antigen level, increased lactate dehydrogenase level or grade of differentiation. The stage of the disease did correlate with positive CTCs (20.7% in stage II, 24.1% in stage III and 60.7% in stage IV, p=0.005). There were no CTCs found in the group of healthy volunteers. The authors concluded CTC detection by CellSearch is a highly reproducible method that correlates with stage but not with other clinical and morphological variables in those with colorectal cancer and further studies are needed.

A prospective multi-center clinical trial (Cohen, 2008) studied individuals with metastatic colorectal cancer to determine if CTCs could predict clinical outcomes. CTCs were counted in the peripheral blood of 430 individuals with metastatic colorectal cancer at baseline and after starting first-, second-, or third-line therapy. Study subjects were divided into unfavorable and favorable prognostic groups based on CTC levels of three or more or less than three CTCs/7.5 mL, respectively. Those with unfavorable levels compared with favorable baseline levels of CTCs had shorter median PFS (PFS; 4.5 versus 7.9 months; p=0.0002) and OS (OS; 9.4 versus 18.5 months; p<0.0001). Differences continued at 1 to 2, 3 to 5, 6 to12, and 13 to 20 weeks after therapy. Conversion of baseline unfavorable CTCs to favorable levels at 3 to 5 weeks was associated with significantly longer PFS and OS compared with subjects with unfavorable CTCs at both time points (PFS, 6.2 versus 1.6 months; p=0.02; OS, 11.0 versus 3.7 months; p=0.0002). Among non-progressing subjects, favorable compared with unfavorable CTC levels within 1 month of imaging was associated with longer survival (18.8 versus 7.1 months; p<0.0001). Baseline and follow-up CTC levels remained strong predictors of PFS and OS after adjustment for clinically significant factors. Limitations of this study, as noted by the authors, included individuals undergoing different lines of therapy, which could potentially influence the ability to generalize results to any one group, individuals having the flexibility to determine the exact date of their blood draws and computed tomography scans, and the percentage of persons with unfavorable CTCs at baseline and overall CTC yield less than in other epithelial malignancies such as breast cancer.

In 2012, Sastre and colleagues performed an ancillary study evaluating the CTC count as a prognostic or predictive marker in 180 individuals with metastatic colorectal cancer who were concurrently enrolled in a phase III trial assessing maintenance therapy with single-agent bevacizumab versus bevacizumab plus chemotherapy. The CellSearch System was used to enumerate CTC counts. The median PFS interval for subjects with a CTC count ≥ 3 at baseline was 7.8 months, versus the 12.0 months achieved by those with a CTC count < 3 (p=0.0002). The median OS time was 17.7 months for subjects with a CTC count ≥ 3, compared with 25.1 months for those with a lower count (p=0.0059). The median PFS for subjects with a low CTC count after three cycles of chemotherapy was 10.8 months, as compared to 7.5 months for those with a high CTC count (p=0.005).

In a single center trial, Nesteruk and colleagues (2014) evaluated the prognostic value of CTCs in nonmetastatic rectal cancer. Between 2008 and 2011, a total of 162 individuals with rectal cancer having received preoperative short-term radiotherapy were recruited for the study. Of these, 113 (69.8%) had complete blood sampling and 91 were enrolled in the molecular analysis. CTCs were detected in 39 (43%) in preoperative blood samples, 11 (12%) 24 hours post-surgery, and 12 (13%) 7 days after surgery. The authors reported that CTC detection 7 days after surgery was of prognostic significance for local recurrence for 60 of the 91 subjects enrolled (p=0.006). CTCs detected preoperatively and 24 hours after resection had no prognostic value in cancer recurrence. Limitations of this study included a small sample size and a lack of additional long term follow up.

Huang and colleagues (2015a) published a meta-analysis aimed to evaluate if CTCs detected in peripheral blood with the CellSearch system have prognostic utility for individuals with colorectal cancer. A total of 11 studies containing 1847 eligible subjects were included. Data analyses revealed that detection of CTCs in individuals with colorectal cancer was associated with 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). Also, an analysis of 3 studies found that the response to adjuvant chemotherapy was lower in individuals with detectable CTCs as compared to those without CTCs (RR=0.79; 95% CI, 0.63 to 0.99). Study limitations reported by the authors included the retrospective nature of the meta-analysis, considerable heterogeneity in the study and possibly an insufficient number of studies analyzed.

In 2023, Jimenez-Fonseca and colleagues published a post-hoc analysis of data from two RCTs enrolling individuals with previously untreated metastatic colorectal cancer. CTC count was determined at baseline using the CellSearch kit. CTC count was categorized as ≥ 3 or < 3. Out of a total enrolled population of 589 individuals, 349 (59.2%) had CTC ≥ 3 and 240 (40.7%) had CTC < 3. Median PFS was 10.9 months in individuals with CTC ≥ 3 and 12.0 months for individuals with CTC < 3; the difference between groups was not statistically significant, HR, 0.81, p=0.0549. Median OS differed significantly between groups (p<0.0001); it was 19.5 months in individuals with CTC ≥ 3 and 32.9 months in individuals with CTC < 3. The study did not evaluate the utility of quantifying CTC at baseline e.g., whether it would impact treatment decisions or patient outcomes.

The NCCN Clinical Practice Guidelines for colon (V4.2023) and rectal cancer (V6.2023) do not include any recommendations regarding CTC testing.

Prostate Cancer

Danila and colleagues (2007) evaluated CTC numbers in individuals with progressive metastatic castration-resistant prostate cancer (CRPC) who were being considered for different hormonal and cytotoxic therapies. In this study, CTCs were isolated from the blood samples of 120 subjects with the disease. Their probability of survival over time was estimated by the Kaplan-Meier method. Sixty-nine (57%) individuals had five or more CTCs and 30 (25%) had two cells or less. Higher CTC numbers were found in those with bone metastases compared to those with soft tissue disease and in individuals who had received prior cytotoxic chemotherapy compared to those who had not. CTC counts were correlated to measurements of tumor burden such as prostate-specific antigen and bone scan index, reflecting the percentage of boney skeleton involved with tumor. The authors noted that baseline CTC was predictive of survival, with no threshold effect and prospective studies will need to be conducted to assess the role of these and future markers for pretreatment stratification in large scale trials.

DeBono and colleagues (2008) conducted a multi-center prospective study designed to establish the relationship between post treatment CTC counts and OS in CRPC. Secondary objectives included determining the prognostic utility of CTC measurement before initiating therapy, and the relationship of CTC to prostate-specific antigen (PSA) changes and OS at these and other time points. A total of 231 individuals with CRPC with progressive metastatic disease starting a new line of chemotherapy prior to treatment and monthly thereafter were evaluated. They were divided into two groups consisting of those having either unfavorable (greater than or equal to 5 CTC/7.5 mL) or favorable (less than 5 CTC/7.5 mL) CTC counts. Individuals in the unfavorable pretreatment CTC (57%) had shorter OS (median OS, 11.5 versus 21.7 months; Cox hazard ratio, 3.3; p<0.0001). Unfavorable post-treatment CTC counts also predicted shorter OS at 2 to 5, 6 to 8, 9 to 12, and 13 to 20 weeks (median OS, 6.7-9.5 versus 19.6-20.7 months; Cox hazard ratio, 3.6-6.5; p<0.0001). OS was predicted better with CTC counts than with PSA algorithms at all time points. The prognosis for those with unfavorable baseline CTC counts who converted to favorable CTC counts improved (6.8 to 21.3 months), while the prognosis for those with favorable baseline CTC counts who converted to unfavorable CTC counts worsened (> 26 to 9.3 months).

A phase III SWOG-led therapeutic trial (SWOG 0421) (Goldkorn, 2015) measured live CTC telomerase activity (TA) obtained from blood samples of 263 men with metastatic resistant prostate cancer. A microfilter and parallel CellSearch enumeration were used to measure CTC TA activity. In subjects with baseline CTC count ≥ 5 (47%), higher CTC TA was associated with worse OS after adjusting for other clinical risks such as baseline CTC counts and PSA levels. The authors concluded that their results illustrated the prognostic potential of CTC-derived biomarkers; however, additional investigation and further validation is indicated.

Scher and colleagues (2015) examined CTCs alone and in combination with other biomarkers as a surrogate for OS. This was accomplished as a secondary objective of an RCT of abiraterone acetate plus prednisone versus prednisone alone in subjects with metastatic CRPC previously treated with docetaxel (COU-AA-301). Biomarkers were quantified at baseline, 4, 8 and 12 weeks, with the most significant measure of interest being at 12 weeks. A total of 1542 subjects were assessed for trial eligibility, of which 1195 were enrolled. The final analysis consisted of 711 subjects with both CTC and lactase dehydrogenase (LDH) data documented at week 12. The abiraterone acetate plus prednisone and prednisone-alone groups demonstrated a substantial survival difference, surrogate distribution at 12 weeks differed by treatment and the discriminatory power of the surrogate to predict mortality was reported as high. At 12 weeks, the 2-year survival of subjects with CTCs less than 5 (low risk) versus those with CTCs greater than 5 cells/7.5 mL of blood and LDH levels greater than 250 U/L (high risk) was 46% and 2%, respectively. A limitation of this study was that only 59% (711 of 1195) of the enrollees had CTC enumeration performed at week 12. The authors concluded that a biomarker panel containing CTC counts and LDH levels demonstrated “individual patient-level surrogacy” and that this further supports its use as a clinical trial endpoint.

Yang and colleagues (2022) evaluated CTCs in 104 individuals with newly diagnosed metastatic castration-sensitive prostate cancer (CSPC). The investigators used a CTC separation and characterization system developed in China (CanPatrol ™) that is not cleared by the U.S. FDA. They further characterized CTCs as those that were CD133+ or CD133- on the basis expression of CD133, an antigen on the surface of cancer cells and stem cells. Study participants received androgen deprivation therapy after enrollment. The primary study endpoint was PFS, calculated from the initiation of androgen deprivation therapy to the occurrence of castration resistance. After a median follow-up of 24 months, the proportion of individuals that progressed to CRPC was significantly higher in the CTC+/ CD133+ group (93.3%) compared with the CTC+/CD133- group (75.0%) or the CTC- group (73.3%), p=0.043. In this study, all individuals were treated with the same drug regimen and the CTC analysis did not impact patient management; the authors did not discuss the potential use of CTC or CD133 analysis for determining optimal treatment.

The NCCN Clinical Practice Guideline for prostate cancer (V4.2023) does not include any recommendations regarding CTC testing.

Other Cancers

Studies have also been published evaluating CTC levels as a diagnostic or prognostic marker for individuals with other types of cancer including melanoma (Hoshimoto, 2012a; Hoshimoto, 2012b), bladder (Guzzo, 2009; Jiang, 2021; Rink, 2010), gastric (Huang, 2015b; Matsusaka, 2010; Yang, 2018), lung (Tanaka, 2009; Krebs, 2011; Gao, 2018; Qian, 2018; Tong, 2018), pancreatic (Court, 2018; Okubo, 2017), thyroid (Ehlers, 2018), endometrial (Kiss, 2018), neuroblastoma (Liu, 2018), and ovarian (Liu, 2013; Huang, 2021) cancer. There are no FDA cleared tests for these indications, and none of the studies evaluated individual health care management decisions using CTCs.

Conclusion

The clinical utility of quantifying CTCs remains unproven. Published data are inadequate to determine how such measurements would guide treatment decisions and whether those treatment decisions would result in beneficial outcomes.

Background/Overview

Studies suggest that the presence of CTCs in individuals with metastatic carcinoma is associated with shortened survival. The CellSearch System is an immunological technique designed to detect CTCs in peripheral blood. Cells are tagged using antibody-coated magnetic beads that recognize cell surface antigens and labeled with fluorescent dyes, which can then be quantified by a semi-automated fluorescent-based microscopy system. The CellSearch System received U.S. Food and Drug Administration (FDA) clearance through the 510(k) process for monitoring of metastatic breast cancer in 2004, for monitoring of metastatic colorectal cancer in 2007, and for monitoring of metastatic prostate cancer in 2008. There has also been some interest for the use of this test in individuals with a variety of other types of cancer. However, published studies have failed to demonstrate a correlation between measurement of CTCs and improved clinical outcomes in the treatment of cancer, including but not limited to breast, colorectal, and prostate cancer.

Breast cancer is the most common cancer among women, other than skin cancer. After lung cancer, it is the second leading cause of cancer death in women. The American Cancer Society estimates that in 2022 there will be about 287,850 American women diagnosed with invasive breast cancer, about 51,400 newly diagnosed cases of carcinoma in situ, and approximately 43,250 women will die from breast cancer.

Colorectal cancer is the third most common cancer found in men and women other than skin cancer in the United States. The American Cancer Society estimates that in 2022 there will be about 106,180 new cases of colon cancer and 44,950 new cases of rectal cancer diagnosed in the United States. Combined, they expected to cause approximately 52,580 deaths in 2022.

Prostate cancer is the most common cancer, other than skin cancers, in American men and is the second leading cause of cancer death in men, behind only lung cancer. The American Cancer Society estimates that in 2022 there will be about 268,490 new cases of prostate cancer diagnosed in the United States and approximately 34,500 deaths from the disease.

Definitions

Metastatic: Spread of a disease from the organ or tissue of origin to another part of the body.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
When the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

86152	Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood);
86153	Cell enumeration using immunologic selection and identification in fluid specimen (eg, 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

ICD-10 Diagnosis

	All diagnoses

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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	02/15/2024	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Rationale, References and Websites sections. Updated Coding section; removed 0317U, other criteria is available.
Reviewed	02/16/2023	MPTAC review. Updated Rationale, References and Websites sections.
	09/28/2022	Updated Coding section with 10/01/2022 CPT changes; added 0337U, 0338U.
Reviewed	02/17/2022	MPTAC review. Rationale, References and Websites sections updated. Updated Coding section with 04/01/2022 CPT changes; added 0317U.
Revised	02/11/2021	MPTAC review. Title changed to “Detection of Circulating Tumor Cells”. Rationale, References and Websites sections updated.
Reviewed	02/20/2020	MPTAC review. Description, Rationale, Background, References, Websites, and Index sections updated.
	06/27/2019	Updated Coding section with 07/01/2019 CPT changes; added 0091U.
Reviewed	03/21/2019	MPTAC review.
Reviewed	03/20/2019	Hematology/Oncology Subcommittee review. Description, Rationale, Background, References, and Websites sections updated.
Reviewed	05/03/2018	MPTAC review.
Reviewed	05/02/2018	Hematology/Oncology Subcommittee review. The document header wording updated from “Current Effective Date” to “Publish Date.” Rationale, References, Websites, and Index sections updated.
Reviewed	05/04/2017	MPTAC review.
Reviewed	05/03/2017	Hematology/Oncology Subcommittee review. Description, Rationale, Background and References sections updated.
Reviewed	05/05/2016	MPTAC review.
Reviewed	05/04/2016	Hematology/Oncology Subcommittee review. Description, Rationale, Background and Reference sections updated. Removed ICD-9 codes from Coding section.
Reviewed	05/07/2015	MPTAC review.
Reviewed	05/06/2015	Hematology/Oncology Subcommittee review. Description, Rationale, Background and Reference sections updated.
Reviewed	05/15/2014	MPTAC review.
Reviewed	05/14/2014	Hematology/Oncology Subcommittee review. Rationale, Background and Reference sections updated.
Reviewed	05/09/2013	MPTAC review.
Reviewed	05/08/2013	Hematology/Oncology Subcommittee review. Rationale, Background and Reference sections updated.
	01/01/2013	Updated Coding section with 01/01/2013 CPT changes; removed 0279T, 0280T deleted 12/31/2012.
Reviewed	05/10/2012	MPTAC review.
Reviewed	05/09/2012	Hematology/Oncology Subcommittee review. Rationale, Background and Reference Sections updated.
	04/01/2012	Updated Coding section with 04/01/2012 HCPCS changes; removed code S3711 deleted 03/31/2012.
	01/01/2012	Updated Coding section with 01/01/2012 CPT changes.
Revised	05/19/2011	MPTAC review.
Revised	05/18/2011	Hematology/Oncology Subcommittee review. Position statement and title of document updated with the removal of the word “metastatic”. Rationale, Background, Reference and Index sections updated.
Reviewed	05/13/2010	MPTAC review.
Reviewed	05/12/2010	Hematology/Oncology Subcommittee review. Title of document, rationale and references updated.
Reviewed	05/21/2009	MPTAC review.
Reviewed	05/20/2009	Hematology/Oncology Subcommittee review. Rationale, background and references updated.
	01/01/2009	Updated Coding section with 01/01/2009 HCPCS changes.
Reviewed	05/15/2008	MPTAC review.
Reviewed	05/14/2008	Hematology/Oncology Subcommittee review. Rationale, background and references updated.
	02/21/2008	The phrase "investigational/not medically necessary" was clarified to read "investigational and not medically necessary." This change was approved at the November 29, 2007 MPTAC meeting.
Reviewed	05/17/2007	MPTAC review.
Reviewed	05/16/2007	Hematology/Oncology Subcommittee review. Rationale and references updated.

Reviewed	06/08/2006	MPTAC review. Rationale and references updated.
Reviewed	06/07/2006	Hematology/Oncology Subcommittee review.
Revised	07/14/2005	MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization.

Pre-Merger Organizations	Last Review Date	Document Number	Title
Anthem, Inc.		No prior document	
WellPoint Health Networks, Inc.	09/23/2004	2.11.23	Detection of Circulating Tumor Cells in the Blood as a Prognostic Factor in Patients with Metastatic Cancer

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