Regence Oregon and Utah | Regence Idaho and select counties of Washington

Medical Policy Manual

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

Date of Origin: July 5, 2005

Section: Laboratory

Last Reviewed Date: May 2014

Policy No: 46

Effective Date: August 1, 2014

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

The prognosis of cancer patients is often determined by the occurrence of metastatic disease. Studies have suggested that the presence of circulating tumor cells in patients with metastatic carcinoma is associated with short survival.

Background

Circulating tumor cells (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 site 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 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™ system (Veridex LLC, a Johnson & Johnson company) received U.S. Food and Drug Administration (FDA) 510(k) approval for monitoring metastatic breast cancer, metastatic colorectal cancer, and metastatic 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.

MEDICAL POLICY CRITERIA

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

SCIENTIFIC EVIDENCE

Although much of the published literature on the detection and quantification of circulating tumor cells is related to metastatic breast cancer, studies have also been performed on other metastatic cancers as well as cancers that have not metastasized. These include lung, bladder, prostate, esophageal, and gastrointestinal cancers and melanoma. Studies for these tumors are more preliminary than those for metastatic breast cancer.

Predicting risk or prognosis does not, by itself, directly improve health outcomes. To complete the causal chain, there must be evidence from prospective, comparative studies that patient management decisions based on circulating tumor cell levels increase the duration or quality of life or decrease adverse events. To date, no large, randomized clinical utility studies have been published that prospectively evaluate health outcomes in patients managed with and without the monitoring of circulating tumor cells.

Metastatic Breast Cancer

Meta-analyses

- 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 positivity 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).

Primary Studies

- Cristofanilli and colleagues reported results from a multicenter prospective trial of 177 patients with measurable metastatic breast cancer who were followed for 38.7 weeks or longer.[3] Using the CellSearch™ System (Veridex LLC), they measured the number of circulating tumor cells before initiating a new line of therapy and at first follow-up (4.5 +/- 2.4 weeks after baseline sample). They also tested 145 normal subjects and 200 patients with benign breast diseases. The authors reported detecting two or fewer epithelial cells per 7.5 mL of blood in all normal subjects and in 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 (7.0 versus 2.7 months; $p<0.001$) and overall survival (greater than 18 months versus 10.1 months; $p<0.001$) 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 circulating tumor cells was the most statistically significant independent predictor of longer progression-free and overall survival of all parameters studied, including hormone receptor status, HER-2/neu status, site of metastases, etc.

  Cristofanilli and colleagues noted, "This study did not address whether patients with an elevated number of circulating tumor cells might benefit from other therapies. Whether such patients might benefit from other therapies is under investigation." Studies are needed which complete the causal chain and address whether this prognostic test may be used as a predictive tool to guide patient

management. Data for the subgroup above threshold at baseline who fell below threshold at first follow-up suggest it may identify responders sooner than currently possible with imaging modalities (approximately 4 weeks versus 2–3 months). This may permit earlier changes in the treatment regimen for non-responders and thus, might improve outcomes.

In an accompanying editorial, Braun and Marth note that evidence is also lacking that measuring circulating tumor cells is useful either to predict prognosis or guide treatment decisions for patients with breast cancer that has not metastasized who are receiving adjuvant systemic therapy after local treatment.[4] The possibility of curing breast cancer is substantially greater among patients with early stage disease than after it has metastasized. Thus, tests are also needed to accurately predict response and guide adjuvant therapy in early stage patients. In the adjuvant, neoadjuvant (i.e., presurgery) and metastatic disease settings, many groups are investigating genomic methods to predict prognosis and responses to treatment. (See Laboratory, Policy No. 42.) If ongoing studies demonstrate the CellSearch™ System can reliably guide treatment decisions for patients with metastatic breast cancer, future trials comparing this test to genomic methods may also be important.

- Nole and colleagues tested 80 patients with metastatic breast cancer for circulating tumor cell levels before starting a new treatment and after four weeks, eight weeks, at the first clinical evaluation, and every two months thereafter.[5] Forty-nine patients had 5 or more cells at baseline. At the multivariate analysis, baseline number of circulating tumor cells was associated with progression-free survival (hazard ratio [HR] 2.5; 95% confidence interval [CI] 1.2–5.4). The risk of progression for patients with 5 or more circulating tumor cells at the last available blood draw was five times the risk of patients with 0–4 circulating tumor cells at the same point (HR 5.3; 95% CI: 2.8–10.4). Patients with rising or persistent counts of 5 or more circulating tumor cells at last available blood draw showed a statistically significant higher risk of progression with respect to patients with less than 5 circulating tumor cells at both blood draws. The authors concluded that circulating tumor cell basal value is a predictive indicator of prognosis, that changes in circulating tumor cell levels during therapy may indicate a clinical response, and that testing circulating tumor cell levels during targeted treatments might substitute for other parameters to determine response to therapy.

- A prospective study was conducted by Yagata and colleagues to evaluate the circulating tumor cell levels in patients with metastatic breast cancer who were being treated at 3 institutions in Japan.[6] The study included 38 patients with a confirmed diagnosis of progressive, metastatic breast cancer prior to initiation of new systemic therapy. With cutoff value set at 2 circulating tumor cells, sensitivity to distant metastasis was 50% (19/38) and specificity was 96.7% (29/30). Both progression-free survival and overall survival were worse for patients with a cutoff score of 5 CTCs, compared with patients with fewer than 5 circulating tumor cells. The authors concluded that, for patients with breast cancer, measuring circulating tumor cell levels can be both an indicator of metastases and an important measure of patient prognosis. Limitations of this study include the small sample size and the variable cutoff levels.

- Pierga and colleagues in France reported findings from a prospective series that included 267 with metastatic breast cancer who were starting first-line chemotherapy.[7] CTCs were analyzed before starting treatment, before the 2nd cycle of treatment, at the first radiological evaluation 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 progression-free survival ($p<0.0001$). 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 overall survival (p=0.0002). In multivariate analysis, baseline CTC positivity was an independent prognostic factor for both PFS and OS.

- Georgoulias and colleagues evaluated the use of CTC levels as a prognostic tool in a randomized trial of 75 patients with HER2-negative breast cancer and CK19 mRNA-positive CTCs.[8] Patients were randomized to either receive trastuzumab (n=36) or observation (n=39) and the primary endpoint was 3 year disease-free survival. Authors reported that 4 (11%) relapses were reported in the trastuzumab arm, compared to 15 (38%) in the observation arm. Although this study noted positive findings associated with CTC guided treatment, it is limited by small sample size and outcomes were not compared to breast cancer patients who did not have CK19 mRNA-positive CTCs.

- A multicenter phase II trial conducted by Pestrin and colleagues evaluated lapatinib treatment in metastatic breast cancer patients with HER2-negative primary tumors and HER2-positive CTC.[9] Ninety-six patients were identified and all were previously treated with a first-line therapy. Only seven patients of the 96 had ≥ 50% HER-2 positive CTC and were then given lapatinib 1500 mg/day. Again, CTC analysis was performed by the CellSearch™ System. Authors reported no objective tumor response to lapatinib treatment.

Conclusion

Overall, the evidence regarding the use of CTC to predict risk of breast cancer progression or alter patient management has been limited to association studies which have indicated longer median progression-free and overall survival in patients with lower CTCs. These studies are limited by a lack of validated cutoff or threshold number of CTCs in which to classify patients as normal versus at-risk. Without an established cutoff value, data from CTC tests will be of little clinical use.

Although association studies may help to establish an evidence base for the use CTCs in breast cancer treatment, questions remain regarding the appropriate patient population in which CTC might be useful. Large, prospective studies which demonstrate how CTC levels could be used to make clinical treatment decisions are needed.

Metastatic Colorectal Cancer

Meta-analysis

A 2013 meta-analysis by Groot Koerkampt and colleagues reviewed studies on the prognostic value of CTCs as well as studies on the detection of disseminated tumor cells (DTCs) in bone marrow.[10] 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 overall survival (HR: 2.47, 95% CI: 1.74 to 3.51, 11 studies) and a worse progression-free survival (HR: 2.07, 95% CI: 1.44 to 2.98, 9 studies).

Primary Studies

- A prospective multicenter industry-sponsored study by Cohen and colleagues examined the association of circulating tumor cells to survival in patients with metastatic colorectal cancer.[11] To

be eligible, patients needed to be initiating any first- or second-line systemic therapy, or third-line therapy with an epidermal growth factor receptor inhibitor. Circulating tumor cells were assessed at baseline and at regular intervals after starting treatment. The authors conducted a pre-planned interim analysis using data from the first 109 patients (training set) to determine the optimal cut-off for an elevated cell count and the optimal length of time after initiating therapy to measure circulating tumor cell level. They determined that levels of circulating tumor cells at the 3 to 5-week follow-up correlated most highly with response at first imaging study (6-12 weeks after initiating treatment), and that at least 3 circulating tumor cells per 7.5 mL blood was the optimal threshold. 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 or an elevated level corresponding to progressive disease. Data from the training set and from the remaining patients (validation set) were combined in the main analysis. A total of 481 patients were enrolled; 37 were found after enrollment not to meet eligibility criteria, 6 withdrew consent and 8 were excluded for other reasons, leaving 430 evaluable patients. Only 320 patients, however, were assessable for the primary outcome. The authors did not specify how many of these patients had been included in the training set. One-hundred and ten patients did not have a follow-up blood analysis or imaging, and data on 8 were unavailable for other reasons. Thirty-eight of 320 (12%) had elevated levels of circulating tumor cells 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). Median progression-free survival and overall survival, secondary outcomes, by baseline and post-treatment initiation CTC status are shown in the table below:

Table 1. Level of circulating tumor cells

Baseline	3-5 week follow-up	n (%)	Median PFS in months (95% CI)	n (%)	Median OS in months (95% CI)
Not elevated	Not elevated	226 (72)	7.3 (6.0-7.8)	227 (71)	17.7 (14.7-19.9)
Elevated	Not elevated	52 (16)	6.2 (4.6-7.0)	53 (17)	11.0 (8.7-18.1)
Not elevated	Elevated	9 (13)	6.0 (0.5 to --)	9 (3)	10.9 (0.6 to --)
Elevated	Elevated	28 (9)	1.6 (1.2-2.7)	30 (9)	3.7 (2.4-8.4)

Elevated= at least 3 circulating tumor cells (CTC) per 7.5 mL blood
PFS= Progression-free survival
OS= Overall survival

Both progression-free survival and overall survival were highest for patients with non-elevated CTCs at both time points, lowest for those with elevated CTCs at both time points, and at intermediate levels for those with elevated CTCs at only one time point. The median progression-free survival and median overall survival were significantly longer in patients who did not have elevated CTCs at either time point than the patients who had elevated CTCs at both time points. Overall survival, but not progression-free survival, was significantly longer in the group without elevated CTCs at either time compared to those whose CTCs were elevated at baseline and then decreased at 3 to 5 weeks. Only 9 patients experienced an increase in CTCs from baseline to 3 to 5 weeks. Study limitations include 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. Moreover, as the authors state in their conclusion, this study was not designed to evaluate whether patient management decisions based on CTC level is beneficial.

- In 2012, Sastre and colleagues published data from a phase III prospective study of 180 patients with metastatic colon cancer receiving first-line chemotherapy plus bevacizumab.[12] CTC evaluation was carried out using the CellSearch™ System and blood samples were obtained at baseline and again after three treatment cycles. In addition, CT scans were completed at cycle 3, 6, and every 12 weeks thereafter to assess tumor response to treatment. Median progression-free survival with a CTC count of ≥ 3 at baseline was reported to be 7.8 months versus 12 months for patients with CTC count < 3 (p = .0002). Median overall survival was 17.7 months for patients with a CTC count ≥ 3 versus 25.1 months for patients with CTC count < 3 (p = .0059). Similar significant differences between patients with CTC counts ≥ compared to those < 3 were observed after three treatment cycles. Although this study adds support to the cutoff value of 3 cells per 7.5ml of blood reported by Cohen, the study is limited in that authors did not compare this cutoff to any other cutoff value. In addition, the study does not demonstrate how CTC levels altered or improved patient treatment decisions.

Metastatic Prostate Cancer

Meta-analyses

Wang and colleagues published a meta-analysis of studies on the association between circulating tumor cells and prognosis in patients with metastatic castration-resistant or hormone refractory prostate cancer.[13] The authors searched the literature for studies with at least 30 patients and sufficient data to calculate relative risk (RR) of overall survival. The authors identified 19 relevant articles of which 4 met study inclusion criteria. The total 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 7.5ml blood); RR=2.51, 95% CI=1.96-3.21. In a sensitivity analysis removing the study with the largest sample size (de Bono et al., 2008, reference 6), the RR was marginally higher (RR=3.25, 95% CI=2.01 to 5.24). The test for study heterogeneity was not statistically significant.

Primary Studies

A prospective multicenter industry-sponsored study, by de Bono and colleagues, addressed circulating tumor cell levels and prostate cancer.[14] The study 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 circulating tumor cells; 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 overall survival. The authors did not report their reasons for selecting the 2 to 5 week follow-up point. An evaluable circulating tumor cell 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 circulating tumor cells 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 overall survival, 6.8 months. Their overall survival was significantly shorter than other groups, specifically the group of patients with elevated baseline CTCs who converted to a non-elevated level after treatment (n=45, median overall survival 21.3 months) and the group of patients with non-elevated CTCs throughout the study (n=88, median overall survival 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 overall survival 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. Similar to the studies discussed previously on metastatic breast and colorectal cancer, this study did not evaluate the role of CTC level assessment in patient management.

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[15,16] and prostate cancer[17] as well as other types of cancer including: bladder[18,19], gastric,[20-22] head and neck,[23,24] liver[21,25], lung, [26-31] melanoma,[32-34] pancreatic[35,36] and ovarian[37] 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 Practice Guidelines

American Society of Clinical Oncology

The American Society of Clinical Oncology recommendations for the use of tumor markers in breast cancer indicated that the measurement of circulating tumor cells should not be used to make the diagnosis of breast cancer or to influence any treatment decisions in those with breast cancer.[38]

National Comprehensive Care Network (NCCN)

The 2014 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.[39-41]

Summary

While levels of circulating tumor cells (CTC) may be associated with the presence of metastatic disease and prognosis, the prospective use of this information to impact care has not been demonstrated. None of the studies identified have evaluated clinical utility through prospective use of this assay in clinical care, limiting conclusions regarding the impact of CTC testing on health outcomes. Therefore, detection and quantification of circulating tumor cells is considered **investigational** in the management of patients with cancer.

REFERENCES

1. Zhang, L, Riethdorf, S, Wu, G, et al. Meta-analysis of the prognostic value of circulating tumor cells in breast cancer. *Clin Cancer Res*. 2012 Oct 15;18(20):5701-10. PMID: 22908097

2. Zhao, S, Liu, Y, Zhang, Q, et al. The prognostic role of circulating tumor cells (CTCs) detected by RT-PCR in breast cancer: a meta-analysis of published literature. *Breast Cancer Res Treat*. 2011 Dec;130(3):809-16. PMID: 21311967
3. Cristofanilli, M, Budd, GT, Ellis, MJ, et al. Circulating tumor cells, disease progression, and survival in metastatic breast cancer. *N Engl J Med*. 2004 Aug 19;351(8):781-91. PMID: 15317891
4. Braun, S, Marth, C. Circulating tumor cells in metastatic breast cancer--toward individualized treatment? *N Engl J Med*. 2004 Aug 19;351(8):824-6. PMID: 15317898
5. Nole, F, Munzone, E, Zorzino, L, et al. Variation of circulating tumor cell levels during treatment of metastatic breast cancer: prognostic and therapeutic implications. *Ann Oncol*. 2008 May;19(5):891-7. PMID: 18056915
6. Yagata, H, Nakamura, S, Toi, M, Bando, H, Ohno, S, Kataoka, A. Evaluation of circulating tumor cells in patients with breast cancer: multi-institutional clinical trial in Japan. *Int J Clin Oncol*. 2008 Jun;13(3):252-6. PMID: 18553236
7. Pierga, JY, Hajage, D, Bachelot, T, et al. High independent prognostic and predictive value of circulating tumor cells compared with serum tumor markers in a large prospective trial in first-line chemotherapy for metastatic breast cancer patients. *Ann Oncol*. 2012 Mar;23(3):618-24. PMID: 21642515
8. Georgoulias, V, Bozionelou, V, Agelaki, S, et al. Trastuzumab decreases the incidence of clinical relapses in patients with early breast cancer presenting chemotherapy-resistant CK-19mRNA-positive circulating tumor cells: results of a randomized phase II study. *Ann Oncol*. 2012 Jul;23(7):1744-50. PMID: 22377561
9. Pestrin, M, Bessi, S, Puglisi, F, et al. Final results of a multicenter phase II clinical trial evaluating the activity of single-agent lapatinib in patients with HER2-negative metastatic breast cancer and HER2-positive circulating tumor cells. A proof-of-concept study. *Breast Cancer Res Treat*. 2012 Jul;134(1):283-9. PMID: 22476856
10. Groot Koerkamp, B, Rahbari, NN, Buchler, MW, Koch, M, Weitz, J. Circulating Tumor Cells and Prognosis of Patients with Resectable Colorectal Liver Metastases or Widespread Metastatic Colorectal Cancer: A Meta-Analysis. *Ann Surg Oncol*. 2013 Mar 2. PMID: 23456317
11. Cohen, SJ, Punt, CJ, Iannotti, N, et al. Relationship of circulating tumor cells to tumor response, progression-free survival, and overall survival in patients with metastatic colorectal cancer. *J Clin Oncol*. 2008 Jul 1;26(19):3213-21. PMID: 18591556
12. Sastre, J, Maestro, ML, Gomez-Espana, A, et al. Circulating tumor cell count is a prognostic factor in metastatic colorectal cancer patients receiving first-line chemotherapy plus bevacizumab: a Spanish Cooperative Group for the Treatment of Digestive Tumors study. *Oncologist*. 2012;17(7):947-55. PMID: 22643538
13. Wang, FB, Yang, XQ, Yang, S, Wang, BC, Feng, MH, Tu, JC. A higher number of circulating tumor cells (CTC) in peripheral blood indicates poor prognosis in prostate cancer patients--a meta-analysis. *Asian Pacific journal of cancer prevention : APJCP*. 2011;12(10):2629-35. PMID: 22320965
14. de Bono, JS, Scher, HI, Montgomery, RB, et al. Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. *Clin Cancer Res*. 2008 Oct 1;14(19):6302-9. PMID: 18829513
15. Bidard, FC, Mathiot, C, Delaloge, S, et al. Single circulating tumor cell detection and overall survival in nonmetastatic breast cancer. *Ann Oncol*. 2010 Apr;21(4):729-33. PMID: 19850639
16. Serrano, MJ, Lorente, JA, Delgado Rodriguez, M, et al. Circulating tumour cells in peripheral blood: potential impact on breast cancer outcome. *Clin Transl Oncol*. 2011 Mar;13(3):204-8. PMID: 21421466

17. Ma, X, Xiao, Z, Li, X, et al. Prognostic role of circulating tumor cells and disseminated tumor cells in patients with prostate cancer: a systematic review and meta-analysis. *Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine*. 2014 Feb 22. PMID: 24563278
18. Guzzo, TJ, McNeil, BK, Bivalacqua, TJ, Elliott, DJ, Sokoll, LJ, Schoenberg, MP. The presence of circulating tumor cells does not predict extravesical disease in bladder cancer patients prior to radical cystectomy. *Urol Oncol*. 2009 Dec 11. PMID: 20005748
19. Rink, M, Chun, FK, Minner, S, et al. Detection of circulating tumour cells in peripheral blood of patients with advanced non-metastatic bladder cancer. *BJU Int*. 2011 May;107(10):1668-75. PMID: 20735381
20. Matsusaka, S, Chin, K, Ogura, M, et al. Circulating tumor cells as a surrogate marker for determining response to chemotherapy in patients with advanced gastric cancer. *Cancer Sci*. 2010 Apr;101(4):1067-71. PMID: 20219073
21. Gao, P, Jiao, SC, Bai, L, Wang, H, Jing, FF, Yang, JL. Detection of circulating tumour cells in gastric and hepatocellular carcinoma: a systematic review. *J Int Med Res*. 2013;41:923-33. PMID: 23908550
22. Tang, L, Zhao, S, Liu, W, et al. Diagnostic accuracy of circulating tumor cells detection in gastric cancer: systematic review and meta-analysis. *BMC Cancer*. 2013;13:314. PMID: 23806209
23. Buglione, M, Grisanti, S, Almici, C, et al. Circulating tumour cells in locally advanced head and neck cancer: preliminary report about their possible role in predicting response to non-surgical treatment and survival. *Eur J Cancer*. 2012 Nov;48(16):3019-26. PMID: 22682019
24. Tinhofer, I, Hristozova, T, Stromberger, C, Keilhoiz, U, Budach, V. Monitoring of circulating tumor cells and their expression of EGFR/phospho-EGFR during combined radiotherapy regimens in locally advanced squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys*. 2012 Aug 1;83(5):e685-90. PMID: 22583603
25. Jin, T, Peng, H, Wu, H. Clinical value of circulating liver cancer cells for the diagnosis of hepatocellular carcinoma: A meta-analysis. *Biomed Rep*. 2013;1:731-6. PMID: 24649019
26. Tanaka, F, Yoneda, K, Kondo, N, et al. Circulating tumor cell as a diagnostic marker in primary lung cancer. *Clin Cancer Res*. 2009 Nov 15;15(22):6980-6. PMID: 19887487
27. Krebs, MG, Sloane, R, Priest, L, et al. Evaluation and prognostic significance of circulating tumor cells in patients with non-small-cell lung cancer. *J Clin Oncol*. 2011 Apr 20;29(12):1556-63. PMID: 21422424
28. Hiltermann, TJ, Pore, MM, van den Berg, A, et al. Circulating tumor cells in small-cell lung cancer: a predictive and prognostic factor. *Ann Oncol*. 2012 Nov;23(11):2937-42. PMID: 22689177
29. Punnoose, EA, Atwal, S, Liu, W, et al. Evaluation of circulating tumor cells and circulating tumor DNA in non-small cell lung cancer: association with clinical endpoints in a phase II clinical trial of pertuzumab and erlotinib. *Clin Cancer Res*. 2012 Apr 15;18(8):2391-401. PMID: 22492982
30. Ma, XL, Xiao, ZL, Liu, L, et al. Meta-analysis of circulating tumor cells as a prognostic marker in lung cancer. *Asian Pacific journal of cancer prevention : APJCP*. 2012;13(4):1137-44. PMID: 22799295
31. Huang, J, Wang, K, Xu, J, Zhang, T. Prognostic significance of circulating tumor cells in non-small-cell lung cancer patients: a meta-analysis. *PLoS One*. 2013;8:e78070. PMID: 24223761
32. Torres, V, Triozzi, P, Eng, C, et al. Circulating tumor cells in uveal melanoma. *Future Oncol*. 2011 Jan;7(1):101-9. PMID: 21174541

33. Hoshimoto, S, Shingai, T, Morton, DL, et al. Association between circulating tumor cells and prognosis in patients with stage III melanoma with sentinel lymph node metastasis in a phase III international multicenter trial. *J Clin Oncol*. 2012 Nov 1;30(31):3819-26. PMID: 23008288
34. Rodic, S, Mihalcioiu, C, Saleh, RR. Detection methods of circulating tumor cells in cutaneous melanoma: A systematic review. *Crit Rev Oncol Hematol*. 2014 Jan 24. PMID: 24530125
35. Han, L, Chen, W, Zhao, Q. Prognostic value of circulating tumor cells in patients with pancreatic cancer: a meta-analysis. *Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine*. 2014 Mar;35(3):2473-80. PMID: 24218336
36. Bidard, FC, Huguet, F, Louvet, C, et al. Circulating tumor cells in locally advanced pancreatic adenocarcinoma: the ancillary CirCe 07 study to the LAP 07 trial. *Ann Oncol*. 2013;24:2057-61. PMID: 23676420
37. Romero-Laorden, N, Olmos, D, Fehm, T, Garcia-Donas, J, Diaz-Padilla, I. Circulating and disseminated tumor cells in ovarian cancer: A systematic review. *Gynecol Oncol*. 2014 Mar 19. PMID: 24657303
38. Harris, L, Fritsche, H, Mennell, R, et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. *J Clin Oncol*. 2007;25(33):5287-312. PMID: 17954709. [cited 03/01/2012]; Available from: http://jco.ascopubs.org/content/25/33/5287.full
39. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Breast Cancer. V.3.2014. [cited 05/05/2014]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
40. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Colon cancer. v.3.2014. [cited 05/05/2014]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf
41. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology™: Prostate Cancer v.2.2014. [cited 06/17/2014]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
42. BlueCross BlueShield Association Medical Policy Reference Manual "Detection of Circulating Tumor Cells in the Management of Patients with Cancer." Policy No. 2.04.37

CROSS REFERENCES

Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20

Analysis of Proteomic Patterns for Early Detection of Cancer, Laboratory, Policy No. 41

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis In Patients With Breast Cancer, Genetic Testing, Policy No. 42

CODES	NUMBER	DESCRIPTION
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
HCPCS	None	