Final Comment and Response

LCD Database ID Number
L32218

LCD Title
Circulating Tumor Cell Marker Assays

Contractor's Determination Number
PATH-033

Comment
The limitation of the Circulating Tumor Cell Assay to the three disease states (breast, colorectal, and prostate cancers) is appropriate.

Response
Thank you for your comment.

Comment
Coverage for this policy allows only one vendor's assay to be reimbursed. The Indications and Limitations section specifically states "This is a coverage policy for the CellSearch (Veridex) CTC assay."

This would eliminate any laboratory developed test (LDTs) and any other vendors that may come on the market from being covered. It is rare to see a laboratory LCD that specifies the vendor of a test. I feel that this would limit innovation in this area and that it is too restrictive.

Response
At the time this LCD was written and published the Cell Search (Veridex) Circulating Tumor Cell Assay is the only FDA approved CTC detection system and is therefore the only test that is covered.

Comment
There is a proposal to approve an LCD for the use of CTC by CellSearch for breast, prostate and colorectal cancer. While there is little controversy about the technical aspect of the test, which measures epithelial cell antigens (EpCAM) on circulating cells that are CD45 negative, the questions have been about clinical utility.

The CTC count after one cycle of therapy for breast cancer or prostate cancer is **prognostic** for progression-free (PFS) and overall survival (OS). The more unusual and perhaps controversial area would be colorectal cancer. A study by Cohen, et al, in the *J Clin Oncol* in 2008[1] also showed that this test is prognostic for both PFS and OS. They did combine the training set an validation set into one trial, somewhat troubling, but indicated that the results were the same. The cut-off for number of cells was 3 for a poor prognosis, while in breast cancer it is greater than 5.

However, it is unclear in any of these studies that CTC is **predictive** of response to therapy, or whether an immediate change in therapy would lead to a better outcome. There are trials

[1] Cohen, SJ, 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* 26:3213-3221:2008.

currently under way to help answer that question. Note that these studies were all done on patients with metastatic disease. As yet, there are no reliable studies of a correlation to adjuvant therapy and prediction of outcome, something that would be potentially quite useful. A search for studies in the JCO uncovered an article by Iinuma, et all, that notes CTC in the title[2], but in fact used a different technique for measuring the cells of interest.

The most important question is whether measurement of CTC adds to any of the tests that we have available to us. Note that all studies have looked at patients with metastatic disease. For colorectal cancer patients, we have excellent ways of measuring response to therapy for most patients, so the benefit of another method is questionable. For patients with breast and prostate cancer, however, the ability to measure response with bone-only disease can be difficult, and another way of confirming response early on is reasonable, especially if one is making the decision to switch from hormonal therapy to chemotherapy.

A good summary of the use of CTC is posted on the Mayo Clinical Laboratory web site.[3]

In summary:

- There are certain situations in metastatic breast and prostate cancer, especially in those patients with bone only disease, where the use of CTC can be helpful in determining the effect of therapy, and may lead to an earlier change to a more effective therapy.

- CTC in metastatic breast cancer, metastatic prostate cancer and metastatic colon cancer are prognostic for DFS and OS. However, since those patients who decrease their CTC after therapy have equivalent survival to the favorable group, CTC cannot serve to decide whether therapy at all should be given.

- CTC are not predictive of response to therapy.

- I am not convinced that there is clear benefit in metastatic colorectal cancer, at least in the papers cited.

- I have not seen any convincing data that CTC are predictive enough to determine whether one should give adjuvant therapy for breast or colon cancer.

- The test appears to be reliable and reproducible.

The test should be approved, but evaluation needs to be done to determine how often CTC should be done, and under what circumstances. It is likely most useful for those patients who have metastatic disease and for whom measurement of response is difficult, or for those who have significant toxicity after one cycle of therapy and the physician is attempting to decide on whether to continue that therapy or not.

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[2] Iinuma H, et al. Clinical Significance of Circulating Tumor Cells, Including Cancer Stem-Like Cells, in Peripheral Blood for Recurrence and Prognosis in Patients with Dukes' Stage B and C Colorectal Cancer. *J Clin Oncol.* 29:1547-1555: 2011

[3] http://www.mayomedicallaboratories.com/articles/hottopics/2011/04-ctc/ Cited on 8-14-11.

Response
Thank you for your comments.

Comment
Requests were received to add these additional ICD-9/HCPCS codes to the final policy:

196.0 Secondary and unspecified malignant neoplasm of lymph nodes of head face and neck
198.3 Secondary malignant neoplasm of brain and spinal cord
198.5 Secondary malignant neoplasm of bone and bone marrow
197.7 Secondary malignant neoplasm of liver
197.0 Secondary malignant neoplasm of lung

Response
With regards to ICD-9 coding, we do need to know the origin of the cancer and therefore we are using the diagnosis codes for breast, prostate and colon cancer. The codes for metastatic disease do not specify the origin of the cancer. On post pay review we would expect to see documentation of metastatic disease.

The ICD-9/HCPCS codes requested are not specific to secondary malignancies related to the covered indications which are metastatic breast, prostate and colorectal cancer and therefore will not be added to the covered ICD-9/ HCPCS codes in the LCD. It is not the intent of the LCD to cover a secondary malignant neoplasm of the bone and bone marrow (for example) if the primary malignancy is not breast, prostate or colorectal.

Comment
A request was received to change the last sentence in paragraph 4 from "Digital fluorescent images are *interpreted* by a technician…." to "Digital fluorescent images are screened by a qualified technician…."

And change the first sentence of paragraph 5 to "The assay findings are **verified by a pathologist** and issued in a report as a numerical result. More than 5 cells…."

Response
The LCD was changed to the following:

Digital fluorescent images are screened by a qualified technician for CTCs; the cell has a nucleus, expresses keratin (EpCAM and CK) and does not express CD45.

The assay findings are verified by a pathologist and issued in a report as a numerical result where more than 5 cells per 7.5 ml of whole blood predicts worse prognosis in patients with known recurrent breast and prostate cancer, and more than 3 cells are predictive of shorter progression free survival (PFS) and overall survival (OS) in metastatic colorectal cancer.

Comment
The Utilization Guidelines section is appropriate.

Response
Thank you for your comment

Comment
Comment from one group that had reviewed the technology. They determined that although the technology could detect trace amounts of cancer cells; the technology did not indicate what it means and were surprised that WPS Medicare was covering it.

And a similar comment, personally, this realm of monitoring cancers has interesting potential, but results of solidly conducted scientific trials are needed to determine whether or not it should be reimbursed in the future, even though it is FDA approved. The literature repeatedly bears out the prediction of progression-free survival and overall survival, but that doesn't translate immediately into therapeutic decision making outside of clinical trials at this time.

Response
WPS Medicare is aware of the technologies limitations and that is why WPS is limiting its use and frequency.