

» On-Conversation with Massimo Cristofanilli, MD, Principal Investigator of the CellSearch Circulating Tumor Cell Test



Massimo Cristofanilli, MD, Associate Professor, University of Texas

Last month, the Cleveland Clinic ranked the technology used in the CellSearch® System to measure circulating tumor cells (CTCs) as the top medical innovation for 2009. CellSearch, a proprietary Veridex technology, received this prestigious annual recognition following a rigorous selection process among technologies likely to have a significant impact on health care next year. CellSearch is cleared by the U.S. Food and Drug Administration (FDA) to predict progression-free survival and overall survival in patients with metastatic breast, colorectal or prostate cancer. The CellSearch System is the first diagnostic test to automate the capture and

detection of tumor cells that have detached from solid tumors and entered the patient's blood. We had a conversation with Dr. Massimo Cristofanilli, principal investigator in the prospective validation trial of CTCs in women with metastatic breast cancer. He is an associate professor at the University of Texas M. D. Anderson Cancer Center's Department of Breast Medical Oncology and Director of the Morgan Welch Inflammatory Breast Cancer Research Program and Clinic.

ferent time points as a way to monitor cancer progression and response to therapy. Again, the concept may be simple, but the practice requires a shift in the philosophy of the treatment of metastatic disease to acknowledge that there may be a large number of patients who can be successfully managed with current treatments for a long time, as indicated by their low CTC numbers.

OBR: *So the CellSearch test results can help you differentiate between patients with good or poor prognoses more easily than you were able to in the past?*

MC: Yes. The magic number of 5 CTCs can help stratify patients into two different groups. Patients with less than 5 CTCs have quite longer progression-free survival than those with 5 or more CTCs and less than 5 CTCs can indicate a good response to current therapy. This has been shown in hundreds of patients that we have studied. Patients with 5 CTCs or more at presentation and during treatment have an illness progression against which our current treatments are not sophisticated enough to treat these patients. In contrast, the patient with less than 5 CTCs may improve with even less aggressive treatment, allowing them to avoid damaging side effects of chemotherapy.

OBR: *How does the CellSearch System work?*

MC: We collect one 7.5 cc sample of blood from the patient in a tube with a special fluid that stabilizes the CTCs at room temperature for up to 72 hours. The sample is placed in an automated system that enriches and separates the epithelial cells from the other cells in the blood. Antibodies are joined to microscopic iron particles, called ferrofluids, and these antibody/ferrofluid combinations attach specifically to the CTCs. Magnets then attract the CTCs out of the blood sample, after which they are stained with additional bio-molecules and chemicals so that they can be positively identified. Images of the CTCs are reviewed by a technician and often also by a pathologist to confirm the presence of tumor cells of epithelial origin. The CTCs are then counted, and that number, which can range from zero to several thousand, is sent to the oncologist. The CellSearch System can reproducibly find a single CTC among approximately 40 billion blood cells in a 7.5 cc blood sample.

OBR: *So the test output to the oncologist is just the CTC number. How is this result interpreted?*

MC: In the context of planning treatment, if the patient has more than 5 CTCs, the treatment will need to be aggressive. In the following weeks, subsequent CellSearch tests can inform about the benefit of the treatment. If the CTC count drops below 5, that is an indication that the treatment is achieving its goal of prolonging the control of the disease and, eventually, survival.

OBR: *What are circulating tumor cells (CTCs) and what is their relationship to cancer progression?*

MC: There is evidence that people with advanced cancer have CTCs that have broken away from the tumor and have entered the bloodstream. During the past five years we've learned that the number of CTCs is related to the stage of the disease and that more advanced disease is associated with a higher number of CTCs. If tests show that CTCs persist in the blood in spite of chemotherapy, it indicates progression of disease and suggests the participation of CTCs in the metastatic process.

OBR: *The concept of using CTCs to monitor and predict cancer progression seems brilliantly simple. How was the technology for the diagnostic test conceived and developed?*

MC: The concept sounds simple, but it took a great deal of teamwork to develop a clinically useful technology. For many years, oncologists have been using imaging to assess disease progression, but we always realized there were limitations. We saw that many patients had the same imaging results, but had different responses to treatment and different survival, which suggested that imaging was not the best way to define the complex biology of metastatic breast cancer, for example. Our goal was to be able to obtain a real-time assessment of the metastatic process by evaluation of CTCs at dif-

OBR: *That implies that in the course of the disease, the test is not given once to a patient, but multiple times?*

MC: Correct. The benefit of using the CellSearch test is not necessarily for a baseline CTC count, but to monitor the outcome of treatment, so it's done multiple times. Knowing the CTC count helps guide the patient and the oncologist through the course of the disease. Other tests, such as serum tumor markers, have been shown to have no value at all in assessing the benefits of treatment. However, oncologists may need time to become comfortable with the power and the benefits of knowing the CTC measure.

OBR: *How is the CellSearch test administered and what is the cost?*

MC: Blood is simply drawn from the patient into a special preservative tube which is sent to a lab for analysis. The cost per test at Quest Diagnostics is about \$500 to \$600 and it is covered by Medicare and by private health insurers. It is very cost effective, especially compared with imaging, which averages several thousand dollars per scan.

OBR: *Patients that are indicated for this test are those with metastatic breast, colorectal or prostate cancer. Are there any other cancers that are considered eligible for the CellSearch test?*

MC: In general, solid tumors with an epithelial component best fit within the concept of the CellSearch technology. There are other types of cancers beyond the three for which the test is indicated; for example, ovarian cancer or gastrointestinal malignancies may also fit within the test parameters.

OBR: *Does the CellSearch System complement or supplant traditional imaging?*

MC: We can definitely say that it currently complements traditional imaging, which offers information about just a moment in the dynamic of the disease. There should be future studies to look at how we can replace traditional imaging, especially if we look at containment of healthcare costs. If you compare the cost of a PET/CT, which is about \$5,000, with the CellSearch test, you realize that the funds saved could perhaps be used for better patient management.

OBR: *Are there any other assays that reliably detect CTCs in the blood of cancer patients?*

MC: This is the only test that is FDA approved for use in the United States. There is a technology available in Europe (Adnagen Breast Test) that looks at CTCs but gives a different type of information. It does not provide the count of CTCs but

instead examines the genetics and biology of the cells. It would be interesting to see if, in the future, other technologies could complement the CellSearch system to provide a more complete set of information for the patient.

OBR: *The Cleveland Clinic designated the CellSearch system the top medical innovation for 2009. In your opinion, what significance does this have for its use in cancer patients?*

MC: The CellSearch technology represents a fundamental change in how we look at metastatic disease in general. To be able to understand the microscopic component in peripheral blood tells us much more than we ever even knew to ask about the anatomical representation of the disease and can also guide us through therapy. This is an extremely important shift in the practice of oncology. To be able to develop patient-specific therapy, according to that patient's CTC count, is valuable and significant. Getting indications about prognosis will help us improve the survival of our patients.

OBR: *How long have you used the CellSearch test in your own practice and how often do you administer it?*

MC: In my own institution, we've used it since 2005. I use it for every one of my patients with metastatic disease. I monitor patients with more than 5 CTCs very closely, retesting them every few weeks at the beginning of treatment. I try to be more flexible with patients with less than 5 CTCs, because that is a good prognostic sign and there is less need to be aggressive. An important question is: Can we use this in early disease, perhaps to identify risk of recurrence? Research on this topic is ongoing, and preliminary results indicate that early knowledge of the measure of CTCs may guide therapy to prevent full establishment of metastatic disease.

OBR: *Do you have any final statement about the CellSearch test you'd like to share with your colleagues?*

MC: I wish and hope that oncologists will embrace this test more and more in their practice. I would encourage them not to be afraid of the information obtained, because it will only help them to communicate with their patients about the progress of their disease and to collaborate with them on their treatment. It is especially valuable in monitoring disease progression and determining prognosis. **OBR**



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