Following Up an Old Theory

In the 1970s, Peter Nowell, M.D., from the University of Pennsylvania School of Medicine, proposed a model for somatic evolution in carcinogenesis. Despite lacking detailed genetic data, his models described mutational heterogeneities in cancer.

Gatenby had written about the natural selection link before this latest article. In the May 28, 2009, *Nature*, he argued that applying the principles of evolution to therapy should abandon cures as the goals. In the piece he wrote, "I am not suggesting that cancer researchers should abandon their search for ever-more-effective cancer therapies, or even for cures. However, instead of focusing exclusively on a glorious victory, they should address the possible benefits of an uneasy stalemate in appropriate situations."

Gatenby said his article did not yield much initial support. "The response ranged from indifference to hostility." Even so, Gatenby had his fans. Pediatric oncologist Nicolas André, M.D., from the Department of Paediatric Oncology, Hôpital pour Enfants de la Timone, in Marseille, France, and research fellow and lecturer Eddy Pasquier, Ph.D., from the Children's Cancer Institute Australia for Medical Research in New South Wales, Australia, called Gatenby's idea of adaptive therapy a tour de force. They wrote that although it could be some time before it could be established whether such a switch in treatment strategy is clinically beneficial, they hoped "stakeholders will be prepared to test Gatenby's approach and to revisit the idea of treating cancer as a chronic disease." Their comments also appeared in *Nature*.

Others are investigating natural selection's influences on cancer. For example, in the UK, Alan Ashworth, F.R.S., chief executive of the Institute of Cancer Research in London, conducts research about the genetic mechanism that helps cancer cells survive by changing how they respond to treatment. Using technologies such as genomewide RNA interference screens, chemical screens, and genome sequencing, Ashworth and colleagues have identified mechanisms of cancer drug resistance and identified new drug targets for therapy.

Gatenby doesn't expect the medical research community to embrace the concept of natural selection's influence on cancer anytime soon. "It's hard to persuade doctors or patients not to give the maximum dose of chemotherapy and kill as many cells as possible, because that seems like the right thing to do, even though our models suggest that it's the wrong thing to do," he said.

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Assessing Cancer With a Blood Draw

By Anna Azvolinsky

One of the simplest medical tests, the blood draw, may become an advanced diagnostic tool in cancer.

Researchers in Italy, whose work was published in the June 28 edition of *Nature*, looked at the blood samples of colorectal cancer patients and found the presence of KRAS mutations in the tumor DNA of patients whose tumors had become resistant to epidermal growth factor receptor inhibitors. This circulating tumor DNA (ctDNA) method assay detected this mutation as early as 10 months before a radiological scan verified the patient's disease progression, said Alberto Bardelli, Ph.D., of the Institute for Cancer Research and Treatment in Turin, Italy, who led the study.

Although drawing blood is easy enough, parsing it for prognostic clues is a sophisticated matter. "The technology is extremely sensitive, but you need to know what you are looking for," said Bardelli. Alongside Bardelli's research results in *Nature* was a similar study by Johns Hopkins researchers who also used a ctDNA technology called BEAMing (beads, emulsion, amplification, and magnetics).

According to Luis Diaz Jr., M.D., the study's first author and an oncologist at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center in Baltimore, 1,100 biopsies would have been needed—an average of seven per patient over 6 months—to obtain the same information shown in his *Nature* study on colorectal cancer patients. He has also used BEAM technology to track PIK3CA mutations in breast cancer patients.

Because ctDNA is probably shed from all tumors in a patient, the technique offers a comprehensive snapshot of the genetic status of a metastatic cancer, Diaz explained—especially because tumors are heterogeneous, and taking a sample from one tumor region through a biopsy may not capture the spectrum of mutations present. "A biopsy assesses only a few million cells from a tumor that has trillions of cells," said Diaz. Therefore, "a single tumor biopsy misses [the] heterogeneity [of the entire tumor] and may miss a mutation that emerges in the presence of selective pressure—as a result of exposure to a therapy, for example."

Luis Diaz Jr., M.D.

Lab to Clinic: A Long Road Ahead

Researchers are trying to expand the types of mutations detected by BEAMing, which so far include point mutations and chromosomal rearrangement detection. Gene amplifications such as the HER2 gene amplification in breast cancer patients may be next. Such progress would be useful to analyze ovarian cancers whose mutations are complex and driven by copy number changes.

Bardelli is optimistic that both the ctDNA technology and available treatments will catch up to the field's growing understanding of tumor targets. "I strongly believe that detection of mutations in the blood by ctDNA will be greatly used in the future to monitor response and resistance to therapy," Bardelli said.

"If we can convert this into an assay that can be used for early detection or diagnosis, that would be really revolutionary."

Diaz believes the most exciting potential of ctDNA assays is early detection. "If we can convert this into an assay that can be used for early detection or diagnosis, that would be really revolutionary," he said. Early detection of a resistance mutation could also lead to adding a second drug early rather than waiting. Another potential application is detection of minimal residual disease after surgery.

But many questions remain before the assays are primed for the clinic. For example, researchers don't know whether the amount of ctDNA or circulating tumor cells detected reflects a particular tumor type or a patient's individual tumor biology.

J. Dirk Iglehart, M.D., director of the Center for Women's Cancers at the Dana–Farber Cancer Institute in Boston, is not convinced that knowing when a new mutation occurs will benefit the patient because a mutation may not depend on response to a therapy. There may also not be a drug available to target the new mutation. "[The success of ctDNA assays] will depend on whether the concept of personalized medicine works—this is still a huge experiment," said Iglehart.

Iglehart also wants to see better evidence for the association between ctDNA and disease burden. "If that is shown, then the assay would be useful to see whether a patient needs neoadjuvant therapy or whether a patient is responding to a particular drug," he said.

Daniel F. Hayes, M.D., an oncologist at the University of Michigan Comprehensive Cancer Center, who helped develop a circulating tumor cell assay called CellSearch, emphasized the need for rigorous clinical validity and utility for any new cancer test. "In my opinion, if we are going to direct care with a diagnostic assay, the bar should be as high as if we are going to treat patients with a new drug. There is a lot of potential for ctDNA, but a lot of hard work is ahead," he said.

For its part, the Italian group is taking the ctDNA assay into a clinical study of patients with metastatic colorectal cancer. The study, called HERACLES, will sample patients' ctDNA every 15 days. More clinical trials in Europe are being planned.

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Chemosensitivity Assays: Still Eyeing the Clinic

By Susan Jenks

Imagine taking a snapshot of a tumor in action as it overwhelms healthy cells to survive—and then using that information in the clinic to monitor which drugs best kill cancer cells. In vitro chemosensitivity assays promise to do that—using proprietary screening tests for clues about each individual's cancer.

But more than two decades after these assays debuted, oncologists remain divided: those who support such laboratory analyses and those who maintain that they unduly raise patients' hopes, often at considerable expense, while not improving survival. "Predicting what doesn't work [as opposed to what will] is not seen by most as an advance," said Jeffrey Abrams, M.D., associate director of the National Cancer Institute's Cancer Therapy and Evaluation Program.

Last year, the American Society of Clinical Oncology (ASCO) performed a literature review of data published between December 1, 2003, and May 31, 2010, on chemosensitivity testing. ASCO concluded, as it had in 2004, that this "in vitro analytic strategy has potential importance" but should be confined to patients participating in clinical trials. The National Cancer Comprehensive Network holds a similar view.

"In vitro testing is an old oncologist's dream," said Alain Hendlisz, M.D., chief of gastroenterology in the medical oncology clinic at the Jules Bordet Institute in Brussels, where researchers are using metabolic imaging to evaluate colorectal cancer treatments after an initial round of therapy.