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.

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.

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.
“In an ideal world, we should know what will be the effect of a treatment before its very beginning. That’s the purpose of in vitro testing, and that’s the philosophical reason why people are attracted by tests with a high positive predictive value,” Hendliz wrote in an e-mail. “However, that’s a philosophical point of view, not a scientific one.”

Still, in certain circumstances, where no standard of care exists, chemosensitivity testing may be useful to determine how best to treat some patients, according to Robert Holloway, M.D., co-medical director of Florida Hospital's gynecologic oncology program in Orlando. Holloway routinely recommends such tests for his ovarian cancer patients, at a cost of $3,500–$4,000.

Although insurance coverage tends to be spotty, Medicare does cover the cost for ovarian cancers, because these tumors account for most of chemosensitivity testing’s use today, Holloway said.

His decision to use the assays is based on “strong retrospective data” in at least two recent studies in ovarian cancers, including one by Julian Schink, M.D., and Larry J. Copeland, M.D., of the Comprehensive Cancer Center of Northwestern University, showing that chemosensitivity assay testing closely predicted patients’ responses and “accurately predicted progression-free and overall survival.” The study was published in the September 2011 Journal of the National Comprehensive Cancer Network.

Also, the development in recent years of several drugs for ovarian cancer, which has a high recurrence rate, makes selecting the right drug problematic for clinicians and the field ripe for this type of testing, Holloway said.

“Through chemosensitivity testing, we try to narrow down the selection,” he said. “Our feeling is it can’t be any worse than random selection, and there is logic behind it. I would caution, however, it’s not something that makes an absolute decision for you. You still weigh toxicities and other risks, such as how readily accessible the tissue is, but it provides another piece of information.”

### Chemosensitivity Assays: No Uniform Standards

Laura Shawver, Ph.D., an ovarian cancer survivor and founder of a nonprofit for ovarian cancer patients called the Clearity Foundation in San Diego, takes a nuanced view of chemosensitivity’s clinical value for ovarian and other cancers. Her main concern: the lack of standardization in these tests.

“Unfortunately, with chemosensitivity testing, it’s not done in a standardized format,” she said. “Some labs use apoptosis, some use cell growth, and still others use 3-D assays where they grow cells in clusters so the assay more closely resembles a tumor.” Even how a tumor is removed from the body can adversely affect the reliability of an assay’s results, she added.

Shawver favors genomic analysis, and her nonprofit helps women diagnosed with ovarian cancer gain access to molecular profiling to find the best treatment options at recurrence. She views genomics as potentially “a way to supplement or even replace chemotherapy” someday and a technique far better poised to capture tumors’ heterogeneity than chemosensitivity testing.

“People need to realize tumors change over time; they are highly mutable,” she said. “There’s heterogeneity at diagnosis, so chemosensitivity testing will test a portion of those tumor cells only, and not wipe them all out.”

But whenever chemosensitivity assays are available (Shawver does not recommend them), she does compare their results with molecular profiling. “We should think of these assays as a way of prioritizing drugs, not as a yes or no,” she said.

David Alberts, M.D., an Arizona Board of Regents professor and director of the University of Arizona Cancer Center, takes an equally pragmatic view, suggesting a limited role for chemosensitivity testing—at least in patients with uncommon tumors, where no “gold standard” of treatment exists. In such cases, he said, “I want as much information as I can get.”

And though he concedes a lack of clinical data, Alberts also sees a similar lack of “adequate clinical testing” of genomic assays. “These tests don’t tell you what proteins are expressed . . . or about drug interactions during treatment.”

In several cases where patients received dire diagnoses, Alberts sent their tumor samples for functional/chemosensitivity testing and to an international genomics center in Tucson for expression profiling. The two assays yielded similar results and helped guide the patients’ successful treatments. “There’s no question from my point of view that there’s a national need for randomized well-designed clinical studies, comparing all these assays,” Alberts said.

Jonathan Lancaster, M.D., Ph.D., chairman of the department of women’s oncology at Moffitt Cancer Center in Tampa, Fla., agreed. But with the expense and the difficult risk–reward balance of proving that an assay works, he said, such studies will probably not be conducted anytime soon. At Moffitt, he said, oncologists rarely use chemosensitivity testing, except when patients’ cancers prove so intractable that, like Alberts, “we feel as if we’re stumbling in the dark.”

Over the years, chemosensitivity tests have become more refined, evolving from detecting only drug resistance to more sophisticated biomarkers that yield better information about a tumor’s biology, Lancaster said. But in his view, two fundamental questions remain: (1) the science of prediction, or whether a biomarker predicts what it’s supposed to predict, and (2) what happens to a patient when you use the information gleaned from these tests.

“[The latter question] has been the real stumbling block,” Lancaster said. “Even if a test predicts a response, you can’t cure that cancer.”
**PDQ (Physician Data Query)** is the National Cancer Institute’s source of comprehensive cancer information. It contains peer-reviewed, evidence-based cancer information summaries on treatment, supportive care, screening, prevention, genetics, and complementary and alternative medicine. The summaries are regularly updated by six editorial boards. The following PDQ summaries were recently updated:


The PDQ Genetics of Colorectal Cancer summary was recently updated to include the results of a randomized, double-blind, placebo-controlled trial of 861 patients with Lynch syndrome (LS) in which aspirin was shown to have a protective effect compared with a placebo in an analysis of colorectal cancer (incidence rate ratio = 0.56, 95% CI = 0.32 to 0.99; P = 0.05) and an analysis of all other LS-associated cancers (endometrial, ovarian, pancreatic, small bowel, gall bladder, ureter, stomach, kidney, and brain) (hazard ratio = 0.65, 95% CI = 0.42 to 1.00; P = 0.05). Participants in the multicenter trial, known as the Colorectal Adenoma/Carcinoma Prevention Programme (CAPP2), were randomly assigned to receive 600 mg aspirin per day, an aspirin placebo, 30 mg resistant starch, or a starch placebo for up to 4 years. A study using lower doses of aspirin is expected to begin in 2013.

To review the summary, please use the following link: [http://www.cancer.gov/cancertopics/pdq/genetics/colorectal/healthprofessional/allpages#Section_1412](http://www.cancer.gov/cancertopics/pdq/genetics/colorectal/healthprofessional/allpages#Section_1412)

The PDQ Screening and Prevention Editorial Board recently completed a major update of the screening by chest x-ray and/or sputum cytology section of the Lung Cancer Screening summary. The Board conducted a review of the published literature and revised the text of the summary and updated the citations. To review the summary, please use the following link: [http://cancer.gov/cancertopics/pdq/screening/lung/HealthProfessional/page1/AllPages#Section_241](http://cancer.gov/cancertopics/pdq/screening/lung/HealthProfessional/page1/AllPages#Section_241)

The PDQ Adult Treatment Editorial Board recently completed a major update of the Intraocular (Uveal) Melanoma Treatment summary. The Board conducted a review of the published literature and revised the text of the summary and updated the citations. To review the summary, please use the following link: [http://www.cancer.gov/cancertopics/pdq/treatment/intraocularmelanoma/HealthProfessional](http://www.cancer.gov/cancertopics/pdq/treatment/intraocularmelanoma/HealthProfessional)

The PDQ Pediatric Treatment Editorial Board recently completed a major update of the Childhood Soft Tissue Sarcoma Treatment summary. The Board conducted a review of the published literature and revised the text of the summary and updated the citations. To review the summary, please use the following link: [http://www.cancer.gov/cancertopics/pdq/treatment/childhoodsofttissuetsarcoma/HealthProfessional](http://www.cancer.gov/cancertopics/pdq/treatment/childhoodsofttissuetsarcoma/HealthProfessional)