Assays that Predict Outcomes Make Slow Progress Toward Prime Time

By Charlie Schmidt

Assays that predict outcomes in chemotherapy or monitor the effects of treatment in real time, such as Oncotype DX and Mammaprint, could see increasing use with the current emphasis on personalized medicine and avoiding unnecessary treatments. Unlike diagnostic assays, such as prostate-specific antigen measurements, these tools are intended specifically to guide decisions about when, and when not, to use chemotherapy.

“We could save a lot of money and avoid a lot of side effects if these tests were more broadly adopted,” said Lee Newcomer, M.D., senior vice president for oncology at Minneapolis-based United Healthcare, one of the largest U.S. health insurance companies.

But clinicians have been slow to endorse and adopt such assays. The reasons have partly to do with continued doubt about the validity of the evidence. Most studies to date have been retrospective analyses, and although large, prospective trials are currently under way on both sides of the Atlantic, none has yet completed accrual. Also, some experts say, practice-related reasons may be behind the slow uptake of the assays.

21-Gene Recurrence Score

The best validated of the new assays is Oncotype DX, a gene expression microarray that predicts whether patients with lymph node–negative, estrogen receptor (ER)–positive breast cancer will experience disease recurrence after treatment. Manufactured by Genomic Health in Redwood City, Calif., Oncotype DX segregates women into low-, intermediate-, and high-risk categories, according to a 21-gene panel. Sixteen of the genes relate to cancer processes, such as proliferation, whereas the rest serve as reference genes to confirm the accuracy of the test results.

Women that the test designates low risk get little to no benefit from chemotherapy, said Steve Shak, M.D., Genomic Health’s chief medical officer. “The aim of the test is to avoid unnecessary toxicity and cost in women who are going to do very well with hormonal treatments,” he said. According to Shak, half of patients generate low scores of 18 or less, whereas 25% yield scores of 31 or higher, which reflect greater levels of tumor cell proliferation and suggest chemotherapy is warranted. Roughly 50,000 patients got the test in 2009, Shak said (about 192,000 women are diagnosed with stage I breast cancer each year). Most insurers cover the U.S. $3,975 cost.

Newcomer added that efforts to encourage wider use of Oncotype DX are a priority at United Healthcare. But in a recent unpublished survey by the company, 16% of oncologists responded that they gave chemotherapy even to women deemed whom Oncotype DX test results deemed low risk, “which is disturbing, because the point of the test is to tell you when chemotherapy has no value,” Newcomer said.

Several recent retrospective analyses of clinical trial data have assessed the 21-gene assay’s prognostic power. One published in April in the *Journal of Clinical Oncology* and led by Eleftherios Mamounas, M.D., of the National Surgical Adjuvant Breast and Bowel Project (NSABP), looked at the association between locoregional recurrence...
rates and Oncotype DX recurrence score. Using specimens from more than 1,700 ER-positive, lymph node–negative patients from two NSABP randomized trials, the researchers found that recurrence scores were statistically significantly associated with locoregional recurrence rates.

Another retrospective analysis, this one involving 367 specimens from clinical trial patients, appeared in the January 2010 issue of the Journal of Clinical Oncology. Led by Kathy Albain, M.D., a professor at Loyola University, it found that Oncotype DX recurrence scores were associated with the efficacy of anthracyline-based chemotherapy in ER-positive, lymph node–positive patients. The association was statistically significant, but some question the validity of the results. “The trend was in the right direction, but the numbers were too small,” said Margaret Piper, Ph.D., director of genomic resources with the Blue Cross and Blue Shield Association’s Technology Evaluation Center.

So far no results have emerged from prospective, randomized trials on OncotypeDX in the clinic, but the National Cancer Institute is now conducting one, the TailorX trial, to assess whether Oncotype DX is accurate among the 25% of women who generate intermediate scores. “We’re [especially] uncertain about the benefits of chemotherapy in women with recurrence scores of 11 to 25,” said Edith Perez, M.D., a study investigator at the Mayo Clinic in Jacksonville, Fla. “We want the study to help us define patient selection, so that we avoid either undertreatment or overtreatment.” Launched in 2006, the trial has yet to meet its accrual goal of more than 10,000 patients.

70-Gene Assay
Oncotype DX’s closest competitor in predictive testing is Mammaprint, a 70-gene microarray that forecasts breast cancer recurrence in ER-positive and -negative patients. Mammaprint was manufactured by Agendia, in Huntington Beach, Calif., and Amsterdam, The Netherlands. The U.S. Food and Drug Administration approved it in February 2007, on the basis of a multinational study that the European Union’s Translational Research Breast International Group (TRANSBIG) conducted.

That study compared 307 lymph node–negative women, each younger than 61 years, who had undergone surgery for stage I or II breast cancer and whose tumors were at most 5 cm. Women whom Mammaprint identified as low risk had a 95% chance of remaining cancer free in 5 years and had a 90% chance after 10 years. But predictions for women that the test deemed high risk were not so accurate: 23% experienced cancer recurrence in 5 years, rising to 29% at 10 years.

Despite the FDA’s approval, many in the field question Mammaprint’s clinical value. “The patients in the study underwent a variety of chemotherapy [regimens]—heterogeneity and confounding influences in the population made it hard to confirm that the test is doing what it’s supposed to be doing,” said Blue Cross and Blue Shield’s Piper. “FDA gathered some excellent data on analytical validity, but we still need to be convinced that the study is clinically useful.”

TRANSBIG is now investigating Mammaprint’s capacity to help women with early-stage breast cancer avoid chemotherapy in a prospective, randomized trial called MINDACT, which launched in 2007. As of fall 2009, it had enrolled slightly more than one-third of its planned 6,000 patients, according to its Web site.

Circulating Tumor Cells
A third test with growing visibility is CellSearch, manufactured by Veridex LLC in North Raritan, N.J. By counting circulating tumor cells (CTCs) in blood, this test is intended to predict overall and progression-free survival and monitors the efficacy of chemotherapy treatment. The test currently has FDA approval for use in patients with metastatic breast, colorectal, and prostate cancer.

“CellSearch offers guidance about the likely path of the disease and whether to continue with treatment,” said Eliel Bayever, M.D., Veridex’s vice president for medical affairs. “Depending on if the cell counts go up or down, it tells how well the patient is doing and how well they will do in the long run.” Those with CTC counts greater than five per 7.5 mL of blood tend to have a worse prognosis.

In the July 10, 2009, issue of the Journal of Clinical Oncology, scientists reported that CTC counts greater than five per 7.5 mL of blood are better at predicting survival in patients with metastatic breast cancer than is imaging with positron-emission tomography, which is also considered a promising new tool for monitoring in patients with metastatic breast cancer. Massimo Cristofanilli, M.D., now at Fox Chase Cancer Center in Philadelphia, led the study.

But CellSearch is not the only CTC assay under study (see News, J. Natl. Cancer Inst. 2010;102:146–8). Researchers at Harvard have developed a CTC Chip, which they have licensed to Cellpoint Diagnostics. In a study presented at the annual meeting of the American Association for Cancer Research in April, they reported finding CTCs for the first time in patients with localized prostate cancers and low-grade cancers, as well as those who had undergone surgery 3 months before. Sunitha Nagrath, Ph.D., of Harvard and Massachusetts General Hospital in Boston, said that she and colleagues found CTCs in 42% of 20 localized prostate cancer patients in a proof-of-concept study. The finding raised hope, she said, that someday the chip might predict the risk of metastatic disease.

In Cristofanilli’s opinion, based on experience with hundreds of patients, he said, CTC counts have several advantages. They are cheaper than imaging (Bayever would not disclose the test’s cost), less invasive than biopsy, and clinically valuable. “I’m convinced,” he said.

But Eric P. Winer, M.D., from the Dana–Farber Cancer Center and Harvard Medical School, offered a more cautious view. “I don’t feel the data [on CTCs] are sufficiently
Slow Uptake in Oncology

Meanwhile, all three tests face barriers to adoption. A comparative lack of clinical data can explain their slow uptake by clinicians, but Newcomer has repeatedly argued that financial incentives also work against CellSearch and Oncotype DX.

“An early sign of resistance to chemotherapy [with CTCs] means stopping treatment immediately,” he said. “And Oncotype DX results can mean giving no chemotherapy at all. Not only is it more profitable for a practice to give three cycles of chemotherapy than one, it’s also emotionally more painful for a doctor to come back and say, ‘This therapy isn’t working.’ If these tests were offered for diagnosis, they’d be adopted quickly, but that’s not what they’re made for; they face too many negative incentives.”

Winer rejects the notion that finances play an overt role in deciding whether to use the tests. “I recognize that in some settings that could be a concern,” he said. “But I also think that if presented with data arguing against chemotherapy, the overwhelming proportion of oncologists would decide not to give it.”

Practically speaking, clinicians also have to contend with coding issues that complicate how predictive tests are submitted for reimbursement. Instead of one code, Piper explained, genetic tests are bundled into a set of procedural codes, none of which explain what the tests were used for. “This complicates life for everyone,” she said. “The insurance companies have no idea what the tests are about, and this has an impact on rational policy decisions.”

Still, predictive tests are gateways to personalized treatment in oncology, and their use seems likely to grow with time. Winer emphasized that next-generation therapies in oncology are expensive and that tests geared toward trimming unnecessary treatments will be crucial.

“Speaking on behalf of the doctors I know, we take these tests very seriously,” Perez added. “We’re aware of them and we’re using them when it’s reasonable to do so, with the understanding that there’s still a lot of research to be done.”