Biomarker Boom Slowed by Validation Concerns

By many accounts, the brave new worlds of genomics and proteomics—and their accompanying technologies—have ushered in a new era of cancer biomarker research. Researchers in cancer detection, diagnosis, and treatment all have a vested interest in discovering these proteins and small molecules that are telltale signs of early cancer, characteristics that make a type of cancer unique, or markers that predict whether a patient will respond to a given treatment. As a result, the number of uses for cancer biomarkers has expanded at a rapid pace.

“Cancer biomarkers are practically pouring out of research laboratories,” said Bruce Zetter, Ph.D., Charles Nowiszewski Professor of Cancer Biology at Boston’s Children’s Hospital. But as researchers and oncologists use and develop technology to uncover a wealth of markers that may ultimately affect cancer detection and diagnostics, many argue that, at least for now, the biomarker research engine is stuck in neutral. What are missing in many cases, they say, are studies to prove a marker’s reliability and clinical worth.

“It’s very rare that a true clinical marker comes along,” said breast cancer specialist Lajos Pusztai, M.D., D.Phil., at the University of Texas M. D. Anderson Cancer Center in Houston. “While a handful of markers appear every year, you’d be hard pressed to find a study that proves its clinical utility.”

In the last decade, he said, only one biomarker—HER2 for some cases of breast cancer—has affected treatment.

“There are correlations with cancer, but so what? The clinician wants to know, ‘Should I use this [biomarker] or not?’” Pusztai said.

For many biomarkers, the answer to that question is no. Many of the tumor marker studies published are poorly done. Pusztai pointed out in a recent editorial that, all too often, biomarker studies are “ancillary” to therapeutic clinical trials and are performed retrospectively. The study “sample size is driven by the availability of tissues” from such trials.

The rigorous rules of science often go out the door when it comes to cancer biomarkers, concurred Daniel Hayes, M.D., clinical director of the breast oncology program at the University of Michigan Comprehensive Cancer Center in Ann Arbor. “It is a problem to develop a biomarker with clinical use,” he said.

Pusztai and Hayes, who co-chairs the American Society of Clinical Oncology’s tumor marker guideline committee, advocate a clinical development structure for cancer biomarkers that is similar to structure for the clinical development of a drug. According to Pusztai, the step-by-step development of a marker might entail a phase I study, for example, that could demonstrate a potential association between marker and outcome. Phase II could measure the association between the marker and clinical outcome, while phase III then would involve a randomized marker validation trial.

“The stepwise approach and widespread application of testing biomarkers in clinical trial–like settings will help push many of these biomarkers through U.S. Food and Drug Administration approval and to clinical use,” said Arul Chinnaian, M.D., Ph.D., assistant professor of pathology and urology at the University of Michigan.

Making validation studies simpler is one of the ideas behind the National Cancer Institute–backed Early Detection Research Network (EDRN), which got off the ground in 2000. The EDRN established a defined development sequence or “road map” outlining five phases of biomarker development (see Vol. 93, No. 14, p. 1054). EDRN has concentrated on the first three phases: marker discovery, marker validation in terms of distinguishing the presence or absence of cancer, and testing markers for their ability to find preclinical and early-stage cancer.

According to Sudhir Srivastava, Ph.D., chief of NCI’s Cancer Biomarkers Research Group, EDRN has several validation studies in progress, including those that focus on microsatellite instability for bladder cancer detection, protein profiling for prostate cancer detection, and several markers for hepatocellular carcinoma (see News, Vol. 95, No. 6, p. 422).

Despite these major efforts to streamline the biomarker validation process, potential biomarker discovery well outpaces validation studies. “There’s always been a sort of a bottleneck—there’s this vast research literature about biomarkers for prognosis assessment, biomarkers for treatment selection—yet it never really seems, except in rare occasions, to lead to clinical use of biomarkers,” said biostatistician Richard Simon, D.Sc., chief of the Biometric Research Branch at NCI. “The question is, ‘Why not?’”

One reason, he said, is that validating cancer biomarkers can be hard.

“Validation is more difficult than discovery,” said Simon, especially when it involves multicenter studies. “I think there’s a real misunderstanding of what external validation [of a biomarker] is. I think the notion of ‘phased’ studies is one way of reinforcing that concept.”

One stumbling block, he noted, is a lack of multidisciplinary collaboration between clinicians, biologists, and statisticians. In addition, not many scientists really have a good grasp of how to perform validation studies.

“People studying biomarkers don’t understand the concept of validation,” Simon said. “They do studies, but they are not hypothesis-based studies.” As a result, he said, “Such studies tend not to get done, and that’s one of the biggest reasons biomarkers don’t get into primetime.”

EDRN is doing its share to try to change some of that. The way the network is set up, scientists from its biomarker development laboratories,
validation laboratories, and clinical and epidemiological centers constantly collaborate on projects, coaxing researchers from various disciplines to communicate and understand what validation really entails.

One company, Genomic Health Inc., of Redwood City, Calif., is trying to take its gene assay into primetime after it reported in December 2003 the results of a multicenter validation study showing that its Oncotype DX 21-gene assay can accurately tell the likelihood of breast cancer returning in node-negative, estrogen receptor–positive women who had taken tamoxifen.

But getting there took years. According to company chief medical officer Steven Shak, M.D., the study was the first large, multicenter prospective clinical validation study of a multigene assay in cancer. Shak thinks Genomic Health’s step-by-step approach to developing and validating the assay is rare—but sorely needed—in the cancer research world.

“There’s no substitution for a multistep approach and a large, independent validation study,” he said.

Scott Waldman, M.D., Ph.D., of Jefferson Medical College at Thomas Jefferson University in Philadelphia, is taking a similar approach. He is in the middle of a multicenter clinical trial aimed at determining the clinical value of a protein biomarker, guanylyl cyclase C, for detection of colorectal cancer recurrence.

“Tests for biomarkers can be simple, such as when they are used strictly for detection,” Waldman said. “Either the cancer is there or not. The steps to validate this are relatively brief and straightforward.”

In contrast, he noted, biomarkers used as prognostic indicators are much more complicated and difficult to validate. “There’s an extra step—you are trying to correlate the presence of a biomarker with how the patient does. For biomarkers being studied for prognostics in terms of disease progression or disease therapy, researchers are asking if they are relevant in a causal way and have some important biological effect. You also have to specify the appropriate population in which to study.”

Some say that for biomarker research to move forward, industry must play a larger role.

“The pharmaceutical companies are very interested in biomarkers as predictors of response to drugs,” Zetter said. “Imagine a drug that only works on 15% of patients with a certain cancer. It’s given to all patients because no one knows which 15%. That means 85% won’t respond. You’d like a test that says these 15% will respond.”

Pusztai sees it differently. “It’s not more difficult to discover a new marker than a new drug,” he said. “The difference is the payoff. Why would a company invest heavily in a potential tumor marker? The payoff for diagnostics has never been very big. They have been less willing to gamble for the most part and do large validation trials. They haven’t been forced to.”

Yet Jeff Ross, Ph.D., senior scientific fellow at Millennium Pharmaceuticals Inc. in Cambridge and chairman of the department of pathology and laboratory medicine at Albany Medical College, argues that biomarker-based drug development has always been important for drug companies. “A company wants to know as early as possible in the development process whether or not a drug could be effective and whether to move forward or cut losses,” he said. “Companies want to avoid the high cost of failure.”

In any case, as companies begin to sort out their investment in and commitment to cancer biomarker development, new technologies will continue to drive the biomarker onrush.

“High-throughput genomic and proteomic techniques will continue to push the envelope, uncovering new biomarkers,” Michigan’s Chinnaiyan said. “In the long run, we will use panels of markers that will give layers of security that we don’t have with single biomarkers to answer relevant questions—is cancer present, is it aggressive, how will the patient respond to a drug?”

“It’s an exciting time,” said Simon, “but we need to get the right people using the right tools effectively.”

—Steven Benowitz