Identity Crisis: Finding, Defining, and Integrating Biomarkers Still a Challenge

As the understanding of cancer evolves, so too has the search for better ways to diagnose and treat the disease. Biomarkers have been used to measure exposure, risk, treatment selection, prognosis, best dose of an agent, early response, residual disease, metastasis, and drug toxicity. But what to one researcher is a biomarker that assesses the presence of disease is to another a classifier from which no relevant question can be derived, and the difference in meaning and intent between these two examples highlights one of the major challenges in field.

“The first challenge we have is to have a vocabulary we agree on,” Gordon Mills, M.D., chair of the Department of Molecular Therapeutics at the University of Texas M. D. Anderson Cancer Center in Houston, said at an October conference on biomarkers at the cancer center. “What are we talking about when we say ‘biomarker’? What is it used for? A biomarker needs to signify something.”

The conference brought researchers from around the globe together to discuss the role of biomarkers in research and clinical trials and how biomarkers should best be used. “The quantum leap forward in our understanding of the molecular basis of cancer over the past two decades has not yet been accompanied by a comparable increase in our ability to diagnose or treat cancer, and so the only relevant question when it comes to biomarkers is if it allows us to do something better than we could do before we had the biomarker,” said Rene Bernards, Ph.D., from the Netherlands Cancer Institute in Amsterdam, one of the speakers at the conference.

Some researchers say that the only biomarkers worth pursuing are the ones that can help improve patient treatment. In other words, measuring proteins or genes that can prognostically predict an outcome that cannot be changed by treatment has little value other than, as one conference participant put it, “to lengthen a researcher’s CV.”

“We have accumulated a lot of technology over the past 50 years, and now I think it is time to use it to make a difference to patients,” said Mills. “But not many people have been thinking through the challenges that involves.”

Conference participant Richard Simon, D.Sc., chief of the Biometrics Research Branch at the National Cancer Institute, maintains that “much conventional wisdom about how to use biomarkers is flawed,” and that “most biomarker studies fail because they don’t have applications for treatment.” Most of these studies attempt to link a patient’s specific genes or proteins to cancer outcome, but “so what?” he asked. “What we really want to know is who does well with a specific treatment. An example of a beneficial biomarker, he says, is Her2-neu, which identifies breast cancer patients that should be offered treatment with Herceptin (trastuzumab).

“My concern is that we are vastly overtreating patients, treating the majority for the minority that respond,” Simon said. Proper use of genomic classifiers, however, can identify which patients benefit from a widely available treatment and can also help focus the development of new treatments, he said.

Another serious issue in biomarker research is introduction of bias into the experiment through different variables that can skew the results, including selection of patients and/or tumor samples, the use of proprietary technology such as mass spectrometry that cannot be reproduced by others, or even the order in which specimens are run, said University of North Carolina–Chapel Hill researcher David Ransohoff, Ph.D. “Bias is so serious that studies are guilty until proven innocent,” he said at the meeting, offering examples of the claims that have been made to date about how protein analysis can be used to screen for cancer and predict prognosis.

“The overarching problem is that the rules of evidence for evaluation of studies of diagnosis and prognosis are not nearly as well developed as they are for studies of therapy,” he said. “For this reason, much ‘omics’ research is unreliable and inefficient. If you let the computer run enough, it will find patterns that don’t say anything about Mother Nature and the real world.”

Also, the problem of finding good genetic markers depends on the quality of the tumor sample used, a theme conference participants dubbed “tissue is the issue.” The best tissue for biomarker research comes from clinical trials testing a homogeneous group of patients, in which the sample set is matched to the research question. But these samples are hard to come by, said Mills. What is more often used, he said, “are samples of convenience that are not quality controlled and [are] poorly annotated, and
without high-quality samples, it is garbage in and garbage out.”

Although protein biomarkers might seem to be more readily available than genetic markers, detecting discrete proteins that could serve as a diagnostic test is “incredibly complex,” said Sam Hanash, M.D., Ph.D., of the Fred Hutchinson Cancer Research Center in Seattle.

“For example, 3,700 genes are expressed in some fashion in lung cancer, but most of these genes do not encode proteins that would be good biomarkers,” he said. “For every 10 proteins that might offer a possible biomarker, you would be lucky to find one in the blood. The challenges of finding serum or blood biomarkers are absolutely tremendous, and the more we do it, the more we see how complicated it is.”

Mills said that solving these problems—and making biomarkers truly relevant to patient management—may require a kind of “big science,” in which scientists from different fields, such as molecular geneticists, pathologists, statisticians, and epidemiologists, work together and with pharmaceutical companies to share tumor samples and a common direction.

It took that kind of collaboration to produce one success story, a genetic biomarker test that is intended to help individualize breast cancer treatment. Steven Shak, M.D., of Genomic Health Inc., of Redwood City, Calif., described how the company worked with academic researchers, including those associated with the National Surgical Adjuvant Breast and Bowel Project (NSABP), to develop a test that could predict which women with node-negative, estrogen receptor–positive breast cancer would have recurrence if they were treated only with tamoxifen. Up to $30 million was spent to optimize, clinically test, and validate the assay, which measures RNA from 21 genes in a paraffin tumor block to produce a “recurrence score.” The $3,460 test, called Oncotype DX, is now available to oncologists to help them identify which of their patients would benefit from chemotherapy.

“Getting the right drug to the right patients is the future of oncology,” Shak said. “And we are now starting to be able to do that. There is no question we are in the midst of a revolution.”

—Renee Twombly