Ten Steps to Advance Biomarker Testing

Report makes suggestions to better understand the tests' utility and strengthen oversight of labs

Matching patients with the most effective therapies for their cancer may require checking their tumors for genetic mutations or expression of the proteins that certain drugs target. However, tests for these biomarkers can vary in quality, and evidence of their clinical value may be lacking. In addition, regulation of different types of tests may seem inconsistent at times, according to some experts.

"Some people have described it as being like the 'Wild West,'" says Harold Moses, MD, chair of cancer biology at Vanderbilt University in Nashville, TN.

To resolve these and other concerns about biomarker testing—and more fully implement personalized medicine—the Institute of Medicine (IOM), recently renamed as a division of the National Academies of Sciences, Engineering, and Medicine, issued a report this past spring that makes 10 interrelated recommendations (available at www.nap.edu/21860). Moses chaired the committee that authored it.

"This is overdue," says Daniel F. Hayes, MD, co-director of the breast oncology program at the University of Michigan Comprehensive Cancer Center in Ann Arbor, who praised the IOM report during a presentation at the annual meeting of the American Society of Clinical Oncology (ASCO) in June.

"We have the ability to come up with better biomarkers that are more accurate and more reliable, but we have to make sure that they are," Hayes continues. "Our patients deserve tests that are safe and effective."

HIGH STAKES

In recent years, numerous molecularly targeted cancer drugs have received FDA approval. For at least 17 of them, the FDA has approved a companion diagnostic test to confirm the presence of a particular biomarker. For example, when approving vemurafenib (Zelboraf; Genentech) for the treatment of *BRAF* V600E–mutant melanoma, the FDA also gave the green light to the cobas 4800 BRAF V600 Mutation Test (Roche Molecular Systems). When approving these tests, the FDA confirms that they identify patients with the biomarker in question and that the biomarker relates to the disease or treatment, but not whether the test itself leads to better clinical outcomes.

Complicating matters, laboratory-developed tests (LDT)—*in vitro* diagnostic tests that are designed, manufactured, and used within a single laboratory—aren't actively regulated by the FDA. Currently, the Centers for Medicare and Medicaid Services (CMS) oversees LDTs through the Clinical Laboratory Improvement Amendments (CLIA) program, which focuses on high-quality lab practices, not clinical validity or treatment outcomes. (However, in 2014, the FDA issued a draft guidance for the regulation of LDTs and plans to finalize the document by the end of 2016 [Cancer Discov 2014;4:1250].)

As a result, an FDA-approved test might not necessarily lead to better health for a patient, but a test the FDA never reviewed "might be terrific," says Hayes. Noting that inaccurate results could mean a patient pursues a treatment that provides little benefit—or worse, causes harm—he says that "a bad tumor marker test is as bad as a bad drug."

"We've been, I think, pretty sloppy about evaluating new biomarker tests," continues Hayes. "Now, I think the stakes are really high....We want to give [targeted therapies] to the right people."

SETTING WHEELS IN MOTION

Addressing flaws in the system will require a multipronged effort incorporating diverse players, ranging from government officials to pathologists to makers of electronic medical records, according to the IOM report. Its authors framed 10 goals that, taken together, will promote the effective use of valid biomarker tests. For example, they recommend establishing evidentiary standards of clinical utility, as well as creating uniform test labels that spell out the likelihood a test will improve patient outcomes. They suggest coordinating federal oversight of tests and the labs performing them between the FDA and CMS. They also recommend that CMS and private insurers find a way to pay for unproven tests so that evidence of their effectiveness can be collected.

Central to the IOM's recommendations is the development of a national database that incorporates the biomarker tests that patients receive, their subsequent treatment, and their disease course. Because the cost of conducting clinical trials to validate biomarker tests is usually prohibitive, such a system would act as a *de facto* post-market review.

"There are wheels turning already on many of these things," notes Mark Fleury, PhD, policy principal in emerging sciences at the American Cancer Society Cancer Action Network in Washington, DC. For example, the American Association for Cancer Research's Project GENIE, launched in November 2015, links next-generation sequencing data from patients at seven leading cancer centers to the treatments they receive and their long-term outcomes.

Another information-sharing effort is ASCO's CancerLinQ database. Designed to help clinicians make treatment decisions for their patients based on treatment and outcomes data from similar patients, CancerLinQ will boast 1 million records by the end of 2016, says Richard L. Schilsky, MD, ASCO's chief medical officer. Although it currently incorporates results from only a few biomarker tests, the number will grow as tests are increasingly used and results added to electronic medical records, Schilsky says.

Experts say the report will act as a wake-up call. "The IOM has a certain credibility and a certain gravitas," Schilsky points out. "I think it will probably help elevate the quality of testing, and most importantly, I think it will stimulate the collection of information so we can learn about these tests as they are being developed." –*Amber Dance* ■

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