Regulating Laboratory-Developed Tests: Devil Will Be in Details

By Caroline McNeil

For 2 days in January, the National Institutes of Health was the epicenter of the debate that has swirled around laboratory-developed tests (LDTs) since last July, when the U.S. Food and Drug Administration announced it would begin regulating them. More than 80 people—representing pathologists, clinicians, patients, and laboratories—spoke during FDA’s unusually large and long public workshop.

The meeting’s size and heated debate reflect the huge impact that the agency’s proposed draft guidance could have on the rapidly evolving field of diagnostic testing.

The new approach to LDTs “represents a sea change for laboratories,” said Gail Vance, M.D., director of the Indiana University School of Medicine Cytogenetics Laboratory in Indianapolis, who was representing the College of American Pathologists. “I would suggest that FDA consider anew.”

FDA defines LDTs as tests “intended for clinical use and are designed, manufactured, and used within a single laboratory.” Currently, laboratories that develop LDTs are inspected and certified by the Centers for Medicare and Medicaid Services through its Clinical Laboratory Improvement Amendments (CLIA) program.

But the field is changing rapidly. With the rise of targeted drugs and genetic testing, LDTs are increasingly used to make crucial treatment decisions in cancer and other common diseases. At the same time, LDTs have migrated from their traditional territory, in labs affiliated with local medical facilities, to commercial firms, which manufacture and market their tests nationally.

Nevertheless, LDTs are not manufactured products and cannot be regulated in the same way, FDA’s opponents say.

“Laboratories develop LDTs as part and parcel of the practice of medicine. They operate in a fundamentally different manner than manufacturers,” said Alan Mertz, M.A., president of the American Clinical Laboratory Association in Washington, D.C., expressing a view articulated repeatedly throughout the workshop.

Risk-Based Approach

FDA’s proposed Framework for Regulatory Oversight of Laboratory Developed Tests, issued Oct. 3, is based on three risk categories, intended to represent the degree of risk to the patient of an inaccurate result. Premarket approvals (PMAs) would be required for all existing tests in the high-risk category. This category would include tests for which an FDA-approved equivalent already exists. PMAs for subsequent high- and moderate-risk tests would be phased in over 9 years. PMAs would not be required for tests in the low-risk category; that would cover traditional LDTs, those used for rare diseases, and those that serve unmet needs, including tests for which no FDA-approved equivalent exists. Under the proposed guidance, labs would also have to notify FDA of all existing and new tests, regardless of risk status, and report adverse events associated with their use.

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The Two Sides

Opponents of the proposed guidance, including many pathologist and clinician groups, argue that CLIA already stringently inspects LDT laboratories and that the proposed regulations could jeopardize timely access to treatment. Opponents also stress the substantial new burdens, in both time and cost, of regulation.

If the provisions of the draft guidance are implemented, “we will be, in essence, at some point in time, driven out of business,” said Lawrence Hertzberg, M.D., medical director of CSI Laboratories in Alpharetta, Ga., a private lab specializing in cancer diagnosis. Others echoed his concern.

Supporters—including many cancer organizations—stress the consequences of false positives and false negatives, which can lead to unnecessary treatment or not using a potentially beneficial treatment. Supporters also argue that CLIA inspections ensure only that a test is analytically valid and do not prove clinical validity—that is, that the variant is associated with a specific disease. Nor does CLIA ensure clinical utility—that using the test improves patient outcome.

There has to be “some certainty at some level that the test does what the test is supposed to do . . . and that when we talk to a patient and do the test that we are really doing a benefit for that patient,” said J. Leonard Lichtenfeld, M.D., M.A.C.P., deputy chief medical officer for the American Cancer Society in Atlanta. “That is a higher bar than exists today.”

Seeking Validity

Clinical validity, and how to establish it, is a major issue in this debate. Laboratorians argue that the association between gene variant and disease has been reported in the literature before they develop a test. But that is not always true, according to Alberto Gutierrez, Ph.D., director of FDA’s Office of In Vitro Diagnostics and Radiological Health, which issued the draft guidance.

“There are many tests currently launched that do not have any published data to support them,” he wrote in an e-mail. “Furthermore, given the number of claims in the literature that have not been reproduced, use of published literature is not always an assurance of clinical validity.”

The guidance document states that “FDA intends to work with the laboratory community, the health care professional community, and other stakeholders to identify those LDTs for which the clinical validity of the analyte/marker has
already been established in the literature”; however, how that would be done is not yet clear.

One counterproposal is that CLIA be improved so that it can address clinical validity. How that would be done also isn’t clear.

Lack of clarity was a recurring theme in other areas as well. Speakers expressed concern that FDA’s definition of LDTs, as tests developed and used in a single laboratory, might exclude multiple labs within a single health care system. Or it might rule out other affiliations, such as between community hospitals and nearby academic medical center labs.

Also unclear is how the proposed guidance would apply to modifications to existing tests, according to many speakers.

“Modifications are part of medical laboratory practice,” said Elissa Passiment, Ed.M., executive vice president of the American Society for Clinical Laboratory Science, McLean, Va. “If modifications to existing tests are considered a new LDT, FDA will be swamped [with notifications],” she said.

**Risk Categories**

But perhaps the biggest source of concern is uncertainty regarding which tests would fall into which risk category. LDTs for which no FDA-approved equivalent exists would serve an unmet need and therefore fall into the lowest-risk category, according to the draft guidance. “But in practice it is unclear what would constitute an unmet need or an FDA-approved equivalent because of different functionality of similar tests,” said Roger Klein, M.D., J.D., F.C.A.P., medical director of molecular oncology at the Cleveland Clinic in Ohio.

For example, the widely followed guidelines of the National Comprehensive Cancer Network now recommend extended KRAS testing in colorectal cancer. That means patients should be tested for KRAS mutations in codon 61 and others, in addition to the more common mutations in codons 12 and 13. The only FDA-approved tests, however, do not cover these additional mutations.

Would an LDT that included a test for codon 61 mutations be considered an LDT for an unmet need? Or would it fall into the same “intended use” category as, for example, KRAS testing for nonresponsiveness to anti–epidermal growth factor receptor therapy, and be lumped in with the FDA-approved test? If the latter, laboratories following National Comprehensive Cancer Network guidelines would need to submit their tests for FDA premarket approval.

“FDA will have great difficulty keeping up with changes” like this, Klein said. “FDA’s tools are not sufficiently nuanced, the medical device regulations are not sufficiently nuanced, to regulate medical practice.”

Even those who support FDA regulation in general acknowledge that fitting the proposed regulations to the real world of laboratory practice will be difficult. “Because LDTs have increased in number and complexity, we do support increased oversight by the FDA,” said Donald Karcher, M.D., from the George Washington University School of Medicine and Health Sciences in Washington, D.C., who was representing the Association of Pathology Chairs. “But the devil will be in the details.”

The risk classification issue is so important to laboratories that the Personalized Medicine Coalition (PMC), an advocacy group in Washington, D.C., is asking FDA to issue a separate draft guidance on the subject.

“It must be explicit and overt about the types of tests that will fall into the high-risk category,” said Amy Miller, Ph.D., PMC executive vice president. “The high-risk category must be well understood so that labs can make management decisions.”

PMC is also asking FDA to issue second drafts of the original documents plus another new guidance on harmonization of the agency’s quality system regulations with those of CLIA inspections.

When the workshop began, Jeffrey E. Shuren, M.D., J.D., director of FDA’s Center for Devices and Radiological Health, said he hoped that the assembled stakeholders would beat swords into ploughshares. When it ended 2 days later, optimism remained in some quarters.

“I think we can move forward in ways that would provide quality patient care and support innovations in laboratory medicine,” Miller said. “That is what both FDA and the community want.”

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Lung Cancer Screening Poised To Expand

By Charlie Schmidt

On February 5, 2015, the Centers for Medicare and Medicaid Services announced formally that it would cover lung cancer screening for the Medicare population. Coming on the heels of a mandate from the Affordable Care Act that private insurers do the same as of the preceding January, this latest move to reimburse for lung cancer screening has life-saving potential. A major study published five years ago in the *New England Journal of Medicine* (N Engl J Med. 2011 Aug 4;365(5):395–409) found that screening with low-dose computed tomography (LDCT) reduced mortality in risk-individuals by 20%. Sponsored by the National Cancer Institute, that study—the National Lung Screening Trial (NLST)—enrolled more than 53,000 individuals at 33 medical centers. Coverage under Medicare and the Affordable Care Act will now be extended to high-risk individuals who meet the National Lung Cancer Screening Trial’s criteria: aged 55–74 years and at least a 30-pack-year smoking history among people who either still smoke or have quit within the last 15 years. Medicare imposes additional requirements, namely that patients must be adequately counseled first and that the screening must be conducted by qualified radiologists at eligible facilities—specifically, those with demonstrated experience? YES in lung imaging by LDCT.

With mechanisms for reimbursement shaping up, experts now predict that more community hospitals will adopt lung cancer screening. But that has some experts worried. LDCT tends to pick up indeterminate pulmonary nodules (IPNs)—lesions that can’t be defined...