From the President’s Desk: A need for clarity on regulation of LDTs, 2/15

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February 2015—Increasingly sophisticated laboratory-developed tests have populated the testing landscape rapidly in recent years, and the CAP has worked with government agencies and private stakeholders to address effective oversight. The Food and Drug Administration has issued draft guidance describing its thinking about that oversight.

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The CAP does not endorse the guidance as written because some provisions would create burdens for laboratory practice. Yet we have had respectful discussions with FDA officials on LDT oversight because at heart we share common goals. I am persuaded, for example, that the FDA is also committed to ensuring patient safety and protecting analytic and clinical validity.

The trouble is we differ significantly on certain requirements we believe could limit access to testing or impede promising innovation. So we will continue to present evidence to clarify the realities of laboratory practice and enlighten their thinking. It’s complicated but also early; the FDA contemplates a lengthy, phased-in process. And by issuing a guidance, as opposed to regulations, the agency will have more flexibility in the long term.

Longstanding CAP policy calls for a regulatory framework that 1) ensures quality laboratory testing for patients, 2) allows for continued innovation in diagnostic medicine, and 3) establishes the least burdensome regulatory requirements for laboratories.

We support a risk-based oversight framework for LDTs driven by a systematic, inclusive public-private partnership that relies on inspection by third-party accreditors to ensure quality and safety of low- and moderate-risk testing. We believe the FDA is best equipped to oversee the introduction of high-risk LDTs because tests with confidential proprietary elements cannot be evaluated via interlaboratory comparison.

LDTs are a high-profile topic. They were on the agenda in September 2014, when the House Energy and Commerce subcommittee on health held hearings as part of the 21st Century Cures Initiative, which is examining advances in

science and technology that affect the field of medicine. The FDA released its draft guidance on Oct. 3, 2014 and held a workshop in January to solicit public comment. We were among the many representatives of laboratories, device manufacturers, and patient groups that testified.

Within the CAP paradigm, LDTs are tests developed by a laboratory certified under CLIA '88, performed by a clinical laboratory in the health care system in which the test was developed, and used in patient management. LDTs are neither FDA-cleared nor FDA-approved but may incorporate FDA-approved or -cleared components, including analytic-specific reagents. LDTs come in all forms, from conventional to molecular, generic to proprietary. Our tiered, risk-based regulatory scheme relies on an assessment that is based on the laboratory's *claims* for the LDT and the potential for harm to patients from a test error when the test order is written in conformance with those claims.

The CAP framework classifies tests as low, moderate, or high risk via several prisms. One is the likelihood that an incorrect result or incorrect interpretation would lead to serious morbidity or mortality. Another is whether or not an independent accreditor can readily review and verify the test methodology. The use of an LDT alone for clinical decision-making is relevant: Those used in conjunction with other evidence to establish or confirm a diagnosis but not determine a prognosis or direct therapy are typically low risk. Laboratories must confirm analytic and clinical validity of all LDTs, but while review of evidence by a deemed accreditor is required before a moderate-risk test is used clinically, a more intensive FDA review is required for high-risk LDTs introduced after April 23, 2003.

Many of our concerns about the draft guidance relate to definitions. For example, under the draft guidance, any companion diagnostic is a high-risk test. This would place some 1,000 LDTs—many of which have long been standard of care—under premarket approval.

The FDA equates making any modification to a test with device manufacturing, placing the laboratory under medical device regulations. The CAP framework would allow those modified LDTs that employ FDA-approved or -cleared kits, do not affect analytic performance, and do not change intended use to remain under FDA enforcement discretion. (Discretion authority permits the agency to forego enforcement of selected regulations.)

We also believe that the use of internally validated research-use-only and investigative-use-only reagents, instruments, and systems in an LDT should be allowed.

Currently, laboratories are permitted to provide LDTs for rare diseases when there is no test available. Rare diseases are generally considered to be those with a prevalence of fewer than 200,000 patients in the United States. The draft guidance would define LDTs for rare diseases as LDTs for which fewer than 4,000 patients are tested annually.

We do not know when final guidance will be issued, but we understand it will be years before these provisions are put into effect. In the meantime, our task is to educate regulators, legislators, and policymakers about the implications of limiting innovation or access to clinical testing. LDTs are critical elements of day-to-day patient care; most are well established and very low risk. The unintended consequences of certain aspects of the draft guidance could be catastrophic.

Gail H. Vance, MD, director of the Division of Diagnostic Genomics at Indiana University School of Medicine and a former member of the CAP Board of Governors, has led CAP advocacy around LDTs from the start. Dr. Vance approaches the task with a great depth of knowledge and consistent finesse; she can cite chapter and verse or bring it down to brass tacks. What we need from the FDA is clarity, she tells me. Clarity on the risk classifications, which should be set by expert panels. Clarity on how certain terms are defined. And clarity around a commitment to regulation that supports innovation.

Stephen J. Sarewitz, MD, of Valley Medical Center in Renton, Wash., and a member of the CAP Council on Accreditation and former governor, reminded me recently that the draft guidance is pointing in the right direction conceptually. Our task, he said, is to ensure that FDA officials understand the impact of what this regulatory regime would do. Properly framed, it may assure patients and other stakeholders and enable us to address the real

problems out there without crushing modern laboratory testing or discouraging innovation—something well worth pursuing.
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