



## EDITORIAL

# Regulating Laboratory-Developed Tests

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As a molecular pathologist for more than 20 years, I have had the opportunity to develop laboratory tests and to assess the efforts of others to develop laboratory tests. As Editor of *The Journal of Molecular Diagnostics* for 5 years, I have had the privilege and responsibility to review a wider range of developments by laboratories and manufacturers alike. In my work with the US government, including two stints at the US Food and Drug Administration (FDA), I've been witness to the means by which laboratories and manufacturers alike draw conclusions from their data. After all of this, I cannot conclude that either laboratories or manufacturers invariably report conclusions that are supported by their data using statistically valid techniques based on unbiased and appropriate experimental design. I've also come to recognize that regulatory activities often fail to accurately and effectively identify important systemic problems and that lack of adequate coordination among agencies creates confusion, increases burden on the general public, may increase the costs of providing medical services (thus increasing taxpayer burden), and has the potential of paradoxically and negatively influencing public health outcomes. In light of my personal experience, this Editorial discusses some of the issues raised by the FDA's proposed framework for regulating laboratory developed tests (LDTs).

### The FDA Weighs in on LDTs

The FDA recently notified the US Congress of its intent to establish a *Framework for Oversight of Laboratory Developed Tests* including a description of the *Anticipated Details* of that the proposed framework (<http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/UCM407409.pdf>, published online July 31, 2014). The agency suggests that increased oversight is appropriate as LDTs are highly complex, manufactured in high volume, used to screen for common diseases, used to direct critical treatment decisions, and are distributed widely, among other reasons. The FDA asserts that the Clinical Laboratory Improvement Amendments (CLIA)<sup>1</sup> and their implementing

regulations do not provide for premarket review, ensure clinical validity, or provide for removal of unsafe LDTs from the market. Specifically, the FDA argues that CLIA fails to provide assurance that LDT test results are safe and effective. The FDA further emphasizes that "LDTs that have not been properly clinically validated for their intended use and are used to make critical clinical decisions potentially put patients at risk of missed or incorrect diagnosis, failure to administer appropriate treatment or administration of potentially harmful treatment with no benefit" (<http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/UCM407409.pdf>, last accessed September 26, 2014). To address these perceived deficiencies, the FDA announcement proposes to require that laboratories provide the agency information about LDTs that are currently on the market and to notify the FDA of any new LDTs or significantly modified LDTs before clinical use. The agency then intends to begin premarket review of LDTs using a risk-based approach that relies in part on the participation of expert advisory panels. The FDA would focus its initial review on LDTs with the same intended uses as existing FDA-approved Class III medical devices. Significantly, the FDA will maintain a significant focus on LDTs used in direct-to-consumer testing.

Reactions to the FDA's notice have been mixed. For example, the Association for Molecular Pathology (which co-owns the *JMD*) has reaffirmed its position that federal regulatory oversight for most LDTs should remain with CLIA, which could be improved ([http://amp.org/documents/AMPResponds-toFDADraftProposedLDTRegulation\\_07.31.14\\_FINAL.pdf](http://amp.org/documents/AMPResponds-toFDADraftProposedLDTRegulation_07.31.14_FINAL.pdf), last accessed September 26, 2014). The Advanced Medical Technology Association Diagnostics, on the other hand, strongly supports more aggressive FDA action (<http://advamed.org/news/117/advameddx-commends-fdas-issuance-of-ldt-draft-framework>, last accessed September 26, 2014).

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For the reasons outlined below, I remain cautious of the proposed guidance by the FDA on LDTs, just as I remain skeptical of the belief that the CLIA framework, as currently implemented, provides adequate oversight in a world in which molecular analysis and the uses to which they are put are radically different from when the CLIA regulations were first promulgated.

## The Regulatory Legal Landscape

At least one policy structure to consider when evaluating the FDA's proposed framework is in President Obama's 2011 Executive Order 13563,<sup>2</sup> which provides that

"each agency must, among other things: i) propose or adopt a regulation only upon a reasoned determination that its benefits justify its costs (recognizing that some benefits and costs are difficult to quantify); ii) tailor its regulations to impose the least burden on society, consistent with obtaining regulatory objectives, taking into account, among other things, and to the extent practicable, the costs of cumulative regulations; iii) select, in choosing among alternative regulatory approaches, those approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity); iv) to the extent feasible, specify performance objectives, rather than specifying the behavior or manner of compliance that regulated entities must adopt; and v) identify and assess available alternatives to direct regulation, including providing economic incentives to encourage the desired behavior, such as user fees or marketable permits, or providing information upon which choices can be made by the public."<sup>3821–3823</sup>

This order suggests that when deciding to undertake a regulatory change (whether through rulemaking or guidance), regulatory agencies should i) be able to clearly define the problem to be solved through regulatory action, ii) be able to quantitatively assess the problem, iii) be able to show that the proposed regulatory action will effectively address the problem, and iv) demonstrate that the regulatory burden is appropriate to the societal costs imposed by the problem. The reason for taking this measured and disciplined approach for LDTs is simple: regulatory activities should not impose an opportunity cost that can impair public health by denying patients medical innovations, particularly when new regulatory burden is substantially disproportionate to the public health deficiency that inspired it.

## Balancing Risk with Reward

It's true that there exist LDTs that are inappropriately validated. However, although LDTs have been blamed for adverse patient outcomes,<sup>3,4</sup> most of the reports cannot be considered high-quality scientific evidence. The widely cited warning letter sent by FDA to 23andMe, Inc. (<http://www.fda.gov/iceci/enforcementactions/warningletters/2013/ucm376296.htm>, last accessed September 26, 2014), perhaps the most widely publicized LDT enforcement action attempted by the agency, cites no evidence of any harm to any patient.

However, it's clear that that direct-to-consumer testing companies have reported disease risk profiles without adequate validation.<sup>3</sup> Authors of papers submitted to *JMD* and other journals have at times drawn conclusions that were not supported by their data, lending legitimacy to concerns about some LDTs. In one highly publicized case, staff at a highly regarded academic medical center developed an LDT that they used in clinical trials, and as a result of an error in test development, the test did not do what it was purported to do.<sup>5–11</sup>

Additionally, the way in which LDTs are marketed has changed. Individual laboratories once collaborated with and developed tests for local clinicians. Now laboratory testing companies conduct large marketing and nationwide testing in a manner that more nearly resembles the operations of a traditional medical device manufacturer than that of the traditional hospital or independent laboratory. These changes have occurred in a highly politicized environment in which such LDT companies and traditional medical device manufacturers see government action as a method by which competition can be limited and market share expanded or contracted. If significant numbers of misleading results are reported to either clinicians or consumers, there is an economic harm that can contribute to adverse health outcomes even in the absence of physical harm. This potential harm should be considered when determining whether the costs imposed by regulatory activities are appropriate to the burden of these activities.

## Failures in Spite of Oversight

It is equally important, however, to consider the question of whether the approach proposed by the FDA will improve public health. Evidence is limited that current LDT implementation results in adverse public health consequences. Although FDA regulation of laboratory devices overall almost certainly has resulted in public health benefit, there are some notable exceptions.

For example, there is little doubt that prostate-specific antigen (PSA) quantitation provides a reasonable screen for prostate cancer. However, clinical trials and epidemiological evidence<sup>12</sup> accumulated in the United States suggest that early detection of prostatic cancer, the intended use for which PSA tests are legally marketed, does not confer a significant survival benefit for most individuals, although long-term outcomes from a European trial reach the opposite conclusion.<sup>13</sup> Since treatment of early prostate cancer seems to offer no advantage over watchful waiting<sup>14–17</sup> but does carry significant morbidity, a reasonable case can be made that the process by which PSA was approved represents a public health failure that resulted from a combination of the legal framework within which the FDA is required to perform review, as well as a misunderstanding of prostate cancer biology on the part of FDA personnel and the medical community alike. The US Preventive Services Task Force thus now strongly recommends against use of PSA for prostate cancer screening, regardless of age (<http://www.uspreventiveservicestaskforce.org/prostatecancerscreening.htm>, last accessed September 26, 2014). Similarly, although

FDA approved PCA3 testing for deciding when repeat prostate biopsies are indicated ([http://www.accessdata.fda.gov/cdrh\\_docs/pdf10/P100033a.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100033a.pdf), last accessed September 26, 2014), a report by the Agency for Healthcare Research and Quality suggests that the quality of evidence supporting the use of this test is low, as is its apparent diagnostic efficacy.<sup>18</sup> Evidence to support its use in improving health outcomes, such as disease-free survival, is lacking.

This example raises uncertainty about the FDA's apparent belief that its regulatory approach, when applied to LDTs, will result in a superior public health outcome. "Clinical validity" of a laboratory test does not assure that its use will improve public health.

## Where Do We Go from Here?

How then should the government respond to legitimate concerns over the accuracy of LDTs, evidence of probable economic harm, or concerns about public health harm? To its credit, the FDA seems to have taken a measured approach and does not intend to disrupt the use of LDTs in traditional patient care settings and where required to achieve good medical outcomes. However, evidence of a significant public health issue that requires attention is not empirically supported. Reporting of adverse events, though somewhat helpful in understanding negative outcomes, does not allow true assessment of the risk-benefit ratio for regulation because outcome assessment is seldom conducted by disinterested observers. Further, premarket approval or clearance does not ensure that laboratory tests have a positive public health impact, though such a process is likely to keep truly harmful tests off the market. However, to suggest that the proposed FDA actions will seriously curb innovation is wildly speculative.

Unfortunately, CLIA alone, as currently implemented, may well be inadequate. There are no strong standards in CLIA for validating LDTs, and there is no centralized reporting mechanism by which the public can become aware of either the magnitude of LDT testing, the benefit derived from this testing, or adverse consequences associated with this testing. Validation and performance data for most LDTs are not available for public inspection, and I believe it is likely inadequate in many laboratories. In some cases, complex algorithms for creating test results are used, and even if these algorithms are made available to inspectors, independent validation is, practically speaking, impossible. As currently used, CLIA does not guarantee the elimination of unsafe tests. However, CLIA regulations can be changed and could benefit from consideration of the generally disciplined approach with which FDA evaluates *in vitro* diagnostic devices.<sup>19</sup>

Although some individuals have suggested that the Centers for Medicare and Medicaid Services does not have the authority under CLIA to assess clinical validity and utility of LDTs, 42 U.S.C. 263a<sup>1</sup> gives the US Secretary of Health and Human Services the authority to include in accreditation standards such factors that the Secretary considers relevant.

Oversight by two separate regulatory agencies, when there is a lawful basis for sufficient oversight by one, does not appear to impose the "least burden on society," although it probably represents the least burden to the individual regulatory agencies. The Centers for Disease Control and Prevention, the FDA, and the Centers for Medicare and Medicaid Services should work together with the professional community to devise a single coherent regulatory approach that minimizes burden on the clinical laboratory while assuring transparency of laboratory operation and providing a means to identify the benefits and risks of LDTs. Such an effort should include the development of strong, and to the extent possible, uniform standards for validating LDTs and should employ sound statistical reasoning; such an effort might well require groups of laboratories to work together to validate LDTs which would then be adopted by all laboratories within the group. This approach should allow for rapid implementation of new LDTs so that innovation is not impeded by sometimes lengthy and expensive FDA premarket review processes and it should be performed under the auspices of a single office, rather than by several regulatory agencies operating independently. Such an approach would increase public confidence in LDT strategies and increase confidence in government by assuring that government agencies with overlapping responsibilities work together to create the least burdensome strategy for government oversight, as required by the President's executive order.

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