

A Call for Participatory Oversight

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INCREDIBLE ADVANCES HAVE BEEN MADE to achieve increasingly “personalized” medicine that will improve patient outcomes and support broader public health objectives by enabling more cost-effective healthcare. A large majority of these advances have resulted from the development of innovative molecular tests by certified clinical laboratories. Indeed, the majority of testing ordered by physicians has been developed or modified by clinical laboratories.

These so-called laboratory-developed tests (LDTs) are subject to the federal regulatory scheme known as the Clinical Laboratory Improvement Amendments (CLIA) and are often subject to additional state certification programs. They are not direct-to-consumer tests, nor are they diagnostic test “kits” that are manufactured, labeled, and sold to clinical laboratories to perform. LDTs are a test system or process for which only a test report to a physician is produced.

The U.S. Food and Drug Administration (FDA) believes that LDTs are also “medical devices” subject to the FDA’s oversight authority, although the FDA has never required laboratories that furnish LDTs to physicians to comply with FDA’s regulatory requirements. Historically, those requirements have applied only to medical device manufacturers that develop and distribute test kits to laboratories. This policy, called “enforcement discretion,” has been the subject of a nearly decade-long debate among the FDA, disease advocacy organizations, laboratories, and other stakeholders (Byrne, 2007; FDA, 2006a, 2006b; Horn and Terry, 2012; Hudson, 2006; Hudson and Javitt, 2006a, 2006b; Hudson et al., 2006a, 2006b; Javitt and Hudson, 2006; Popeo and Samp, 2006; Secretary’s Advisory Committee on Genetics, Health and Society, 2007; Zonno et al., 2009; Zonno and Terry, 2009a, 2009b).

The FDA has stated publicly that it intends to regulate these laboratory services as medical devices, primarily because of concerns that CLIA oversight is limited to the analytical validity of the test. Under the CLIA regulations, when a laboratory uses a laboratory-developed test system that has not received FDA clearance or approval, the laboratory may not release any test results prior to establishing certain required performance characteristics in order to ensure that the test produces accurate and reliable test results for patients.

The FDA’s chief public health concern with this long-established laboratory regulatory framework is that CLIA does not, before allowing a clinical laboratory to offer a test,

require that the *clinical* validity of the test be verified. That is, CLIA does not evaluate the clinical claims for the use of the test results, such as how well the results of the test can predict disease or direct treatment decisions. Historically, that has been left to the ordering physicians and the laboratory director as part of the practice of medicine.

Because these new innovative molecular test services do not fit neatly within the FDA’s medical device framework, which was established in the 1970s to oversee the safety and effectiveness of such things as implants, hearing aids, and surgical tools, the FDA has reportedly written one or more high-level draft guidance documents that describe how it intends to regulate LDTs. It is unclear when such guidance may be issued, but the FDA Commissioner and other federal agency leaders have explained that because of the advances in genomic sequencing, they believe it is necessary to establish a risk-based regulatory framework for the FDA to ensure the clinical validity of LDTs.

The FDA’s public health objectives for additional regulation are purported to be ensuring the safety and effectiveness of information provided to physicians by LDTs. It is particularly troubling that the FDA plans to use nonbinding “guidance” to establish these new policies rather than notice and comment rulemaking. Additionally, many unaddressed concerns continue to challenge the FDA’s efforts to move forward with such draft guidance.

As the pace of personalized medicine accelerates, with more and more targeted testing and treatment options available to patients and their physicians, it is important that these concerns be addressed directly and on the record. For example, stakeholders would like to understand how the FDA plans to minimize the potential for creating substantial burdens for laboratories seeking to offer LDTs, complications with institutional review board review, and lack of FDA resources available to regulate LDTs in a timely manner.

Likewise, the lack of actual examples supporting FDA’s contention that additional oversight is required has many stakeholders worried about the impact of a new supplemental FDA regulatory scheme on patient care and patient access to LDTs.

Although it is necessary that all laboratory testing demonstrate accuracy and reliability, concerns about the potential curtailment of the ability of innovative laboratories to attract and retain essential capital investment, as well as the creation of reimbursement issues for innovative testing, are likely to further limit both the near- and long-term benefit that

patients gain from physician access to new and better medical information.

Critical operational questions that have yet to be addressed by the FDA include conflicts between CLIA regulations and FDA restrictions on off-label promotion with CLIA clinical consultation requirements in practice of laboratory medicine and the application of FDA quality system regulations to laboratory services when there is no definable “device.” Likewise, where there is no product to “label,” what is meaningful labeling and to whom is the labeling directed?

Consequently, it would seem prudent for FDA to use substantial caution before publishing any guidance documents, even in draft. Moreover, the FDA should involve stakeholders, including members of the interested public, patients, and physicians, to inform development of appropriately balanced requirements that are specifically tailored to fill specific regulatory gaps identified by the FDA. This could be achieved through informal work groups charged with addressing key operational issues, the deliverables from which could be used to inform a proper rule-making process. Participatory engagement has become standard in many forms of oversight; it certainly should be a part of this important agency’s deliberations and decision.

In its recent report on personalized medicine, the FDA suggested that it is aware of “a number of examples where clinical decisions made on the basis of faulty tests resulted in harm to patients” (Simoncelli, 2013). Yet, after all of these years we have been provided no further information on what these examples might be or any ability to publicly debate whether new additional FDA oversight would have actually made any impact in those cases. Broad high-level draft guidance could be more of a disservice to patients and physicians if it results in policies that outweigh the public health objectives FDA is charged with protecting and advancing.

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