Point-Counterpoint: The FDA Has a Role in Regulation of Laboratory-Developed Tests

Angela M. Caliendo, a, b Kimberly E. Hanson a

Department of Medicine, Alpert Medical School of Brown University, Providence, Rhode Island, USA; Departments of Medicine and Pathology, Divisions of Infectious Diseases and Clinical Microbiology, University of Utah, Salt Lake City, Utah, USA

Since the Food and Drug Administration (FDA) released its draft guidance on the regulation of laboratory-developed tests (LDTs) in October 2014, there has been a flurry of responses from commercial and hospital-based laboratory directors, clinicians, professional organizations, and diagnostic companies. The FDA defines an LDT as an “in vitro diagnostic device that is intended for clinical use and is designed, manufactured, and used within a single laboratory.” The draft guidance outlines a risk-based approach, with oversight of high-risk and moderate-risk tests being phased in over 9 years. High-risk tests would be regulated first and require premarket approval. Subsequently, moderate-risk tests would require a 510(k) premarket submission to the FDA and low-risk tests would need only to be registered. Oversight discretion would be exercised for LDTs focused on rare diseases (defined as fewer than 4,000 tests, not cases, per year nationally) and unmet clinical needs (defined as those tests for which there is no alternative FDA-cleared or -approved test). There was an open comment period followed by a public hearing in early January of 2015, and we are currently awaiting the final decision regarding the regulation of LDTs. Given that LDTs have been developed by many laboratories and are essential for the diagnosis and monitoring of an array of infectious diseases, changes in their regulation will have far-reaching implications for clinical microbiology laboratories. In this Point-Counterpoint, Angela Caliendo discusses the potential benefits of the FDA guidance for LDTs whereas Kim Hanson discusses the concerns associated with implementing the guidance and why these regulations may not improve clinical care.

POINT

When I wrote the pro to this point counterpoint feels a bit odd as I have spoken and written in opposition to the FDA draft guidance on the regulation of laboratory-developed tests (LDTs). Over the past few years this topic has been hotly debated, and multiple organizations have put together counterproposals to the FDA draft guidance. This broad discussion along with input from many perspectives has led to some interesting and creative ideas on how to regulate LDTs. My comments focus on microbiology testing. The fields of oncology and genetics offer different challenges, and we want to avoid throwing the microbiology baby out with the oncology/genetics bathwater. However, it seems inevitable that LDTs will be regulated in some manner.

It is clear that LDTs are essential for the practice of infectious diseases and should not be removed from clinical practice. There are many essential LDTs in use, and eliminating them would have a negative impact on the quality of care. These tests were developed to meet important clinical needs for which there are no commercial assays. Eliminating LDTs is not the goal of the FDA guidance; rather, it is to put processes in place to ensure the quality of these tests.

Given the widespread use of LDTs for diagnosis and monitoring serious infections, there is a need to ensure that these tests have acceptable performance characteristics, that they do not cause harm, and that they are used appropriately. The current oversight of LDTs has several gaps that raise concerns. These include the Clinical Laboratory Improvement Amendment (CLIA) regulations requirement for biennial survey, so the independent assessment of the analytical data may well occur after the test is put into clinical practice; lack of review of clinical validation data, so there is no assurance that the test is clinically useful; lack of adverse-event reporting; and the absence of a mechanism to remove an unsafe test from clinical use. Let us look at some of these issues in more detail.

Though many of us feel that our LDTs are of high quality, it is possible there are inadequate tests in use because the extent of the analytical and clinical validation can vary greatly between laboratories. Really, how many positive clinical specimens did you test before offering your LDT for detection of herpes simplex virus (HSV) DNA from spinal fluid? While detection of HSV DNA is considered the standard of care for the diagnosis of HSV encephalitis (1), what do we really know about the performance of many of the LDTs in clinical use? I am not implying that this LDT is not clinically important. This test has undoubtedly reduced the morbidity associated with HSV encephalitis as well as the unnecessary use of acyclovir. However, it is key that there is an assurance of quality for these tests; wherever a clinician is practicing, they should have access to high-quality LDTs. Clinicians do not understand the nuances of test performance characteristics, nor should they need to; this is the responsibility of the laboratory director. But laboratory directors can be unaware of performance issues with their LDTs, particularly when testing is done in a reference laboratory where they do not have access to clinical information.

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Editor: A. J. McAdam

Address correspondence to Angela M. Caliendo, acaliendo@lifespan.org, or Kimberly E. Hanson, kim.hanson@hsc.utah.edu.

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A recent Institute of Medicine report states that “getting the right diagnosis is a key aspect of health care. Diagnostic errors persist throughout all settings of care and continue to harm and unacceptable number of patients” (2). Diagnostic errors contribute to approximately 10% of patient deaths (2). There is no reason to think that LDTs are excluded from this problem with diagnostic errors. The FDA recently published a series of case studies describing problems with LDTs and the need for better regulation (3).

Currently, the process that a commercial test goes through to be cleared by the FDA is more rigorous than that performed for most LDTs. This leads to a tilted playing field; laboratories can offer a test after completing a less rigorous validation than is required for commercial companies. This is a reason that so many are opposed to the proposed FDA guidance: they realize that they could not meet the regulatory requirements for a 510(k) submission to the FDA. While it is true that few hospital-based laboratories have the resources to submit a 510(k) application, a modification to the guidance in which a test is considered to represent an unmet need until at least 2 or 3 tests have been cleared by the FDA would be a reasonable middle ground (see below).

This is not the first time that LDTs have been threatened. Before the modification of the analyte-specific reagent (ASR) rule, commercial companies offered nearly complete kits as ASRs and were allowed to them to sell these without going through the regulatory process. When the FDA stopped this practice there was great concern that this would put an end to LDTs, limit access to testing, and compromise patient care. So what really happened? Some ASRs were eliminated by the manufacturers, and laboratories had to redesign tests or develop new LDTs, which was time-consuming and expensive. This chaos was short-lived as many companies modified their ASRs to meet the new regulations and companies put a greater focus on getting tests cleared or approved by the FDA. The FDA realizes that LDTs are essential for the practice of medicine, which is why the LDT guidance has a 9-year phase-in period. An additional modification to the guidance that would be very useful would be for the FDA to continue to find ways to remove barriers and simplify the process for getting tests cleared or approved. This has been done in recent years, by allowing the use of archived specimens and mock (spiked) specimens to validate tests for rare pathogens.

The Clinical Laboratory Improvement Act (CLIA) was implemented to improve the quality of laboratory testing, and the laboratory inspection process is a key component of the regulation. Many opposed to the FDA guidance feel that it is the role of CLIA to ensure the quality of LDTs. However, this depends on the thoroughness of the laboratory inspections, which can vary widely. While I served as the Director of Clinical Laboratories in a previous position, our laboratory underwent many surveys. Some of these inspections were outstanding, while others were not because the inspectors were inexperienced in specialized laboratories such as molecular diagnostics. As a result the validation and verification data for LDTs implemented since the previous inspection were not always thoroughly reviewed. An independent review of data prior to implementation of an LDT is reasonable, but it would need to be done in a manner that was efficient and not burdensome to laboratories.

The Association of Molecular Pathology (AMP) has been very active in training inspectors of molecular laboratories to improve their competence. But there are still gaps in the expertise of inspectors, particularly if they do not perform LDTs. Both the College of American Pathologists (CAP) and AMP have written proposals in response to the draft guidance that call for the modernization of CLIA. This is an approach that could go a long way to improving LDTs without limiting access to the tests, as well as addressing concerns regarding offering and/or marketing tests without proven clinical value.

The draft guidance proposes a risk-based approach beginning with regulation of high-risk LDTs. In clinical microbiology the high-risk pathogens are limited to human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B virus (HBV), human papillomavirus (HPV), and several transplant-associated viruses, including cytomegalovirus (CMV) and possibly Epstein-Barr virus (EBV). It is unclear how tests for BK virus and adenovirus will be classified. Given that there are a number of FDA-approved tests for HIV, HCV, HBV, and HPV and the vast majority of laboratories use these approved tests, the draft guidance will have little or no impact on testing for these pathogens.

LDTs are widely used for transplant viruses primarily because there are no FDA-approved or -cleared tests with the exception of viral load tests for cytomegalovirus. Viral load testing for transplant viruses is essential for clinical management, and submitting an application for premarket approval (PMA) is not feasible for most laboratories. One option that has been proposed is reclassifying the transplant viruses to the moderate-risk category. The key to reclassifying these pathogens is providing an approach to mitigating the risk of an incorrect test result. Several factors mitigate the risk of an incorrect result with these tests: patients are monitored repeatedly over time and results are interpreted in conjunction with other data such as clinical signs and symptoms and pathology results and in light of the state of immunosuppression. In addition, there are now WHO international standards for CMV, EBV, and BK virus DNA, with adenovirus standards in development. The availability of these standards will help improve the analytical performance of these tests, further reducing risk. Reclassification of these pathogens could be done by convening a group with expertise in both the clinical management of transplant infections and laboratory testing for these infections. If the FDA agrees with this approach, a process needs to be implemented that is thorough and rapid. Creating a cumbersome process that requires years for reclassification will not be helpful.

LDTs for unmet clinical needs are subject to oversight discretion in the current draft guidance. Low-risk tests will need only to be registered, leaving a need for a reasonable solution for moderate-risk tests. The draft guidance states that once a single test is FDA cleared for an analyte, this will no longer be considered an unmet need. With some flexibility this could be managed by modifying the guidance to allow 2 or 3 tests to be cleared before loss of the unmet-need status. This would give laboratories some flexibility and eliminate the need to purchase multiple test platforms, each performing only one test. It would also provide the opportunity to compare performance characteristics between these tests and their LDTs. It is important to appreciate that once FDA-cleared tests are available they are often adopted by clinical laboratories. Though they may be more expensive, the quality control needed is substantially less than that for an LDT and the performance characteristics are well understood. For example, few laboratories perform LDTs for detection of respiratory viruses, the mefA gene, or Clostridium difficile, all of which were commonly detected with LDTs before FDA-cleared tests were commercially available. If this guidance is implemented, fewer
laboratories may continue to use LDTs when FDA-approved or cleared tests are available, and so this may serve as an incentive for commercial companies to develop tests that are clinically necessary but considered less profitable and over time substantially increase the number of FDA-cleared or -approved tests available for clinical use. One of the biggest challenges for clinical microbiology laboratories is the requirement for submission of a 510(k) with the change of a specimen type. Non-FDA-cleared specimen types are often tested in infectious disease testing because diagnostic companies are not always interested in conducting clinical trials for unusual specimen types. One important example is nucleic acid-amplified testing for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* on pharyngeal and rectal swabs. There is a study under way sponsored by the Antimicrobial Resistance Leadership Group (ARLG) to conduct a clinical trial of *C. trachomatis* and *N. gonorrhoeae* testing on rectal and pharyngeal swabs that involves simultaneously evaluating tests from multiple manufacturers. This is a very creative approach, as it reduces the cost for any one manufacturer while increasing the number of tests available for this clinical indication. Another example of use of an alternative specimen type that is commonly cited is HSV testing on cerebrospinal fluid (CSF). While there are numerous PCR tests cleared for testing HSV from genital and mucocutaneous lesions, there is only one test cleared for testing spinal fluid. However, this situation is very different from the *C. trachomatis/N. gonorrhoeae* example given above because the analytical sensitivity needed to detect HSV DNA from a genital or mucocutaneous lesion is much higher than that needed for detection of DNA in a CSF specimen, as the concentration of HSV DNA in lesions is often several log_{10} higher than that seen in spinal fluid, especially for HSV meningitis. So using a test designed for genital or mucocutaneous testing on spinal fluid without a thorough evaluation could lead to false-negative results, as the test may not have adequate analytical sensitivity. In this case, requiring a review of test performance prior to clinical implementation seems prudent.

In summary, though there is much concern about the regulation of LDTs, there is a need to “level the playing field,” ensure the quality of all LDTs, and ensure that the test has clinical utility. Moreover, the impact of this guidance on clinical microbiology could be managed with some reasonable changes. Hopefully, the extensive and thoughtful feedback that FDA has received will lead to modifications of the guidance and compromises can be reached that will allow continued use of LDTs while ensuring their quality.

Angela M. Caliendo

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**REFERENCES**


**COUNTERPOINT**

Oversight of diagnostic testing in the United States currently involves governmental agencies, health care payers, and professional associations. In 1976, the Medical Devices Amendments Act granted the Food and Drug Administration (FDA) jurisdiction over commercially distributed test kits as *in vitro* diagnostic devices. The FDA also claims that the statute gave them regulatory authority over laboratory-developed tests (LDTs), which are defined as *in vitro* diagnostic tests that are intended for clinical use and designed, manufactured, and used within a single laboratory.

The Agency has historically exercised “enforcement discretion” over LDTs, reasoning that most were well-characterized, low-risk tools. As a result of changing medical needs and technological advances, LDTs have evolved to become more complex and are now widely applied in clinical practice. In response to these trends the FDA has now determined that the characteristics of modern LDTs create potentially increased risks for patients despite current regulation under CLIA and the Federal Food, Drug, and Cosmetic Act.

On 31 July 2014 the FDA notified Congress of the Agency’s intent to issue an oversight framework for LDTs. Draft guidance was then officially posted on the FDA website on 3 October 2014 (1). The regulation included a phased-in premarket review (premarket approval [PMA] application) for higher-risk LDTs followed by registration and listing [510(k) submission] with adverse-event reporting for moderate-risk LDTs. These proposed changes would almost certainly have a variety of negative, unintended consequences that could detrimentally affect patient care.

Clinicians rely heavily on both commercially available assays and LDTs to diagnose, monitor, and assess risk for a variety of medical conditions. In the field of infectious diseases (ID), diagnostics are essential to identify an infecting pathogen, for determining antimicrobial susceptibility, and to monitor treatment response, assess prognosis, and potentially anticipate complications for an individual patient. A short turnaround time to results is critical for life-threatening infectious diseases, where even a few hours of delay may negatively impact patient outcomes. Microbiologic tests are also essential for public health, hospital infection control, and antimicrobial stewardship initiatives. There are, however, relatively few or no FDA-approved tests for a variety of important infectious diseases, and LDTs have become the established standard of care for many conditions. Reliance on well-vetted LDTs is especially important for centers that serve the most medically complex and/or critically ill patients.

Clinicians and microbiologists have voiced significant concern that the FDA’s proposed regulation will impede patient access to high-quality ID tests. Additionally, regulatory barriers may stifle innovation and the ability to rapidly respond to emerging or re-emerging infectious health threats. The vast majority of ID LDTs, including those that would be considered high-risk tests under current FDA definitions (e.g., molecular assays for viral encephalitis, quantitative viral load testing for transplant-associated infections and genotype databases for HIV, HCV, and CMV drug resistance), have an established track record of validity and safety and are often integral components of evidence-based practice guidelines (2–4).

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FDA review of moderate- and high-risk LDTs is impractical from both cost and administrative perspectives. While the FDA has made provisions for a grandfather clause designed to minimize disruption of LDTs currently in use, the creation of new and improved tests may suffer because the majority of clinical laboratories lack the financial and clerical resources to navigate the PMA or 510(k) submission process. Instead of developing robust LDTs that address unmet medical needs or that significantly improve upon existing methodologies, most institutions will be forced to send testing out to a reference laboratory or rely on FDA-approved, commercially available kits. Referral testing may unnecessarily increase the time to critical results. Furthermore, FDA-approved assays are typically more expensive than LDTs and often require dedicated instrumentation that cannot be used for additional applications.

The proposed regulation would also limit innovative off-label use of FDA-approved tests. For example, matrix-assisted laser desorption ionization—time of flight mass spectrometry (MALDI-TOF MS) platforms are currently FDA cleared for the identification of certain bacterial and yeast species using cultured isolates. This technology has revolutionized the clinical laboratory’s ability to quickly, accurately, and cost-effectively identify human pathogens from culture, but the upfront equipment purchase is expensive. To address unmet clinical needs as well as to further capitalize on investment, clinical laboratories have found additional ways to exploit the power of MALDI-TOF MS technology for patient care. Creative LDT applications include the identification of other classes of organisms (e.g., mycobacteria, filamentous fungi, and Nocardia), the detection of carbapenemase production in Enterobacteriaceae, and the identification of organisms directly in clinical specimens such as urine or positive blood culture aliquots.

These same regulatory hurdles may delay the availability of new tests developed in response to ID outbreaks. Flexibility and timely response are needed to keep pace with the ever-changing landscape of emerging infectious diseases. Public health and clinical laboratories must have the freedom to develop and use validated LDTs when commercial sources for reagents do not exist and/or when the infection is not covered under a secretarial declaration of a public health emergency or emergency use authorization (EUA).

As a counter to these arguments the FDA has raised valid concerns about the potential risks associated with some LDTs, particularly in the fields of oncology and genetics. The Agency recently highlighted 20 clinical vignettes in which harm or potential harm was caused by inaccurate LTDs (5). Of note, only 3 of the examples illustrated 20 clinical vignettes in which harm or potential harm, particularly in the fields of oncology and genetics. The Agency recently raised valid concerns about the potential risks associated with some LDTs, particularly in the fields of oncology and genetics. The Agency recently highlighted 20 clinical vignettes in which harm or potential harm was caused by inaccurate LTDs (5). Of note, only 3 of the examples illustrated 20 clinical vignettes in which harm or potential harm occurred (5).

false-positive LDT PCR results. A significant number of health care workers with false-positive PCR tests (i.e., DNA detection not confirmed by culture and/or serology) received unnecessary post-exposure prophylaxis and were furloughed from work. What was not mentioned in the FDA report, however, was that the reasons for false-positive pertussis PCR results are complex (6).

Environmental sampling of the clinic and laboratory space was not reported in the original Morbidity and Mortality Weekly Report investigation (7). It is conceivable that an FDA-approved molecular assay for B. pertussis, which currently does not exist, would be similarly affected by environmental contamination or colonization states. Retrospective interviews with 90% of health care personnel (HCP) tested during the suspected outbreak indicated that 21% never had cough, a hallmark symptom of pertussis; of those with a cough, 35% reported never having classic disease features like paroxysms, whoop, or posttussive emesis (7). These observations suggest that there was a relatively low pretest probability for disease in many of the HCP and, therefore, a higher likelihood of false-negative test results regardless of the assay used. The next cases were related LDTs for infections by human papillomavirus (HPV) and Borrelia burgdorferi. These are two infections for which robust FDA-approved tests exist and for which professional guidelines specifically recommend against the use of LDTs (8, 9).

In conclusion, laboratory tests that are analytically and clinically valid as well as prospectively monitored for quality are an essential component of best clinical practice. Regulatory oversight that is focused on test validity and patient safety has the potential to minimize risk in select settings; but overall, the potential harm posed by ID LDTs is dwarfed by their demonstrated positive impact on patient care. The proposed FDA guidance should be revised to minimize the burden on clinical laboratories and allow for continued innovation as well as patient access to state-of-the-art tests for infectious diseases. Regulatory exemptions for special categories of tests, including those for rare diseases, unmet medical needs, and public health surveillance, are also needed. As a community of health care professionals and laboratories, we must work together to ensure that patient care does not suffer as a result of changes in LDT regulation.

Kimberly E. Hanson

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6. Centers for Disease Control and Prevention. 2015. Best practices for healthcare professionals on the use of polymerase chain reaction (PCR) assays, as well as to laboratory error or carryover contamination. Environmental
SUMMARY

Points of agreement

• Laboratory-developed tests (LDTs) have an important role in the clinical management of infectious diseases. They are particularly useful in the management of viral infections in immunocompromised patients but are also important in testing samples that are not included in the FDA clearance for some commercial tests. This is reflected in their widespread use in clinical care and by the many laboratories that offer these tests.

• Implementation of the Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests would result in a significant burden for laboratories. Extensive resources would be needed to comply with these guidelines. Some laboratory directors might decide to stop offering LDTs and send samples to commercial laboratories instead. This would delay reporting of patient results and might reduce the quality of clinical care.

Issues to be resolved

• What are the significant gaps in current regulatory oversight of LDTs, and are these gaps best addressed by modifying the proposed guidance from the FDA before implementation or by modifying the laws that regulate clinical laboratories, such as the Clinical Laboratory Improvement Amendments?

• Have the LDTs in clinical use been adequately validated, and has the clinical utility of these assays been rigorously established?

• To what extent are protests against the implementation of the proposed FDA guidelines motivated by concern for the quality of patient care, and to what extent are they motivated by concern about the resources that would be needed to comply with the guidelines?

Alexander J. McAdam, Editor in Chief, Journal of Clinical Microbiology