VIEWPOINT

FDA Regulation of Laboratory-Developed Diagnostic Tests

Protect the Public, Advance the Science

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Counter Viewpoint

Should the FDA regulate laboratory-developed diagnostic tests? —Yes.

In April 2014, the Centers for Disease Control and Prevention and the US Food and Drug Administration (FDA) published a warning in *Morbidity and Mortality Weekly Report* about a commercially available test for Lyme infection. The test returned the result "culture positive," when in fact the procedure was far more complex than a routine culture. There also were "serious concerns about false-positive results caused by laboratory contamination," leading to "the potential for misdiagnosis."[1]

The questionable assay was a laboratory-developed test, meaning an "in vitro diagnostic test that is designed, manufactured, and used within a single laboratory."[2] Laboratory-developed tests exist in a regulatory crevice. Because of its broad statutory authority over products "intended for use in the diagnosis of disease or other conditions,"[3] the FDA considers laboratory-developed tests under its jurisdiction. Yet for many years, the FDA has taken the position that there were too few of these tests, and that they were of sufficiently low risk, to merit oversight. As a result, tests "designed, manufactured, and used within a single laboratory" are not subject to the standards for quality and validity applicable to other diagnostic tests, such as those made by medical device manufacturers.

Recently, however, the FDA has expressed concern with the proliferation of laboratory-developed tests, their marketing, and their potential to mislead physicians and patients and undermine clinical care. On July 31, 2014, the agency notified Congress that the agency would shortly release a draft guidance document containing a framework for the application of agency standards for quality, safety, and validity to laboratory-developed tests. On September 30, the agency posted the draft guidance document to its website and opened a comment period lasting until February 2, 2015.[4] The agency will hold a public meeting on the topic on January 8 and 9, 2015, at the National Institutes of Health in Bethesda, Maryland.

Why the FDA Is Acting Now

The FDA is moving forward with oversight of laboratory-developed tests because of profound changes in the nature of these products since medical device regulation began in the 1970s. At that time, a "laboratory-developed test" generally meant a hospital laboratory using a manual technique to assess an individual patient. Over time, however, laboratories became separate business entities outside of health care institutions and began marketing highly complex and automated assays across the country. By performing these tests, these businesses have been able to claim the "laboratory-developed test" exception to oversight. Yet their tests are often as complex as those manufactured in kits by device companies and fully regulated by the FDA. Some laboratories are even marketing products as laboratory-developed tests that claim to provide the same clinical value as FDA-approved diagnostics.

With changes in technology and proliferation of these tests have emerged new concerns for patients. The FDA has stated that the agency is aware of "faulty" laboratory-developed tests that may have led to "patients being over-or undertreated for heart disease; cancer patients being exposed to inappropriate therapies or not getting effective therapies; incorrect diagnoses of autism; unnecessary antibiotic treatments; and exposure to unnecessary harmful treatments for certain diseases such as Lyme Disease."[2] Yet without even the requirement that laboratories report adverse events, it is extraordinarily difficult for the agency to understand key problems and respond. One highly suspect test marketed as helping to determine whether patients should receive statin therapy was used among more than 150 000 patients before it was recognized that the technology had serious flaws, including being based on an antiquated approach associated with "false positive results and a notorious inability for variants originally identified to be subsequently validated in additional studies."[5] Despite the refutation of its value, this test is still widely available and broadly marketed.

Beyond direct threats to safety, the current lack of oversight for laboratory-developed tests is undermining the availability of new evidence for clinical practice. A device manufacturer seeking approval of a novel diagnostic test must conduct studies to show that the product actually measures what it claims to measure and actually accomplishes what it claims to accomplish. By contrast, a company making its own laboratory-developed test does not need to conduct any research to make a claim. With greater numbers of laboratories making unverified claims, device manufacturers have less incentive to pursue the approval process. The result is that physicians and patients are forced to make critical decisions in the dark.

Supporters of the FDA's proposal to regulate laboratory-developed tests include the American Cancer Society Action Network, the American Society

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of Clinical Oncology, and the Association of Public Health Laboratories. These groups have based their support of regulation both on the risks to patients when laboratory tests fail to perform as advertised and on the benefits of a stronger evidence base for diagnostics.

Objections to FDA Oversight

Opponents of FDA regulation of laboratory-developed tests include the American Hospital Association, the American Clinical Laboratory Association, and the American Medical Association. In addition to raising legal questions of jurisdiction, opponents have made 3 principal arguments.

First, they contend that the tests are already well regulated under the Clinical Laboratories Improvement Act (CLIA). CLIA addresses whether a laboratory is able to implement a test according to instructions and detect what is intended to be detected. However, CLIA (1) does not require external review before the test is used in clinical practice; (2) does not address the clinical validity of a test, which is its accuracy in assessing the presence or absence of a condition; (3) does not provide for reporting of adverse events; and (4) does not impose standards for quality in manufacturing. CLIA is not a regulatory framework that provides for meaningful review of key clinical issues that matter to clinicians.

Second, opponents argue that regulation will eliminate many laboratory-developed tests essential to patient care today. This would be a valid concern—if the FDA were proposing to ban all laboratory-developed tests until they were reviewed by the agency. In fact, the FDA's draft guidance provides for exemptions for tests applicable to rare diseases and for tests offered within health care facilities or health care systems when there is no FDA-approved test available. The proposal also authorizes a slow phase-in for oversight of other types of tests. The reason the FDA is soliciting public comment and holding public meetings is to modify the guidance in such a way that maximizes benefit and minimizes risks.

Third, opponents claim that FDA regulation will stifle innovation in personalized medicine. This claim is based on a misunderstanding of the concept of innovation. Innovation is not just novelty; it is novelty that works. There were thousands of novel drug therapies for sale at the turn of the 20th century, but the golden age of genuine pharmaceutical innovation did not arise until the FDA established core requirements for safety and effectiveness—and high-quality medications could outcompete those without evidence.[6] Similarly, responsible FDA oversight of laboratory-developed tests should foster the kind of research and development that drives medical progress.

Conclusions

A patient travels by an ambulance that is regulated, to a hospital that is regulated, for care using medicines that are regulated, administered by nurses and physicians, who are regulated. Yet today, that same patient's life or death could hinge on whether a single, unregulated diagnostic test result is meaningful. The FDA is right to bring a measured approach to ensuring the quality, safety, and validity of laboratory-developed tests.

ARTICLE INFORMATION

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Additional Information: Dr Sharfstein was FDA Deputy Commissioner from 2009 to 2011.

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