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U.S. Food and Drug Administration
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Dear Dr. Shuren,

The American Cancer Society Cancer Action Network (ACS CAN) is pleased to offer comments in support of the U.S. Food and Drug Administration's (FDA's) proposed guidance, *Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs),* (Docket No. FDA-2011-D-0360).

Introduction

Because cancer is literally hundreds of different diseases, the ability to accurately diagnose the type of cancer and to identify the patient's particular genetic characteristics is absolutely critical for optimizing each patient's treatment. Molecular tests have become an increasingly integral part of critical treatment decision-making about whether or not a patient can benefit from a course of therapy and have helped improve patient outcomes. As patients and doctors become more reliant on molecular tests to provide this information, it is imperative that the tests are reliable and accurate.

Currently, tests sold as complete kits are required to undergo pre-market clearance and approval from the FDA to verify safety and effectiveness of the test. Similar tests that laboratories create for their own use are not subject to the same level of safety review and performance. The latter tests, known as laboratory developed tests (LDTs), were originally relatively simple, low-risk tests and the FDA therefore chose to not exercise active oversight over these tests. Now LDTs encompass even the most advanced molecular diagnostics, such as higher risk tests that are essential for safe and effective use of cancer therapeutics or are critical determinants in the treatment of serious, life threatening diseases. With diagnostic testing and targeted therapies on the rise, the stakes are now much higher for cancer patients

and others. LDTs are becoming more numerous, more complex, and have the potential to have a significant impact on health care decisions. Accordingly, we agree with FDA's decision to begin providing oversight of LDTs that could pose risk to patients if not fully understood. This oversight should allow the medical community to take full advantage of these new tests by providing physicians and patients with confidence that they can trust and safely act on test results.

Shortfalls in existing system

While clinical testing laboratories are currently subject to oversight by the Centers for Medicare and Medicaid Services (CMS) through the Clinical Laboratory Improvement Amendments (CLIA), this oversight is focused on general laboratory and personnel accreditation rather than oversight over individual tests. Specifically, CLIA does not require pre-market review for individual tests, demonstration of clinical validity, independent review of clinical claims, adverse event reporting system for tests. Nor does CLIA include a process for corrections, recalls and informed consent for patients who participate in LDT clinical studies.

One of the greatest concerns for cancer patients about LDTs is the current lack of assurance of their clinical validity. Cancer typically develops from genetic aberrations that are either inherited or developed during a person's lifetime. While we continue to learn more about the wide variety of mutations that contribute to cancer, we still only understand a fraction of the relationships between genetic changes and cancer, or the accompanying changes in body biochemistry that can manifest as protein signatures in blood, serum, urine, etc. The ability to detect and diagnose cancer early by picking up on these changed molecular signatures has long been pursued, but the development of reliable tests for clinical use is still in its infancy.

The incredible potential and the desire to exploit gene and protein assays to provide clinical insight into disease have driven much of the diagnostic development in the oncology space. It is important, however, that the enthusiasm for potential cancer diagnostics does not outstrip the scientific validation available to support clinical use on patients. Clinical validity is the demonstration that a given gene, protein, or other marker is actually relevant to a given disease. A test that poses a risk to patients, whether an LDT or a kit, should have demonstrated clinical validity before being marketed to patients and physicians. A test for a marker where a valid connection between that marker and a disease has not yet been made should be considered investigational and treated as such while validation is underway. While it is critical that clinical validity be demonstrated, it should be noted that a laboratory would not

necessarily need to conduct its own clinical trials to establish such a linkage if existing peer-reviewed research has already proven such a linkage. Currently CLIA does not require a demonstration of clinical validity prior to marketing, while the FDA oversight framework would.

A glaring example where this premarket check on clinical validity did not occur is an LDT that was known as OvaSure. In 2008 OvaSure was commercialized as a test claiming to diagnose ovarian cancer through the detection of protein markers in the blood. The test was sold for four months before being pulled from the market after it was determined that it could not reliably diagnose ovarian cancer. During those four months it was used by many women and their physicians who hoped to gain important information to help them manage their disease, but who were instead given unreliable information. [1] The proposed oversight framework would have required validation of OvaSure before it was used on patients, and would likely have prevented the marketing of this test.

Transparency

Much of today's regulatory oversight of drugs and devices stemmed from early negative experiences in which inert or dangerous products were sold to patients. With specific regard to labeling and marketing, sometimes outrageous claims were made about drugs and devices that were unsupported by evidence, hence the current requirement for approval of labels and subsequent marketing that adheres to labeled indications. With respect to diagnostic tests, patients and their physicians should not be presented with false, misleading, or unsubstantiated claims about a test's performance or diagnostic capability, regardless of whether a test is considered a kit or an LDT. While LDTs may not have a "label" in the same sense as other devices, we nonetheless support oversight of how all diagnostic tests are advertised and marketed to providers and patients to ensure transparency of a test's proven capabilities.

Balancing innovation patient safety and access

The continual improvement of existing tests is an important facet of today's testing environment and creating a system to encourage improvement to the performance of existing tests while maintaining standards of safety and efficacy will be a difficult balance. Performance modifications may improve the efficiency or analytical performance of a test, but these changes may also impact a

[1] Buchen, "Missing the Mark: Why is it so hard to find a test to predict cancer?" Nature, Vol. 471, 24 March 2011, pp 428-432.

test's clinical validity. When modifications may affect the clinical validity of a test, it will be important to review such changes for the impacts on patients. It will be critical for FDA to work with the laboratory community to create as much clarity as possible around the types of changes that would and would not trigger further review.

The oversight framework contains three notable areas where FDA has expressed the intention to exercise at least partial enforcement discretion over LDTs. These areas include LDTs that are rarely used, serve unmet medical needs and fit a traditional definition of an LDT. We recognize the importance of a flexible framework in order to ensure continued availability of tests that are important to patient care and support innovation.

It will be extremely important to carefully and clearly define the qualifications for tests that can take advantage of these exemptions. The goal should be to tailor the qualifications narrowly enough that the exemptions are not exploited in a way that exempts more tests from oversight than intended, while at the same time not being so narrow as to restrict patient access to tests for which these exemptions were designed. The following are areas where we feel careful attention should be focused.

Definition of a health system: Exempted LDTs for unmet medical needs and those considered "traditional" are restricted to tests conducted within a patient's health system. We agree that this restriction is appropriate as closer communication is more likely between laboratory and clinical personnel when they are part of the same organization. It will be important to craft a definition of what constitutes a health system in a way that ensures such a system has close communication, for example through a shared electronic records system and common administrative processes. Health systems should be able to take advantage of this exemption to create innovative LDTs as new science becomes available, but it is unclear what effect that this provision will have on independent practices or small systems that have no or minimal internal laboratory capacity and therefore may not be able to utilize this exemption. The unmet medical need exemption for any given use should ideally be temporary while data is collected for demonstration of clinical validity and FDA approval of a new test, but potential disparate effects of this restriction on patients served by small versus large systems should be monitored closely by FDA during implementation of the framework for any potential negative effects on patient care.

Definition of "available FDA approved IVD": The unmet medical need exemption from oversight exists only so long as there is not an FDA approved IVD available for the same purpose, which includes LDTs. There is no requirement for an individual health system that seeks and obtains FDA approval for an LDT to sell their test commercially outside of their own health system, which means that it may be possible for a given test to be FDA approved, but not actually "available" to any outside entities. It will therefore be critical to clearly define the conditions governing the applicability of this exemption to ensure that it is implemented as intended.

Risk determination

A central aspect of the proposed framework deals with treating LDTs differently according to their risk. Low-risk tests have different oversight obligations than medium- and high-risk tests, and the amount of time allowed for transition into the new framework is also scaled to a test's risk. We agree with this risk-based approach. As the public risk-evaluation process is developed, it is important to keep patients at the heart of that process. Risks posed by LDTs come from the clinical use of test results, and those risks are borne by patients. In the case of cancer, the decisions facilitated by test results can often have very serious consequences for a patient's health and prognosis. Patients should therefore play an important role on any risk evaluation advisory panel, and their perspective should be prioritized as the most important stakeholder.

Conclusion

The current molecular testing landscape has developed over the years and has been influenced by FDA's decision not to actively regulate LDTs. We support the FDA decision to begin active oversight of LDTs, but recognize that it will take time and effort for all of the stakeholders to adjust to this new paradigm. The nine-year phase in period of the framework is an acknowledgement of the effort required, and we encourage FDA to closely monitor implementation of the framework and adjust as necessary to achieve the common goal of delivering the safest and most innovative testing to patients.

As development and implementation of an oversight framework for LDTs continues, patient needs and concerns must be central to all decision making. While there are other important stakeholders as well, ultimately molecular tests are developed and used for the benefits of patients and that patient benefit should be the primary goal of any oversight framework. That means ensuring the validity of tests and preserving patient access to the latest testing developments.

Thank you for the opportunity to provide comments and we look forward to continuing to work together to create appropriate oversight for LDTS. Please do not hesitate to contact Mark Fleury (mark.fleury@cancer.org) if you have any questions.

Sincerely,

Kirsten Sloan
Senior Policy Director
American Cancer Society Cancer Action Network

The American Cancer Society Cancer Action Network, the nonprofit, nonpartisan advocacy affiliate of the American Cancer Society, is the nation's leading cancer advocacy organization that works to make cancer issues a national priority