STATEMENT

of the

American Medical Association

for the Record

U.S. House of Representatives
Committee on Energy and Commerce
Subcommittee on Health

Re: 21st Century Cures: Examining the Regulation of Laboratory-Developed Tests

September 8, 2014

Division of Legislative Counsel
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The American Medical Association (AMA) applauds the U.S. House of Representatives Committee on Energy and Commerce Subcommittee on Health's (Subcommittee) efforts to identify policies that will accelerate the development and wide-spread clinical application of 21st Century Cures. The AMA appreciates the opportunity to provide comments on the two central goals of this initiative—to encourage innovation and to embrace the rise of personalized medicine. The AMA shares the Subcommittee's focus on achieving better clinical care for patients, better health for our communities, and lower costs through cures driven by the unprecedented rate of clinically significant genetic and genomic discovery applied to medical practice. Given the impact that personalized medicine is already having and is expected to have on patient testing and treatment in the future, it is critical that applicable frameworks for oversight and policies for coverage and payment of laboratory developed tests (LDTs) support rather than undermine these goals.

In this statement, we wish to highlight the following:

- LDTs are a critical part of the practice of medicine, drive innovation, provide a critical safety net to combat outbreaks of infectious diseases and bio-threats, and often constitute the only test option for patients with rare diseases where a large commercial market does not exist.
- Clinical laboratories where LDTs are performed are currently regulated through federal, state, and, frequently, third party accreditation bodies.
- The AMA supports congressional efforts to provide a federal agency with the authority to assert greater oversight of laboratories for certain LDTs that the AMA has identified as high-risk—where incorrect results cause harm to patient and test methodology is not

transparent nor well understood (as in the case of tests that use complex algorithms to produce results, for example).
- The AMA questions the FDA's legal authority to regulate LDTs and, even if such authority exists, the significant changes proposed require notice and comment rule-making.
- The FDA's proposal as currently fashioned would prevent physicians from providing medical care that constitutes the most appropriate and clinically necessary care, severely limit patient access to life-saving tests, and slow innovation and integration of personalized medicine into modern medical practice.

We urge the Subcommittee to carefully consider that nearly all Food and Drug Administration (FDA) approved or cleared commercial test kits began as procedures—LDTs—in clinical laboratories regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). In fact, the number of FDA-cleared or -approved tests represents an extremely small set of tests relative to LDTs. In addition, the AMA urges the Subcommittee to consider the impact of recent highly disruptive policy changes to coverage by federal health care programs including Medicare, Medicaid, and the VA. The new policies have resulted in major confusion, loss of access among Medicare, Medicaid, and VA patients to tests that represent the standard of care, and have created ongoing instability. While the primary focus of today's hearing concerns the FDA's congressional notice and accompanying draft guidance documents proposing to impose new regulatory requirements on physicians developing and offering LDTs, careful consideration should be given to the tsunami of policy changes underway related to pricing and coverage that have already chilled and undermined efforts to accelerate 21st Century Cures in this space.

Laboratory Developed Tests: Overview

The current regulation of laboratories primarily under CLIA allow physicians from varied medical specialties such as pathologists, oncologists, infectious disease specialists, and medical geneticists to rapidly and safely develop, improve, and modify laboratory medical practice in response to new and validated medical findings, public health challenges, and the individual testing needs of patients. As noted above, the overwhelming majority of laboratory tests provided in the U.S. are LDTs in contrast to the very limited number of commercial kits cleared or approved through the FDA.

LDTs play an essential role in protecting the public health when there is an infectious disease outbreak, ensure the availability of diagnostic tools for rare diseases where a large-scale commercial market for kits does not exist, and accelerate innovation. LDTs also promote value, competition, and encourage the clinical application of patient-centric tests. Personalized medicine including the use of genetic tests and gene-based treatment modalities constitutes the practice of medicine. Given the training of physicians and their direct relationship to patients, physicians have a central role to play in the development of laws, regulations, and policies that impact the clinical implementation of personalized medicine, which includes genetic and genomic testing, the interpretation of testing within the clinical context, and identification of targeted therapies. Testing alone will not dictate patient treatment. Rather, a physician's clinical expertise, including developing, validating, and performing a test along with interpreting the test results in the context of the patient's condition and preferences, guide treatment options. The foregoing may frequently involve

the clinical expertise and judgment of a number of physicians and other highly trained medical experts. In short, physicians, patients, and LDTs are not widgets manufactured in a factory and shipped around the country. Instead LDTs reflect the highest level of clinical expertise, including education and experience of physicians tailored to specific patient medical needs.

LDTs Innovation Driver

Physicians have played a key role in driving the ongoing discovery and rapid application of research validated clinical findings to patient care. The Institute of Medicine and others have wrestled with the unacceptably slow rate of adoption into medical practice of research findings with relevant clinical use. In area of personalized medicine, physicians and laboratories developing and validating LDTs have dramatically cut the seven to fifteen year lag in the application into clinical practice. Increasing the regulatory burden and duplicating existing regulation would likely slow significantly what is currently an area of medicine where such lengthy delays have been diminished.

LDTs providing genetic and next-generation testing and screening have already become common in certain medical specialties. For instance, newborn screening is universal, and carrier, pre-implantation and prenatal testing is commonplace. These continue to improve with new discoveries and associated diagnostic/screening improvements. For example, prenatal screening for some chromosomal abnormalities can now be done noninvasively by examining fetal DNA circulating in the mother's blood. Other areas where genetic and next generation sequencing testing services and treatment have delivered game-changing results in clinical practice include infectious as well as rare diseases. The rapid translation of new medical information into clinical practice via LDTs has most notably begun a transformation of oncology. A number of academic medical centers have announced well-funded initiatives to develop the infrastructure for widespread adoption of genomic-based testing and treatment in oncology—and they are not alone. A large network of community-based oncology practices have also invested in the development of infrastructure that will propel adoption of personalized medicine as a standard of care in testing, risk assessment, and treatment.

In addition, it is important to highlight targeted therapeutics and companion tests. Targeted therapeutics, usually drugs or biologicals, are treatments designed to benefit a particular subpopulation, or whose use in another subpopulation might be especially disadvantageous or require different dosing. Companion tests are accompanying laboratory testing procedures and professional services identifying or measuring genes, proteins, or other substances that delineate the subpopulation that will derive benefit from the targeted therapeutic and yield important information on the proper course of treatment for a particular patient.

There are a number of examples that underscore this point, but tests for the BRAF mutation stand-out. BRAF is a specific gene that can mutate and can cause normal cells to become cancerous. This mutation is frequently found in the aggressive form of skin cancer called melanoma, which has a poor prognosis in advanced stages. The BRAF mutation has also been found in colon, ovary, and thyroid cancers. A treatment was developed to specifically inhibit the BRAF gene mutation when it is known to be the cause of the cancer. In 2010, a clinical trial was performed to treat patients with advanced melanoma using a traditional

drug or a BRAF inhibitor biological. The response rate to the BRAF inhibitor biological was 48 percent versus five percent with the traditional drug. At six months, 84 percent patients taking the BRAF inhibitor biological were still alive versus 64 percent of the patients receiving the standard treatment. In August 2011, the FDA approved for market the BRAF inhibitor biological for use in patients with a specific BRAF mutation, demonstrating how urgent the need was for this treatment. The key to the treatment of this deadly form of skin cancer is ascertaining whether a BRAF gene mutation is present in the patient's cancer cells. There are, however, different BRAF mutations, and treatment outcomes are impacted by which mutations are present, which include:

V600E—estimated to account for 80 percent of BRAF mutations.
V600K—estimated to account for most of the remaining BRAF mutations.

The FDA approved the BRAF inhibitor biological to treat the more common V600E mutation, and while it can be used to treat the V600K mutation, it is less effective and the treatment for this latter type of mutation considered an off-label use. It is critical to physicians and patients to know which BRAF mutation the patient has. However, the current FDA approved commercial kit for the BRAF mutation cannot distinguish between V600E and V600K. In contrast, the LDTs that physicians offer are designed to detect and distinguish the various mutations, making these tests more clinically relevant than the FDA commercial kit.

Testing for the BRAF mutation is an example of how pathologists, oncologists, medical geneticists, and other physicians engaged in laboratory medical practice are able to offer testing services to facilitate the rapid translation of new medical knowledge into clinical practice and provide patients access to the most up to date treatment options. Increasing the regulatory burden on laboratory medical practice will decrease patient access to most appropriate care and stifle the development of the next generation of tests that save lives and decrease health care costs through targeted and precision medical treatments.

Public Health Safety Network

Burdensome additional regulation of LDTs will slow the ability of physicians and clinical laboratories to develop tests to respond to infectious disease epidemics and bio-threats in the future. As one physician noted to the CLIA Advisory Board "…the ability of clinical laboratories to respond as they did [to the H1N1 epidemic] was very much tied to their ability to develop and validate their own assays, adhering to CLIA and CAP guidelines."[1]

In April 2009, an unknown respiratory outbreak emerged in the U.S. and Mexico. The virus was identified as H1N1, which is a subtype of the Influenza A virus. The disease spread rapidly and there were over 2,000 cases reported by May. In June, the World Health Organization declared an H1N1 pandemic. By August 2010 when the pandemic was declared over, the novel H1N1 virus had spread to more than 214 countries and was the cause of death for over 18,000 people. A large number of CLIA regulated clinical laboratories employ physicians and other health care professionals who perform molecular testing for influenza on a routine basis. During the first week of the H1N1 outbreak, an

[1] Dr. Jan Nowak statement to CLIA Advisory Board, 2009.

informal survey of 43 laboratories by the Association of Molecular Pathology found that 40 of them had LDTs that could distinguish Influenza A from Influenza B and approximately 16 laboratories had LDTs that could identify H1N1 from other H1 viruses. Most results from these tests were available within 24 hours, speeding treatment of patients and decision-making by public health officials. Many of these laboratories were able to identify the existence and magnitude of the outbreak in advance of public health laboratories—in some cases many days in advance. The large network of physicians and other health care professionals in academic and community hospital laboratories throughout the U.S. who were able to develop and validate molecular tests in the first week of the outbreak to rule out H1N1 as the cause of a patient's illness played a critical rule in controlling the H1N1 pandemic. The FDA did not have an approved commercial kit available for broad public use. It is essential to emphasize that efforts to shrink the number of laboratories or even to prevent physicians from offering such tests when competing FDA commercial kits exist degrades the capability of the nation's physicians and clinical laboratories to address the ever growing public health danger presented by the outbreak of infectious diseases and bio-threat. Creating legislative or regulatory exceptions for LDTs fails to account for the skill and expertise and experienced required to develop and validate such tests.

Current LDT Oversight and Regulation

Clinical laboratories have been subject to extensive federal and to lesser extent, except in New York, state laws and peer review "deemed" authorities. Presently, commercialized test kits that are manufactured and shipped to laboratories are regulated by the FDA, and testing services offered by physicians fall under the purview of laboratories, which are subject to CLIA oversight. Most testing in the U.S. is subject to the oversight of the College of American Pathologist (CAP) accreditation program, the State of New York program, or another accreditation program, which by law have the authority to deem laboratories compliant with CLIA. Both New York State and the CAP require that laboratories demonstrate the clinical validity of tests they offer and both demand considerably more from laboratories than CLIA requires.

AMA's Framework for Oversight

Assuring the quality of laboratory tests is important in delivering optimal care to patients. Accordingly, the AMA supports an oversight framework for LDTs including tests for genetic and acquired mutations that will ensure accuracy, reliability, and validity. An oversight framework should recognize the importance of the physician's role in the practice of medicine, and should not unduly restrict access to tests that physicians deem necessary and appropriate in the care of their patients.

The AMA supports a tiered, risk-based approach that confers assurance of analytic and clinical validity for all LDTs including genetic tests, but this does not mean such a framework serves as an endorsement of FDA oversight and regulation. Rather, the AMA would strongly support efforts to modernize the CLIA oversight infrastructure and enhance CLIA authorities. Risk should be determined by the potential for a misinterpreted result to cause harm to patient, and by test characteristics, e.g., test methodology that is not transparent nor well understood (as in the case of tests that use complex algorithms to produce results) would be in highest risk category. Any new oversight measures must be developed in collaboration with physicians and other health care providers who have

experience in accreditation and proficiency testing for laboratories conducting genetic tests, such as CAP and ACMG, for example. The oversight must preserve the clinical discretion of physician to choose test that he/she determines is appropriate for the clinical situation, whether or not it is a LDT or is FDA approved/ cleared. Furthermore, the labeling of drugs or biologicals for which tests inform indication and dosage decisions should not include the brand name of the test, nor make stipulations that the drug can only be prescribed with the prior use of an FDA-approved/cleared test.

The FDA Notice and Proposed Guidance Documents

The AMA has two broad legal concerns and a host of specific substantive clinical questions about the proposed guidance that we look forward to discussing with the agency. First, however, the AMA strongly urges this Subcommittee to consider the compelling need to avoid duplicative and confusing regulation by two federal agencies, a number of states, and accreditation bodies with deeming authority. The FDA has proposed a framework for regulation of LDTs, but has not clarified or coordinated with CMS, which is charged with administering CLIA compliance.

Just as Congress charged the FDA, the Federal Communications Commission, and the U.S. Department of Health & Human Services Office of the National Coordinator for Health Information Technology to develop a proposed regulatory framework for digital health to avoid duplicative and burdensome regulation, there is similarly an urgent need to, at a minimum, require CMS and the FDA to engage major stakeholders in a similarly transparent process and propose a framework that clearly and specificity identifies areas where the agencies will avoid duplicative, contradictory, and ambiguous oversight.

First, the AMA questions the FDA's legal standing to regulate LDTs. LDTs are not medical devices as defined in the Food, Drug, and Cosmetics Act (FDCA). LDTs are procedures for performing a test using inputs—reagents and laboratory equipment (which are regulated by the FDA). LDTs represent the technical expertise and clinical judgment of the physician who developed and validated the test. As a result, a LDT cannot be shipped to another laboratory nor are they manufactured. LDTs are procedures performed in a single laboratory and physicians continue to be legally responsible and accountable for LDTs.

Second, even assuming that the agency does have statutory authority, the agency in the past, through regulation finalized after notice and comment expressly limited the scope of its LDT regulation. As a result, the agency is precluded by well-established administrative law principles from imposing new and significant substantive changes through guidance documents. This is all the more important as the physicians, other health care professionals, and laboratories that the agency proposes to regulate are not manufacturers; therefore, there are a number of requirements that apply to medical devices—that do not have an obvious application to laboratory medical practice. If the agency does proceed with the current draft proposal, the AMA intends to strongly urge the agency to issue the new requirement through notice and comment. It is essential that an economic impact analysis is completed and analysis released outlining the anticipated impact of the new regulatory burdens on impacted stakeholders. Furthermore, given the large number of LDTs and the exceedingly small number of commercial kits that the FDA has approved/cleared, the AMA also would strongly urge the FDA and Congress to consider whether the agency has the requisite capacity to regulate in this space. The FDA has assumed a number of substantial new

regulatory authorities and has rapidly grown over a very short period of time in the past several years. There is a real danger that the relatively small number of existing FDA staff charged with oversight of commercial kits will not be adequate and scaling capacity with qualified and experienced individuals difficult given the expertise required.

On the substantive, front, the proposed framework provides that enforcement authority will be exercised for LDTs for rare diseases, "traditional" LDTs offered by a health care facility for a patient who is being diagnosed and/or treated at the same health care facility or the health system, and LDTs offered where no FDA approved or cleared commercial kit exists. We support the foregoing carve outs broadly speaking. However, the FDA's proposed limitations of these carve outs are extreme and inadequate. The AMA also finds the FDA's proposed treatment of LDTs where FDA commercial kit has been approved, troubling and contrary to efforts to innovate and provide the most appropriate medical care as demonstrated by the BRAF example provided above. Finally, the FDA's proposed listing requirements for LDTs will represent a major regulatory and cost burden for physicians and laboratories. The list of information required is quite long, requiring every physician and laboratory in the United States to complete notification for every test they perform, even ~~if~~ those tests that qualify under one of the carve-outs.

We appreciate the Subcommittee's critical role in advancing policies that accelerate and support the development and application of 21st Century tests and treatments into clinical practice and look forward to working with the Health Subcommittee, Congress, patients, regulators, and insurers to realize the promise of personalized medicine.