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Advocacy, Education and Research

January 5, 2015

VIA email to: cures@mail.house.gov

Honorable Fred Upton, Chairman
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

RE: 21st Century Cures – Request for Feedback: A Modernized Framework for Innovative Diagnostic Tests

Dear Chairman Upton:

This comment on the 21st Century Cures Initiative is being submitted on behalf of LymeDisease.org (LDo). We appreciate this opportunity to share our views.

LymeDisease.org is a national non-profit patient advocacy organization dedicated to research, education, and advocacy. We were founded in 1989 and have one of the broadest reaches of any organization serving patients with Lyme disease through our nationwide network of state groups, website presence, and print journal, *The Lyme Times*. One of our central roles in the community is collecting, compiling, analyzing and disseminating information about Lyme disease. For example, we conduct large scale surveys—over 5,000 patients—to help characterize the disease and some of the burdens Lyme patients face in terms of quality of life and access to care. We have worked with Stanford and Carnegie Mellon University to publish the results of these surveys in peer-reviewed journals.

Lyme disease is as an emerging zoonotic disease spread by the bite of a tick. It is the most common vector-borne disease in the United States. A single bite can transmit more than one pathogen; co-infections with more than one pathogen are not uncommon. Over 14 other tick-borne pathogens have been identified to date. Hence, when we talk casually about patients with Lyme disease, we are frequently talking about a stew of pathogens. A number of pathogens transmitted by ticks have no commercially available test, and new pathogens are discovered regularly.

A proportion of patients (estimates range between 20-50%, depending on the stage of the disease and length of time to diagnosis) with Lyme disease develop debilitating symptoms that persist in the absence of initial treatment or following short-course antibiotic therapy. Chronic Lyme disease is associated with a worse quality of life than most other chronic illnesses, including congestive heart failure, diabetes, multiple sclerosis and arthritis. Over forty percent of patients with chronic Lyme disease reported that they currently are unable to work because of Lyme disease and 24% of patients report that they have received disability at some point in their illness.

The diagnosis of Lyme disease is primarily a clinical diagnosis based on exposure to ticks, history of a tick bite, the presence of a rash, physical examination and history as well as diagnostic tests. Few patients remember the tick bite and 30% or more never develop the characteristic rash. A good diagnostic test can

accurately detect disease, help monitor treatment effectiveness, and determine when infection has been eliminated. Unfortunately, no such test exists for Lyme disease.

Although Lyme disease is a clinical diagnosis, many physicians and insurers require a positive lab tests notwithstanding the poor quality of commercially available lab tests. Hence, testing is the gateway to diagnosis, treatment and insurance coverage for Lyme patients. Patients select their physicians carefully for their expertise and physicians determine and interpret the results of laboratory tests. Patients view the right to select among diagnostic tests and to rely on the interpretation of those tests by their physicians as an access to healthcare issue.

Current serological tests are based on 20-year old technology using indirect detection of antibodies. Unlike the tests for HIV/AIDS, which have a sensitivity of 99%, lab tests miss more than 50% of the cases. Early treatment of

Lyme disease can be highly successful but depends upon timely diagnosis. Misdiagnosis and delayed diagnosis are all too common. Most patients in our large-scale surveys of over 5,000 patients with chronic Lyme disease report that they were not diagnosed within two years of contracting the disease.

Treatment failures occur with all current treatment regimens in both early and later Lyme disease, and, when they do, no lab test can determine whether infection requiring additional treatment persists. The lack of an accurate biological marker for the disease also hampers clinical trials which depend upon an accurate end point to determine success.

Considering that what we commonly call Lyme disease is often a stew of pathogens, the ideal test would analyze the patient's blood to determine which of these pathogens are present. The clinician would then have a clear picture of the infectious etiology involved to help inform treatment approaches for the individual patient. Although today's testing options fall far short of this ideal, DNA-based serology may unlock this potential in the near future if we encourage and foster innovation in test development.

Given all of this, it should not be surprising that Lyme patients really care about testing. Better lab tests are necessary for diagnosis, to monitor treatment efficacy, and to run the clinical trials essential to establish effective treatment regimens to cure patients.

The remainder of this comment will address the specific questions you have raised.

1. Multiple stakeholders have expressed the urgent need to have clear and logical lines separating the practice of medicine, the actual conduct of a diagnostic test and the development and manufacturing of diagnostic tests. How should these lines be defined and what are the key criteria separating each of these activities?

The state of Lyme disease testing is—at this point—rudimentary. The physician needs all of the information, imperfect though it is, available to assess and diagnose patients. It is too early in the game to centralize best testing approaches as these are just beginning to emerge and depend on advances in diagnostic technology.

The role of the physician is integral in selecting the lab test and interpreting the results of the test. There is no direct to consumer marketing for Lyme lab tests. Lab tests are ordered by the physician after examining the patient and determining that they have signs and symptoms consistent with Lyme disease.

Experienced physicians request tests that provide information regarding the specific antigens that the patient is producing antibodies to and use these to determine the likelihood that the patient has Lyme

disease. For example, antibody tests may be reported with different bands that have more or less significance in determining whether a patient has Lyme disease. Point-of-care determinations regarding whether a test is providing a false negative in the face of the patient's clinical presentation is essential in diagnosis and treatment.

The effect of the test is subject to interpretation by the clinician. The clinician may use the lab results together with clinical findings, symptoms and history to develop a clinical picture that leads to a diagnosis and treatment plan. If the test results are uncertain or if the test is known to have false negative and false positive results, these risks can be assessed by the physician. They can be explained to the patient in determining treatment options.

Where the treatment intervention is invasive (e.g. surgery), the clinician and patient will place a greater emphasis on safety, carefully assessing the potential that a test may be a false negative. Perhaps additional testing will be done to develop a greater sense of certainty. When the patient is severely compromised by illness, there may be a greater willingness to bear the risk of a false positive if the treatment is not invasive and further corrections to the course of treatment may be made.

The physician will then monitor the patient's progress and if the diagnosis and treatment assessment is not improving the patient's quality of life, the physician may re-assess and perhaps re-diagnose the patient. In this way, even false positive results may be ruled out as the clinician monitors and adjusts course.

A laboratory test is a tool used by physicians, together with other information, to assist in diagnosis. Physicians have the expertise to interpret the test results in the context of the patient's circumstances, physical exam, and course of illness. They have the flexibility to adjust course should a diagnostic path prove to be a dead-end. There is a risk of diagnosing an illness that is not present, which the physician can monitor and mitigate with the exercise of clinical judgment. However, the effect of the new FDA guidance may be to preclude patients from having access to tests that they need to obtain diagnosis and treatment. If a test is not on the market, there is no way to mitigate the risk of failure to diagnose an illness nor the flexibility to adjust course.

CLIA provides oversight of laboratory devices and permits clinicians to use their clinical judgment to adjust course based on real time clinical evidence relevant to the patient being treated. Because of this, LDT's should remain subject to the provisions of CLIA and the current regulatory scheme without further FDA intervention.

2. In FDA's draft regulatory framework, the agency describes the extent to which it proposes to regulate LDTs as medical devices under the Federal Food, Drug, and Cosmetic Act (FFDCA). It is relatively clear with respect to distributed test kits what constitutes a "device", but less clear when considering a test developed and performed in a laboratory. What should comprise the "device" subject to regulation by the FDA?

Unlike most medical devices currently regulated by the FDA, diagnostic tests are not articles, products, or static pieces of hardware, such as synthetic hip joints, which are inserted into the patient for a lifetime of use. Diagnostic serology testing and its interpretation are part and parcel of the physician's tool kit for clinical diagnosis. In general, they are transitory and non-invasive in nature. The device may be the needle used to extract blood. The remainder is a service that takes place outside the patient's body. In the case of antibody tests, it involves a service by the lab of providing certain antigens and interpreting how the blood interacts with these. The service then continues with the physician's interpretation of the test results in the context of the individual patient. The FDA should defer to the regulatory system that is already in place under CLIA.

3. FDA intends its regulation of diagnostics to be risk-based. How should risk be defined? Are the types of risks posed by diagnostic tests different from therapeutic medical devices? Are these risks different with LDTs compared to distributed test kits? Is the traditional medical device classification system appropriate for these products?

Therapeutic medical devices pose risks different from those of diagnostic tests. Product safety in terms of manufacturing and design defects loom large with devices inserted into the body. In contrast, the risks associated with diagnostic tests are clinical in nature. They include the risk of misdiagnosing (and perhaps treating) a disease that is not present and the risk of failing to diagnose (and not treating) a disease that is present. Both of these risks are moderated by the exercise of clinical judgment of the treating physician. Key issues that physicians and patients need to weigh in this context are a) how acceptable is the patient's current quality of life (e.g. how severe is the condition?), b) how invasive is the test/treatment, c) how accurate is the test, and d) what are the consequences of "getting it wrong" (e.g. can the physician monitor, reassess and adjust diagnostic course?)

These types of assessments require weighing risks and benefits associated with false positives and false negatives in the context of the individual patient including that patient's tolerance for risk and the acceptability of the quality of life for that patient. Physicians make this type of assessment in conjunction with patients as part of their exercise of clinical judgment, taking into account the values and preferences of the patient. This is part of the practice of medicine which the FDA should not regulate.

The FDA believes that it can improve the quality of lab tests by requiring FDA approval or clearance and monitoring adverse events associated with tests. Both processes are flawed when applied to diagnostic tests, however.

For example, in the case of Lyme disease, there are over 80 FDA tests, but these tests were never demonstrated to be sensitive or specific. Instead, they were cleared as being equivalent to other cleared tests. Equivalency is not synonymous with quality when the reference test used is insensitive and lacks specificity as is the case with Lyme disease. Unfortunately, peer-reviewed literature indicates that these FDA tests are highly insensitive for the detection of Lyme disease. Hence, FDA clearance or approval does not indicate that tests are sensitive enough to accurately diagnose a disease.

Equally alarming, the FDA system of determining adverse events does not work for lab tests in Lyme disease (and presumably many other diseases). It requires that patients or their physicians know the manufacturer of the underlying test. However, the laboratory service middlemen who draw and process patient blood, like Lab Corp, do not use their own tests. They use test kits manufactured by others. One physician spent two weeks trying to track down the manufacturer of a test used by laboratory service provider without success. The end result is that the FDA has a number of complaints filed against "unknown" manufacturers. This problem is compounded by the fact that misdiagnosis caused by false negatives arising from an insensitive lab test may take years to uncover. This does not allow poor lab tests to be tracked, reported, or held accountable.

The FDA cannot competently assess or mitigate the risks of misdiagnosis or failing to diagnose on a centralized basis for patients it does not see. The traditional medical device classification system is not appropriate to regulate testing. The existing CLIA systems and state and federal regulatory system provides the flexibility and oversight necessary for diagnostic testing.

4. The current pre-market review standards that apply to *in vitro* diagnostics use the same terminology of safety and effectiveness that apply to all medical devices. Should the medical device concepts of safety and effectiveness apply to test kits and LDTs?

Neither safety nor effectiveness are appropriate standards for assessing LDTs. The key issue for patients and physicians is the probability that the test will aid in the diagnosis of the disease. The diagnosis itself

may use the test as one of the tools in the physician's tool kit in determining the correct diagnosis and course of treatment for the individual patient. This is the exercise of clinical judgment which is and should continue to be regulated under professional standards of care.

5. Are there areas where the balance between pre-market review versus post-market controls should be reconsidered? How can post market processes be used to reduce barriers to patient access to new diagnostic tests?

Conceptually, it is better to provide patient access to new innovative tests early and monitor post market. In our experience, however, current FDA tests should not be regarded as having a higher quality than non-FDA approved tests because cleared tests may merely be equivalent to other FDA insensitive tests. Our experience also shows that substantial changes would be necessary to effectively monitor post market given third party laboratory test providers and the lack of a method for tracking who is marketing what test.

6. A number of stakeholders have expressed concerns about uncertainty as to when a supplemental premarket submission is required for a modification. When should they be required prior to implementing modifications? Should the requirements for submission of a supplemental clearance or approval differ between LDTs and distributed test kits?

Incremental modifications and improvements of tests are desirable and should be encouraged. Regulatory constraints should be minimized to ensure innovation. Unlike medical devices, laboratory tests are constantly evolving as labs are by nature receiving and evaluating lab specimens on a continual basis. Hence, it is critical that the regulatory environment provide for and foster this type of innovation.

7. We have heard a lot of about the practice of medicine and its relationship with medical product "labeling". What should comprise "labeling" for diagnostic tests? Should different standards for dissemination of scientific information apply to diagnostic tests versus traditional medical devices? What about for laboratories that develop, perform, and improve these tests? Should there be regulatory oversight of the information that is provided to the individual patient or health care provider or is that the practice of medicine?

Patients and physicians should be aware of the sensitivity and specificity of laboratory tests. They also need to know what the reference standard is. For example, in Lyme disease this is no gold standard culture test that can be used as a reference standard. This means that all tests are compared relative to each other. The fact that a test may result in false positives and false negatives should be disclosed to both physicians and patients so that informed medical decisions can be made.

8. The Section 1143 guidance documents raise important questions about the relationship between the FFDCIA and the Clinical Laboratory Improvement Amendments (CLIA), administered by the Centers for Medicare & Medicaid Services (CMS). Is there overlap between the requirements of the guidance documents and CLIA? For instance, how do FDA's quality systems compare with CLIA quality systems requirements? Are there areas of duplication where there would be efficiencies to having either CLIA or FDA regulate, rather than both?

Duplication of efforts and the costs associated with them should be avoided. We believe that the CLIA certification process is working effectively now, while permitting innovation. We are at a point in history where innovation in lab testing is rapidly making possible better diagnostic tests. We need to err on the side of innovation to continue our progress with diagnostic tests that can accurately identify pathogens directly using DNA sequencing. This is critical to accurately diagnose Lyme disease as well as the tick-borne co-infection pathogens that are emerging regularly.

Shifting towards a more bureaucratic system that is inherently more costly and time intensive can only slow down the progress necessary to improve health quality across the board. A good diagnostic test is necessary not only for diagnosis, but also to determine the clinical beginning and ends points in treatment trials to establish cures. This is the wrong time in history to put the brakes on diagnostic innovation by imposing new regulatory constraints. The FDA assumes that the greatest risk to patients are the risks associated with false positive test results leading to misdiagnosis and treatment for a condition the patient does not have. However, patients whose quality of life is poor—those who are unable to work or who are on disability as many Lyme patients are—know that the risk of failing to diagnose and treat is the greater risk.

In LDo's recent patient survey, which drew more than 6,800 responses over a period of ten weeks, 98% believe the risk of not being diagnosed and treated for Lyme disease because of a false-negative is one of the greatest risks to patients. Further, 89% believe that it is most important to develop new innovative tests and make them available to patients more quickly.

9. How should any regulatory system address diagnostic tests used for rare diseases or conditions, customized diagnostic tests and diagnostic tests needed for emergency or unmet needs (e.g., rare cancers or blood disorders, Ebola)?

Lyme disease is not an uncommon disease. However, it was not until last year that the CDC increased its estimates of the incidence of the disease from 30,000 a year to roughly 300,000. Before the CDC revision it met the definition of a rare disease and certainly has been an orphan disease in the sense that it is a research-disadvantaged disease. For example, while it is six times more prevalent than HIV/AIDS, it receives only 1/6th of NIH funding allotted to HIV/AIDS. A similar lack of interest is seen with pharmaceutical companies on the treatment side as treatments are generic antibiotics. Only three NIH-funded treatment trials have been published and these involved samples of less than 75 patients. Also, like rare diseases, patients are generally very well educated about the disease. Hence, it is critical that any fast track options be available to all research-disadvantaged diseases.

Research-disadvantaged diseases face substantial challenges in obtaining funding and attracting investment interest from commercial organizations. Barriers to innovation imposed by regulatory environments can suppress innovation for years and require financial investments that smaller companies likely to lead the charge in innovation cannot meet. Those with tests on the market would not have the spur of competition necessary to disrupt a status quo where they hold the competitive advantage. The disruptive innovation necessary to bring diagnostic testing into the 21st century may be stopped in its tracks by overly burdensome regulatory requirements.

10. Any new regulatory system will create transition challenges. How should existing products be handled? Should all current diagnostic tests be “grandfathered” into the marketplace? What transition process should be used for new product introductions?

The current state of laboratory testing in Lyme disease is poor. The hope for the future lies in innovative tests developed based on emerging technology. We need to favor innovation over tests developed in the past. We believe that providing FDA oversight of LDTs for Lyme disease will diminish both the availability and accuracy of laboratory test and harm patients by denying them access to diagnostic tests necessary to obtain treatment and improve their quality of life.

If FDA guidance is unavoidable, we believe that existing LDTs should be grand-fathered in. Finally, we believe that new diagnostic test should not be held to a higher standard of sensitivity or specificity than those of the currently FDA-approved or cleared Lyme tests. (Innovation should not be placed at a competitive disadvantage compared to tests currently on the market.)

11. What incentives can be put in place to encourage the development of new, more accurate or more efficient diagnostic tests?

Innovation in testing depends upon a level competitive playing field that permits smaller companies to enter the market in a timely fashion without economic barriers. In Lyme disease, most lab tests are based on technology that is over 20 years old. Those holding interests in the lab tests have not felt the competitive need to innovate.

The FDA is proposing to use expert panels to help with the review of new technology. Expert panels have come under increased scrutiny because of commercial conflicts of interest. Beyond simple financial ties, expert panels may also have organizational loyalties that lead to researcher cronyism that favors products on the market over newer tests which pose a competitive threat to those products.

In Lyme disease panel members on the Lyme disease treatment guidelines of the Infectious Diseases Society of America were found to have commercial ties with laboratory test manufacturers. The guidelines, which require positive serology for diagnosis, require laboratory testing for diagnosis even though the sensitivity of existing lab tests is quite low. These guidelines have created significant access-to-care barriers for patients.

Expert panels may also favor researchers with expertise or commercial ties as panel members. It is critically important that experts with such ties not be permitted to sit in judgment of newer technologies of competitors. Patient representation of those who will be affected by such tests should be included on the panel and provided with a meaningful voice.

Very truly yours,



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Empowering patients through advocacy, education and research