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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,



Lorraine Johnson, JD, MBA, Executive Director
LymeDisease.org, formerly CALDA
Empowering patients through advocacy, education and research



January 5, 2015

Chairman Fred Upton
Committee on Energy & Commerce
U.S. House of Representatives
2125 Rayburn House Office Building
Washington, DC 20515

DELIVERED ELECTRONICALLY

RE: Response to December 9th, 2014 White Paper, “21st Century Cures – Request for Feedback: A Modernized Framework for Innovative Diagnostic Tests”

Dear Chairman Upton:

This letter is submitted on behalf of the American Clinical Laboratory Association (ACLA) in response to the Energy & Commerce (E&C) Committee’s December 9th, 2014 White Paper entitled, “21st Century Cures – Request for Feedback: A Modernized Framework for Innovative Diagnostic Tests” (hereinafter “White Paper”).

ACLA is a not-for-profit association representing the nation’s leading providers of clinical laboratory services, including local, regional, and national laboratories. Our diverse membership represents a broad array of clinical laboratories, including national independent labs, reference labs, esoteric labs, hospital labs, and nursing home laboratories. ACLA members are actively engaged in the creation and performance of innovative and much-needed Laboratory-Developed Testing services (LDTs) that have helped transform the standard of clinical care in the country and provide great hope for further improvements.

ACLA applauds the 21st Century Cures Initiative launched in partnership with Rep. Diana DeGette and your continued recognition of the value of diagnostics and the need for robust innovation in, and patient access to, clinical laboratory services. As ACLA testified before the E&C Health Subcommittee on September 9th, 2014, these services are integral and longstanding components of the practice of medicine. They also enable and guide diagnostic and treatment decisions by physicians and patients.¹ First and foremost, ACLA strongly advocates policies that will ensure robust and uninterrupted patient access to innovative, accurate, reliable, and meaningful clinical laboratory diagnostic services.

¹ Mertz, Alan, “Statement of Alan Mertz, President, the American Clinical Laboratory Association for U.S. House of Representatives, Energy and Commerce Committee, Subcommittee for Health, Hearing on ‘21st Century Cures: Examining the Regulation of Laboratory Developed Tests’”, September 9, 2014, available at: <http://www.acla.com/acla-written-statement-for-21st-century-cures-hearing-on-ldt-regulation/>.

The Food and Drug Administration's (FDA) October 3rd, 2014 draft guidance proposals to regulate these laboratory testing services as devices (hereinafter, "draft proposals"), however, represent direct threats to clinical laboratory innovation and to patient access to such medical services. Rather than improve the public health (as the FDA contends), the draft proposals: 1) are unauthorized by the relevant statutes; 2) represent improper agency encroachment on the practice of medicine; and 3) will harm patient access to vital and innovative clinical laboratory services without offering any clear offsetting benefit. In short, these proposals are starkly contrary to the spirit of the 21st Century Cures Initiative, which seeks to "accelerate the pace of cures and medical breakthroughs in the United States"², not to increase and duplicate costs and regulatory burdens that would pose significant new barriers to medical innovation and to prompt patient access to the benefits of that innovation.

Given this harmful overreach, ACLA calls on the FDA to rescind its draft proposals to regulate LDTs as though they were "medical devices," and ACLA further urges the Committee and Congress to continue the statutory precedent of treating laboratory testing services and medical device manufacturers as the separate and distinct entities that they in fact are within the health care system.

1) Regulating LDTs as medical devices is contrary to statute.

Question 2 of the E&C Committee's White Paper appropriately points out the difficulty of identifying the "device" subject to regulation in the context of a laboratory-developed testing service. This difficulty is inherent in the FDA's pending proposals and highlights the fatal flaw in those proposals: it is that laboratories are *not* medical device manufacturers at all, and that laboratory-developed testing services simply are not medical devices as the relevant legal provisions, or ordinary speakers, use that term.

For decades, Congress and the Administration have recognized that testing laboratories and manufacturers are separate and distinct entities within the health care system. Since 1967, these laboratories have been governed by the Clinical Laboratory Improvement Act, renamed the Clinical Laboratory Improvement Amendments (CLIA) with the last major overhaul in 1988, administered through the Centers for Medicare and Medicaid Services (CMS), an entity within the U.S. Department of Health and Human Services. Since 1976, medical device manufacturers, in contrast, have been regulated under the Medical Device Amendments to the Federal Food, Drug and Cosmetic Act (FFDCA), administered through the FDA.

² Upton, Fred & DeGette, Diana, "A Path to 21st Century Cures", Energy & Commerce Committee, April 30, 2014, <http://energycommerce.house.gov/press-release/path-21st-century-cures>.

This distinction carries through to reimbursement, whereby laboratories receive direct reimbursement as health care providers through federal health programs such as Medicare. Manufacturers receive no such direct reimbursement. The Affordable Care Act (ACA) in 2010 recognized this difference through its use of distinct budgetary offsets from both industries: a medical device tax for manufacturers, and a Medicare reimbursement cut for laboratories.

A simple tour of either type of facility bears out the differences. A medical device manufacturing facility revolves around the production of a physical product that is shipped and sold around the country to laboratories, physician offices, and hospitals. On the other hand, a laboratory that provides testing services revolves around the appropriate handling and processing of patient specimens, the application of the laboratory's own protocols, and the provision of clinical testing as ordered by health care providers. While a device is a finished, packaged, off-the-shelf article of commerce accompanied by instructions for use by others, a testing service is a proprietary methodology that only the developing laboratory can execute and that does not move in interstate commerce.

Laboratory-developed tests cannot be deemed "medical devices" solely for the convenience of an agency seeking new regulatory power. Calling a service, "a device", cannot make it one. As explained in ACLA's September 9th testimony, "[LDTs] are know-how, not physical articles."³ LDTs are not "articles" or "commodities" as contemplated by well-settled medical device law; rather, LDTs are services provided by highly trained and certified laboratory personnel, such as pathologists, microbiologists, and other laboratorians. Nor can LDTs be captured by the FDA merely because they may share some of the same purposes and functions with *in vitro* diagnostic (IVD) test kits. If that functional overlap could suffice, the interpretive services of a radiologist could be deemed "medical devices" merely because they are based on images produced by devices such as x-ray or CAT-scanning machines.

If the Committee chooses to legislate in the area of diagnostics, ACLA strongly urges the Committee to continue the practice of regulating laboratories and manufacturers as separate and distinct entities and again clarifying that, as current law establishes, laboratory-developed testing services are not medical devices. Thus, the Committee's focus should be on the legitimate question whether CLIA could be revised to enhance the legal authority and funding authorization for CMS. Unfortunately, the FDA has chosen to bypass the Committee and Congress altogether by seeking, illogically and unlawfully, to treat laboratory services under the FFDCAs.

³ Mertz, p. 7-8.

2) The FDA is encroaching on the practice of medicine.

Since its creation, the FDA has been charged with ensuring that medical products made available to physicians and patients are safe, effective, and free from adulteration, misbranding, or putrefaction. Similarly, since its creation, the FDA has *not* been granted the mandate to govern how health care providers (in particular, physicians) utilize their education, training, and know-how to diagnose and treat individual patients, also known as the practice of medicine.

Trained and certified pathologists, microbiologists, geneticists, and other laboratorians perform diagnostic test services in response to orders from physicians treating particular patients. These trained and certified laboratory personnel utilize their education, training, and knowledge to test patient specimens to provide vital clinical information to help the treating physician arrive at a diagnosis and to recommend a course of treatment. These laboratory-developed testing services are part and parcel of the practice of medicine. To regulate the generation of information that a physician asks a consultant or a consulting laboratory to provide – by performing tests on specimens provided by the physician in order to assist that physician in diagnosing the patient’s illness or in prescribing a course of treatment – interferes with that physician’s decisions of what to prescribe or administer to his or her patient.

Question 1 of the E&C Committee’s White Paper asks how clear and logical lines can be drawn separating the practice of laboratory medicine from manufacturing. The answer already exists through the CLIA designation of a high complexity laboratory. This is the only category of laboratory allowed by law to create LDTs, because this kind of lab is required to have highly-trained and certified laboratory personnel possessing the appropriate education, training, and know-how.⁴ A high complexity laboratory is engaged in the practice of medicine through the performance of LDT services, not in anything that could be called manufacturing.

⁴ The FDA has put forward other actions to potentially impinge on the practice of laboratory medicine, such as limitations on communications between manufacturers of Research Use Only (RUO) and Investigational Use Only (IUO) products and the laboratories that utilize these products. The agency’s 2011 Draft Guidance for RUO/IUO products would have restricted even the marketing of RUO/IUO products. The 2013 RUO/IUO Final Guidance still creates ambiguity as to what communication between an RUO/IUO manufacturer and client laboratory may be deemed “inappropriate” by the FDA. These actions can choke off areas of access and innovation by chilling the collaborative relationship between laboratory professionals and the manufacturers of laboratory products. In the end, the patient suffers through less availability of innovative and higher quality diagnostics. H.R. 3005, *the Medical Testing Availability Act of 2013*, as introduced by Rep. Michael Burgess, is an example of a solution to the FDA’s actions particular to RUO/IUO.

3) FDA regulation would entail an unnecessary and inefficient increase in costs and burdens.

a) Regulatory Uncertainty and Duplication

As previously discussed, laboratories are currently regulated by CMS under authority expressly granted by CLIA. Distilled to its most basic framework, CLIA establishes quality standards, inspections, user-fees, and penalties for non-compliance. In addition, all such laboratories are subject to inspection and licensure by state health authorities. For example, New York State requires separate test-specific pre-market approvals and inspections by its own authorities if a lab seeks to analyze specimens from patients in New York, regardless of whether the lab is physically located in the State of New York.

The laboratory marketplace has taken this oversight regime even further. A majority of moderate and high complexity laboratories often seek additional accreditation from “deemed authorities”, such as the College of American Pathologists (CAP)⁵, and, in some cases, are even subject to vendor qualification audits by clients. Under this regime, in any given year, a laboratory could find itself inspected by CMS, CAP, New York State, the state of the lab’s location, its clients, and potentially others such as the American Society for Histocompatibility and Immunogenetics, if the lab handles samples related to organ donation.

Through this range of authorities and reviews, a laboratory is subject not only to government compliance inspections, but also to multiple reviews by private entities such as CAP. This has created a rigorous regulatory environment in which a lab is part of a collaborative medical community seeking to improve patient care through the exchange of information between laboratory professionals. This combination of compliance and collaboration leads to better quality for patients.

In contrast, the draft proposals from the FDA offer little clear benefit, but *do* offer clear and significant increases in costs and burdens. Distilled to its most basic elements, the FDA’s proposals would impose an overlaying set of quality standards, inspections, penalties, and, inevitably, user-fees, even though the agency has said it would initially seek to waive user-fees for labs.⁶ These would be imposed on top of the quality standards, inspections, user-fees, and penalties already imposed under CLIA.

⁵ A lab may opt into CAP accreditation under CLIA, as CAP is a CLIA “deemed authority”; however, even if a lab is CAP accredited, CMS still periodically sends its own inspection teams to the given lab.

⁶ While the FDA has said in public comments that it intended to waive user fees initially for laboratories submitting LDT applications, the Food Drug Administration Safety and Innovation Act of 2012 (FDASIA) explicitly limits the FDA’s waiver authority to no greater than 2 percent of user-fee revenues for a given year. (21 USC 379j(f)(2)). This limitation foreseeably would constrain FDA’s ability to keep its promise to waive user-fees for *all* LDT applications unless FDA revises its draft proposals to limit the number of required applications.

The FDA's proposed overlay clearly threatens to impose unnecessary duplication on laboratories. Specifically in terms of quality standards, there is a tremendous overlap between (i) the regulatory requirements under the FDA medical device framework under 21 CFR §820 and (ii) the existing regulatory requirements under CLIA in 42 CFR §493 as they pertain to quality systems requirements, design controls, document controls, production and process controls, acceptance activities, nonconforming products, corrective and preventative actions, and records.

There is no reason to imagine that any of FDA's requirements is tailored to meet some demonstrable gap in the CLIA framework established by Congress – and, if there were any such gap, it would obviously be the role of Congress, not the FDA, to address it, just as Congress addressed gaps in the 1967 CLIA regime by enacting the 1988 amendments to CLIA. Bypassing Congress to impose potentially crippling redundant federal regulatory oversight at the FDA's unilateral initiative would imperil the rapidly advancing field of diagnostics at a time when, as Congress well understands, innovation and advancement are more urgently needed than ever.

On various occasions, FDA representatives have asserted in public comments that the agency is working with the Clinical Laboratory Standards Institute (CLSI) – a private laboratory standards setting organization made up of representatives of various laboratory stakeholders – to develop “education modules” that would purportedly aid a laboratory to both meet the FDA's new quality standards and guide the laboratory through potential duplication with CLIA. The nature and authority of these “modules” create questions and sources of uncertainty. At some times, the FDA has implied the CLSI is preparing the modules under contract; at others, the FDA has implied that the agency is merely “fact checking” the CLSI product. ACLA strongly objects to the FDA's action utilizing a private organization to provide guidance in an area that is beyond FDA's authority in the first place.

None of these proposed FDA interventions into the CLIA regulatory framework carefully designed by Congress is warranted either by law or by common sense. As of now, stakeholders have no clarity as to what force of law any FDA-developed CLSI “education module” might carry and whether such modules will first be issued in draft form for stakeholder comment. Even if comments were allowed, education modules would not alter the fact that laboratories would suddenly be subject to oversight by two distinct federal agencies and two separate and potentially conflicting federal regulatory structures, rather than by one, as Congress clearly contemplated. FDA has yet to offer any coherent means by which laboratories could discern how to comply with CLIA while at the same time meeting FDA's new proposed requirements.

A partial answer to the Committee's White Paper Question 8 would therefore be that (i) FDA's congressionally unauthorized proposals invariably would create duplication and inefficiency, and (ii) FDA's unsupported notion that CLSI somehow will resolve conflicts between CLIA and the FDA lacks grounding in reality and would create nothing but confusion. The legal and regulatory uncertainty occasioned by the FDA's ill-advised proposals would only hinder the Committee's regulatory objectives.

b) Patients left waiting

The costs and burdens threatened by FDA's proposals will not come in the form of dollars alone. The FDA is proposing to subject LDTs and laboratories that offer them to an excruciating and costly process that is already overburdened and not working effectively for in vitro diagnostic devices.

A recent analysis by the *FDA Law Blog* of medical device 510(k) application review times at FDA found that not only have the review times of medical device 510(k) applications increased, but that *in vitro* diagnostic device 510(k)s already take “significantly longer to review than 510(k)s for other types of devices.”⁷⁸ This review of 510(k) application times does not even include *de novo* or premarket approval (PMA) applications. Looking at PMAs, the FDA only approved 21 premarket applications in 2013. The FDA has said publicly that it is anticipating at least 100 LDTs to qualify as high risk and require a PMA in the first round of the proposed framework. Assuming that the number of other device PMAs remains constant, LDTs would create a five-fold increase in PMA workload.

In short, attempting to include LDTs will affect not only LDTs, but traditional IVD manufacturer applications as well; overall, patients will have to wait longer to access increasingly accurate, precise and higher quality laboratory diagnostic services.

The very real risk of “FDA overload” will color any answers to Committee Questions 3 through 6. Any complete evaluation of benefits and costs of regulation must assess the various theoretical approaches in light of the practical effects of such regulation. Here, the FDA's overreach will have potentially harsh impacts on public health. Indeed, the FDA proposals themselves will create danger, and threaten the overall efficacy of laboratory medicine as a key component of the health care system.

c) New barriers to innovation and access

In partial answer to Committee Question 11, the FDA's proposals would create *disincentives* to the development of new, more accurate and more efficient laboratory tests. In particular, the draft proposals would create barriers to in the areas of LDTs for unmet needs, as well as hospital-based LDTs.

⁷ Gibbs, Jeffrey & Mullen, Allyson, “New Article Shows Surprising Trends in 510(k) Review Times”, *FDA Law Blog*, December 14, 2014, http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2014/12/new-article-shows-surprising-trends-in-510k-review-times.html.

⁸ See also Gibbs & Mullen, “Contrary to expectations, there is no review-time advantage to submitting and Abbreviated 510(k) to a Traditional 510(k).” The Abbreviated pathway having had been sold as a faster path to FDA approval.

In the case of unmet diagnostic needs the FDA proposes to continue what it calls “enforcement discretion” by not exercising the regulatory jurisdiction it claims to possess over laboratory-developed tests if laboratories should choose to develop tests for those particular unmet needs, subject to various restrictions. However, the enforcement discretion would cease once a single comparable laboratory diagnostic device was approved or cleared by the FDA.⁹ This proposal creates three dilemmas that will dangerously discourage innovation.

First, while labeled an accommodation for unmet needs, the proposal actually drastically increases the hazard for a lab choosing to develop an LDT. The lab would have to be willing to accept the risk that it would later have to obtain FDA review, once a competitor received FDA approval or clearance for a device claimed to serve comparable purposes. Especially given the amorphous and inevitably contested character of such a claim, no laboratory would have any objective way to assess the magnitude of that risk *ex ante* and thus would need to be highly risk-prone in order to invest significant resources in pursuing the development path.

Second, whereas today, laboratories can improve an LDT to enhance accuracy or broaden the test’s applicable patient population, the added risk of FDA oversight and uncertainty of FDA approval would chill this kind of incremental innovation, because each new iteration would require FDA premarket approval. Labs routinely modify existing laboratory developed tests in order to improve performance, respond to the latest scientific advancements, and advance the diagnostic capabilities of tests. Requiring full premarket approval for any modification to an existing test, no matter how insignificant, as the FDA proposes, would result in a stagnation of the science and sharply curtail innovation.

Third, the proposal creates a new form of market exclusivity within laboratory medicine whereby any organization (laboratory or IVD test kit manufacturer) could “clear the field” of competing products for a given unmet need by simply filing with the FDA and receiving approval. Such approval would not guarantee that the “first filer” offered the highest quality or most accurate test, merely that the filer was the first to volunteer for duplicative and burdensome FDA regulation. While the burden will fall on all laboratories in the diagnostic space, this approach creates an even greater barrier for smaller, innovative labs.

Fourth, FDA is proposing to exercise enforcement discretion where the particular LDT is developed and performed in a hospital laboratory for a patient being treated at that same facility.¹⁰ This arbitrary restriction would threaten patient access to LDTs developed and performed in non-hospital independent laboratories, unnecessarily leaving unmet the needs of the countless patients for whom no hospital-based LDT is developed and no approved test kit exists – a common gap often filled by independent laboratories today.

⁹ FDA, “Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs) Draft Guidance, October 3, 2014, at p. 22, available at: <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM416685.pdf>.

¹⁰ *Id.* at 21-22.

Whereas an academic medical center laboratory could tailor an LDT for a patient within its walls, the same LDT would be considered high-risk and subject to burdensome FDA review if, instead, it were offered by the same academic medical center lab to patients of a rural hospital or Veterans Affairs Hospital – even if the hospital were across the street. Instead of the smaller hospital simply being able to send out a patient sample, the FDA would require the transfer of the patient. This extreme result would cost time and money, in addition to creating delay and medical risk for a patient already receiving appropriate diagnosis and treatment.

d) Costs beyond FDA

The FDA's draft proposals not only risk levying needless costs on laboratories directly through the FDA, but could also trigger obligations beyond the FDA. As previously mentioned, the ACA levied a fee specific to laboratories in the form of a 5-year cut to the Medicare Clinical Laboratory Fee Schedule. Separately, the ACA also levied a tax on the medical device industry. As implemented by the Internal Revenue Service (IRS), that tax is paid by medical device manufacturers, and not by clinical laboratories. However, under the FDA's draft proposals, laboratories would be required to list LDTs with the FDA as medical devices once their test service received either clearance under 510(k) or approval under a PMA.¹¹ For medical device manufacturers, this listing is the regulatory trigger under the IRS for the medical device tax. Laboratories already pay the tax indirectly as purchasers of medical devices, but now actions by the FDA could also force laboratories to pay the tax directly on LDTs cleared or approved by the FDA. Thus far, the IRS has not needed to distinguish between manufacturers and laboratories, inasmuch as the ACA clearly targeted the tax on medical device manufacturers. The FDA proposals now, however, risk subjecting an industry to a tax for which the tax was not intended.

In addition to medical device tax liability, FDA regulation of LDTs as medical devices could subject laboratories to the compliance costs of federal and state "physician payment sunshine" laws applicable to medical device manufacturers. It could also trigger the more onerous strict liability standards of civil liability under state product liability laws, in addition to the negligence standard of civil liability to which laboratories are currently subject.

All of these problems not only point to the folly of the FDA's proposals but confirm that laboratory-developed testing services simply are not medical "devices." The FDA's proposals are an attempt to fit a square peg in a round hole.

¹¹ The FDA draft proposals would permit "notification" in lieu of registration and listing for LDTs during an applicable enforcement discretion period, but this alternative would only temporarily delay application of the medical device tax, since registration and listing would be required once enforcement discretion ends as specified under the draft proposals.

e) The FDA is no panacea

Throughout its history, the FDA has played a vital role in our healthcare system to ensure patient access to safe and effective medical products. The agency, however, also bears significant limitations. First, the FDA is not the source of medical innovation in the United States. The sources of innovation in the United States are medical researchers and health care providers working collaboratively to share knowledge and give birth to new discoveries to improve the quality of care available to patients. The federal agencies primarily tasked with discovery and innovation are the National Institutes for Health and the Centers for Disease Control and Prevention. The intervention of the FDA cannot settle a debate in medical science, nor can it discover the next cure.

Suggestions that, despite these limitations, the FDA's intervention with respect to laboratories is needed because there may have been instances in which CLIA regulation by CMS has proven to be imperfect make no sense. Without ruling out the possibility that Congress might make useful improvements in the CLIA regime, the Committee should resist proceeding on the misleading premise that absolute perfection is attainable in any regulatory regime. If that is not obvious on the face of it, it has been demonstrated anew with respect to FDA as recently as 2014. The FDA's experience last year reaffirmed that not even that agency can offer a guarantee that a device or product cleared or approved under its jurisdiction is totally safe or effective. Just in the past twelve months, the FDA placed the strongest form of warning on a surgical device for hysterectomies. Various versions of the device have been used by surgeons *for decades*, yet only recently has the FDA determined that the device's use can actually *worsen* a patient's cancer.¹² Similar recalls have occurred with hip replacements¹³ and anti-inflammatories¹⁴; and we have seen post-approval discovery of life-threatening side effects that have sharply curtailed use of other products such as antibiotics.¹⁵

None of this is to deny that the FDA does, of course, play a vital role in reviewing medical products for safety and effectiveness. However, when the agency's inherent limitations are combined with the significant burdens and costs the agency is set to impose upon laboratories and patients, there is substantial doubt whether the agency could genuinely improve rather than endanger the public health by duplicating regulation on an already heavily regulated industry, intruding into the practice of medicine, and interfering with patient access to testing services that have proven essential to the successful diagnosis and effective treatment of disease.

¹² Kamp, Jon & Levitz, Jennifer, "Surgical Tool Gets Strongest Warning", *The Wall Street Journal*, November 24, 2014, available at <http://www.wsj.com/articles/fda-adds-new-warning-to-labels-for-laparoscopic-power-morcellator-1416842439>.

¹³ Meier, Barry, "With Warning, a Hip Device is Withdrawn", *The New York Times*, March 9, 2010, available at <http://www.nytimes.com/2010/03/10/business/10device.html>.

¹⁴ Neilan, Terence, "Merck Pulls Vioxx Painkiller From Market, and Stock Plunges", *The New York Times*, September 30, 2004, available at <http://www.nytimes.com/2004/09/30/business/30CND-MERCK.html>.

¹⁵ Harris, Gardiner, "FDA Warns of Liver Failure After Antibiotic", *The New York Times*, June 30, 2006, available at <http://query.nytimes.com/gst/fullpage.html?res=9407E5D81430F933A05755C0A9609C8B63>.

Conclusion

Laboratory developed testing services have been an American success story in medical innovation and patient care. Under the CLIA framework, laboratories competitively and nimbly put into practice advances in medical science and knowledge that ultimately lead to improved patient access to higher quality diagnostic services. These improved services allow for more accurately diagnosed disease, and better selection of appropriate treatments that lower the cost of patient care and increase its quality.

The FDA is proposing to increase costs, duplicate regulatory burdens, discourage collaboration among laboratory practitioners and between health care providers, choke off paths to innovation, and slow, even harm, patient access to increasingly accurate, precise, and meaningful laboratory diagnostics.

For these reasons, ACLA calls on the FDA to rescind its draft proposals to regulate LDTs as medical devices, and ACLA further urges the Committee and Congress to continue the legislative precedent of treating laboratories and medical device manufacturers as separate and distinct parts of the health care system.

ACLA welcomes the opportunity to work with the Committee on these and other questions raised by the Committee related to the oversight of diagnostics. Above all, consistent with the Hippocratic Oath by which medicine is wisely bound, we ask that no harm be done through duplicative and unnecessary federal regulation on the path to the new cures we all seek, particularly through the ill-advised framework currently proposed by the FDA. Working together, we can foster robust and undisrupted patient access to innovative, accurate, reliable, and meaningful laboratory-developed testing services.

Sincerely,



Alan Mertz
President

Response of 20/20 GeneSystems, Inc.,
to the

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

January 5, 2015

20/20 GeneSystems, Inc., Rockville, MD (www.2020gene.com) is one of only three companies in the U.S. that currently markets a blood test for the early detection of lung cancer. This novel laboratory developed test (LDT) measures a panel of tumor antigens and autoantibodies in the blood of patients at a high risk of developing lung cancer, namely, smokers and former smokers. A proprietary algorithm is used to provide primary care physicians with a score that designates the likelihood that the patient has lung cancer compared to others of comparable age and smoking history. Those with a high score are recommend to be further examined with a low-dose CT scan. If lung cancer can be surgically removed in stage 1A the patient’s survival rate can approach 80%. In contrast late stage lung cancer—when lung cancer is usually diagnosed—have survival rates of under 5%.

We welcome and appreciate the opportunity to respond to the following questions of the House Energy and Commerce Committee on how the government should approach innovative test:

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?

Companies that provide LDTs should be regulated as information service providers not as medical practitioners nor device manufacturers. In some ways our deliverable is equivalent to that of a health IT company or healthcare publisher.

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?

The device regulations are should not be applied to LDTs due to the static nature of the former and dynamic nature of the later. Optimal tests today involve multiple biomarkers, diverse analytes, and bioinformatics algorithms that evolve as more patient test results are generated and analyzed. To apply traditional device regulations to these types of test will discourage developers from aggressive post market surveillance and improvements. The unintended consequence of these regulations will be to make

novel tests worse, not better. Thus, it is imperative to exempt truly innovative tests from these rules.

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?

The risk from diagnostics is considerably lower than that for invasive devices since the former does not enter the human body. Increasing regulation for “high risk” tests sounds good in principle but could be destructive in practice since the diagnostics industry is already extremely risk adverse. Thus, the menu of tests in the hands of most physicians has changed little over the past 2-3 decades. This industry should be encouraged to take more risks not less!

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?

No. There are no inherent safety issues with IVDs apart from the test accuracy. Diagnostics companies, especially those selling LDTs, should be regulated as information service providers rather than device makers.

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?

Post-market surveillance—not pre-market approvals--should be the primary means for regulating innovative diagnostic tests. The cost and burden of a statistically significant prospective trial outweighs the likely return for the overwhelming number of tests. Retrospective (case/control) studies often do not predict how a test will perform in the real world. Thus, novel tests should be permitted to be marketed with minimal pre-market scrutiny as long as test performance in the real world and adverse events reporting are policed for a few years post-launch.

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?

Improvements should be encouraged for both LDTs and distributed kits but more so for innovative LDTs that involve (a) panels of biomarkers, and (b) sophisticated algorithms.

Otherwise, diagnostics companies would be discouraged from frequent improvements and innovations.

7. We have heard a lot 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?

There should be some oversight to ensure that the information provided is not exaggerated or deceptive. The information standards for health IT companies (internet, mobile, or wearable) should be the same as for diagnostics.

8. The Section 1143 guidance documents raise important questions about the relationship between the FFDCAs 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 regulations 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?

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. Ebola)?

The policy justifications for a lower regulatory bar for tests that target rare or urgent diseases should apply to all unmet disease areas, including those that address large populations. There are few successful business models for commercializing novel or esoteric diagnostics. Without government incentives including, but not limited to, low regulatory thresholds, the diagnostics industry will remain a commodity business with “me-too” products dominating the portfolios of the leading companies.

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?

Special exceptions should be offered to innovative tests that address substantial, unmet medical needs. The standards for such tests should be equivalent to those for humanitarian devices.

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

Neither institutional investors (venture capital firms) nor large diagnostics companies typically invest in small, entrepreneurial diagnostics companies. Thus, the field of molecular diagnostics and personalized medicine is largely stagnant. According to Corinne Solier, Ph.D, head of external research, pharmaceutical sciences at Hoffman-La Roche, “the introduction rate of biomarkers into clinical use has been static at approximately one or two per year for the past 15 years,” (*Genetic Engineering News*, page 1, Nov. 2014) To energize this stagnant field a major thrust of the *21st Century Cures Act* should be to incentivize investment. Awarding priority drug review vouchers to investors in diagnostics start-ups would be the ideal mechanism to accomplish this essential goal.



5 January 2015

cures@mail.house.gov

Subcommittee on Health
Committee on Energy and Commerce
U.S. House of Representatives
Washington, DC 20515

Esteemed Representatives:

I am writing in response to your Request for Feedback on *A Modernized Framework for Innovative Diagnostics Tests* following your September 9, 2014 hearing on the *21st Century Cures Act*.

My perspective is that of the CEO of a provider of innovative molecular diagnostic tests that give oncologists information on the activity of key proteins that govern the proliferation of cancer cells. This information is used by oncologist to inform the selection of the optimal cancer treatments for their patients. Unlike current genomic tests like OncoTypeDX™ or Mammoprint™, wherein a the pattern of expression of hundreds of genes is analyzed by black-box algorithms, or genomic assays such as Foundation One™, that measure hundreds of specific genes that are not directly linked to the mechanism of action of the drug, my Company offers an innovative protein assay that directly measures whether or not the drug targets (taken right from the FDA approved package insert) are activated and “in use” in any given patient’s tumor. My company’s lab-develop test (LDT) has demonstrated continuing compliance with all CAP and CLIA standards, and we believe the *21st Century Cures Act* provides a vehicle for diminishing the current state of regulatory uncertainty that slows adoption of innovative tests like ours by physicians and payers alike, thus delaying the benefits they deliver to patients hoping to beat their cancer. Below is my feedback to four of the eleven questions posed.

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

In addition to assessing the invasiveness of the test itself, FDA’s definition of risk needs to balance the benefit of earlier and/or more appropriate treatment (or non-treatment, in the case of negative test results) against the risk that the diagnostic test in question will provide incorrect information about the patient’s diagnosis, leading to incorrect treatment or non-treatment. As such, the risk has as much to do with the risk profile of the underlying disease (if left untreated or treated incorrectly) and of the treatments available (if deployed incorrectly).

As just one example, the FDA’s newly approved labelling of 10 currently-marketed cancer drugs includes information (usually listed under “Clinical Pharmacology”) on the specific protein and/or protein pathway

where that drug acts. Paradoxically, while the package insert describes the specifics of the protein and activated protein drug targets directly tied to the mechanism of action of the drugs, physicians still generally prescribe these drugs with little, if any, information on the activation status of those proteins or protein pathways these drugs affect. LDTs like our assay, are commercially available today, and provide such information, and thus can inform physicians of the likely efficacy of these drugs, which are generally expensive and prone to serious side effects. Our LDT assay does not require a complicated algorithm to discern meaning. In our case, the results of our LDT assay are easy to understand, and entirely in keeping with the same reporting method as is used to report HDL/LDL tests or common liver function tests, etc. – all of which are measured routinely in millions of patients to help physicians inform their prescribing decisions without incident. Importantly, our LDT test provides key information that is supported directly by the FDA approved labeling that can help identify patients most likely to benefit from each drug, while reducing the risk of unnecessary adverse side effects in others.

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

Yes, in fact hundreds of effective LDTs already are being used effectively in clinical practice. LDT assays are regulated by CAP and CLIA, and these inspections are very rigorous and require extremely detailed assay validation documentation, proficiency testing documentation, and evidence of assay robustness. This type of oversight is not less than that what the FDA would require. Society clearly benefits from additional research on the clinical utility of such tests, but that evidence should continue to be collected and evaluated in the context of post-market patient registries. Such efforts provide regulators and physicians with valuable information on test performance, allowing timely access to patients while the clinical utility is defined in larger, more diverse populations that are economically impossible to provide in a pre-market setting. CMS's existing authority to Coverage with Evidence Development provides an excellent vehicle for simultaneously ensuring expeditious patient access while also ensuring a robust research program on clinical utility. Transitioning this authority to the FDA does not provide any additional scientific rigor, but it will lead to longer product development timelines, and reduce investment and job creation in this innovative industry.

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., Ebola)?*

When defining “rare diseases or conditions” and “unmet needs,” it is vitally important to recognize that our understanding of diseases – and their classification/nomenclature – is advancing in parallel with our understanding of disease pathways. For example, while “breast cancer” does not meet any accepted definition of a “rare disease,” our understanding of cancer is rapidly evolving and it is now recognized that there are many different sub-types of the disease, like the small percent of women who have Inflammatory Breast Cancer. Thanks to efforts such as the acclaimed TCGA project, we now understand that each patient’s tumor is unique at the molecular level. Indeed, there are massive re-classification efforts underway that not only are re-orienting our understanding of a cancer such as “breast cancer” to be

dozens of different sub-types, but we now understand that there are some breast cancers that resemble prostate cancers more closely than they do other breast cancers. It is very likely that over the next few years we will have hundreds of different sub-types of cancers, with many of these transcending even organ type. Already, the U.S. House of Representative recognized March 3, 2013 as “Triple Negative Breast Cancer Awareness Day” to draw attention to the 10-15% of breast cancer cases that do not express the genes for estrogen receptor (ER), progesterone receptor (PR) and HER2/neu. Moreover, these 10-15% “triple negative” patients, may in fact be categorized into 7-10 further distinct molecular subtypes (of which Inflammatory Breast Cancer is just one subtype) that each could very well be defined under current guidelines as a “rare” disease. In other words, because of the results of the detailed molecular analysis of diseases such as cancer that have been generated over the past 5-10 years, we now recognize that cancer is an extremely heterogeneous disease comprised of hundreds of “rare” subtypes. Indeed, many LDTs have been developed precisely to help physicians correctly identify these relatively “less” common patient sub-populations to help physicians make an appropriate diagnosis and allow treatment planning that matches the right patient with the right drug.

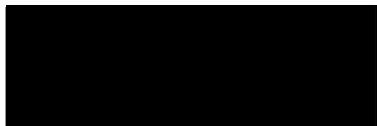
11. What incentives can be put in place to encourage the development of new, more accurate or more effective diagnostics tests?

We support the proposal of the Small Biotechnology Business Coalition that the FDA provide provisional approval for the marketing of innovative, “high-impact” (Class III) tests that address an unmet need (that is, with no FDA predicate), without full pre-approval by FDA so long as test volume remains under 8,000 tests per year and revenues are under \$8,000,000 annually. This approach has numerous precedents in U.S. regulatory policy and strikes the right balance among:

- fostering innovation, capital-formation, and job-creation in a high-tech industry,
- expediting patient access, especially for conditions affecting small populations, and
- providing a continuing incentive for rigorous clinical utility studies in real-world clinical practice.

As noted above, CMS should be encouraged to make much greater use of its existing Coverage with Evidence Development process to extend provisional coverage to innovative LDTs while ensuring the ongoing systematic collection and analysis of evidence of clinical utility in the intended patient population(s).

Thank you for the opportunity to provide this feedback.



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January 5, 2015

The Honorable Fred Upton
U.S. House of Representatives
1531 Longworth Building
Washington, DC 20515

The Honorable Diana DeGette
U.S. House of Representatives
2368 Rayburn Building
Washington, DC 20515

Submitted electronically.

Re: 21st Century Cures White Paper on Laboratory Developed Tests

Dear Representatives Upton and DeGette:

The Blue Cross Blue Shield Association (BCBSA) is a national federation of 37 independent, community-based and locally operated Blue Cross and Blue Shield companies that collectively provide healthcare coverage for more than 105 million members – one-in-three Americans. Blue Cross and Blue Shield Plans offer coverage commercially in every market and every zip code in America. BCBSA thanks you for your leadership in assessing how to reduce barriers to healthcare innovation and improve access and affordability of the innovations for consumers.

In response to your December 9 paper entitled, “21st Century Cures – Request for Feedback: A Modernized Framework for Innovative Diagnostic Tests” we submit the attached comments. We agree with the Committee that additional review of the safety and efficacy of laboratory developed tests will be beneficial to consumers, and we generally support the FDA guidance issued on this topic.

We look forward to working with you on your 21st Century Cures initiative.

Sincerely,


Alissa Fox
Senior Vice President
Blue Cross and Blue Shield Association



Re: Response to 21st Century Cures Request for Feedback: A Modernized Framework for Innovative Diagnostic Tests

January 5, 2015

To the Members of the Committee:

We appreciate the Committee's leadership and initiative in providing an opportunity to share feedback regarding the pending changes in regulation of the diagnostic testing industry. We concur that an open dialogue will most effectively inform the implementation of new regulation.

We believe any regulatory framework should prioritize patient access to innovative and powerful diagnostic technologies as its single highest mandate. The unparalleled pace of technological development over the past decade has delivered commercially robust and clinically appropriate tools that should be expeditiously integrated into the clinical workflow. In our view, these technologies offer the most cost effective opportunity to improve patient care and drive efficiency throughout the healthcare system. In 2014, the National Institutes of Health spent approximately \$30.1 billion on basic medical research.¹ Molecular diagnostics offer a return on that investment in the form of clinically valuable information that can guide the intelligent deployment of myriad other technologies whose development has also been supported by federal spending.

A corollary to establishing commercial diagnostic technologies that are accessible to clinicians and patients is a robust pipeline of the commercial diagnostic tests themselves. The cost and time required to develop diagnostic assays is considerable and requires developers to undertake substantial risk. Creating a sensible, targeted and navigable set of criteria for gaining regulatory approval and a responsive and coordinated mechanism for reimbursement decisions is essential to buttressing the molecular diagnostics industry, which is still reeling from the dramatic changes in oversight that have disrupted the space over the past two years.

We believe the implementation of FDA oversight of the diagnostic test industry has the potential to streamline the currently uncertain and shifting system for demonstrating validity and utility. The FDA's role in verifying safety and efficacy in both the medical device and pharmaceutical space, implemented intelligently, should be adaptable to the laboratory testing environment. By contrast, the current regulatory framework relies on CMS-appointed administrative contractors (MACs) to assess the value proposition of these technologies. The current system is complex, opaque, lengthy and highly uncertain. It seems quite likely that many of the companies that have delivered the most successful and widely adopted tests

¹ www.nih.gov.



currently specified in clinical guidelines would not have had sufficient funding or resources to navigate the process as it currently exists were they to initiate the same development activities today. These factors constrain the rate at which new tests reach the market, impede access to investment capital, and thus limit patient access to innovative and potentially transformative technologies.

The adaptation and implementation of FDA regulations to the diagnostic testing industry is in motion, and we believe reflects an appropriate and possibly useful exercise of regulatory authority. The major concern from our perspective is not the specifics of how FDA tools and processes are adapted, but rather how the FDA will coordinate its oversight efforts with other federal agencies (and their surrogates) currently overseeing this industry. We believe that elected officials are uniquely and singularly positioned to broker this discussion.

Key questions that we believe are essential to an integrated and effective regulatory framework include:

- 1) The future role and potentially duplicative nature of the MolDx program (designed and administered currently by Palmetto GBA on behalf of CMS) in light of impending FDA oversight of safety and efficacy.
- 2) The interface between CLIA laboratory regulations as administered by CMS and FDA regulation. While there are any number of CLIA regulations that appear necessary in verifying laboratory quality, many of these measures could unnecessarily duplicate analogous functions the FDA could serve.
- 3) The purview of FDA in the “manufacturing” process and/or laboratory operations, e.g., with regard to reagent, equipment and materials suppliers that are currently designated Research Use Only.

Thank you again for the opportunity to broach these critical topics in a broader dialogue. It is our opinion that the proper design and implementation of the holistic regulatory landscape that test developers must navigate in order to commercialize technology will be the single most important factor in deciding the viability of the diagnostics industry. We’ve attached our answers to specific questions as an Addendum to this letter. Please let us know how we can continue to support this discussion.

Sincerely,

Joe Wiegel
Chief Executive Officer

Jeff Keller
Director of Technology
Commercialization

Addendum 21st Century Cures – Questionnaire

- 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?*
 - a) PCLS has no response to this question.

- 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?*
 - a) The analog of the “device” in the context of an LDT should be the operational workflow that derives diagnostic information from the processing and analysis of the patient specimen. Laboratory workflows could be developed under a Quality Management System (QMS) administered via CLIA, by translating any number of currently in-use tools and processes (e.g., Verification and Validation procedures).
 - b) Although the lab industry already has regulation of a QMS via CLIA, there may be a role for additional oversight. In particular, a novel test procedure could voluntarily be submitted for “device” classification subject to FDA approval. We believe this voluntary system could be incentivized by market forces if payers (especially CMS) would permit FDA approval to provide a streamlined path to reimbursement.
 - c) FDA regulatory oversight might be appropriate for LDTs classified as “high risk” if there were reasonable algorithms published to allow test developers to properly classify their test in a pre-development framework. Tests that do not meet the definition of “high risk” should not be classified as “devices” or should possibly fall into a lower classification (e.g., Class II). This would allow labs to develop more cost effective diagnostics and make modifications to meet market demand.

- 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?*
 - a) Risk should be defined by the role the diagnostic information plays in the decision making process of the physician, and thus by the intended use of the diagnostic

assay. On one end of the spectrum, the LDT result may form the sole basis for the diagnosis of a disease state, and dictate an entire suite of subsequent procedures and tests that are ordered only as a result of this piece of information. On the other end, the LDT result may inform some relatively minor component of patient treatment (i.e., ordering an additional test, prescribing an alternative medication to avoid the risk of a minor side effect).

- b) Risk should also take into account test compatibility to existing, approved technologies. Analytical and clinical validation that compares favorably to a currently marketed test should be excluded from regulatory oversight; comparable tests could claim a predicate that would correspondingly reduce the regulatory hurdles that developers must meet. Limits could be placed on this exemption through definitions in the regulation.
- 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?*
- a) PCLS has no response to this question.
- 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?*
- a) The current arrangement is heavily back-end weighted, meaning that companies have to demonstrate significant efficacy and utility before they can reasonably hope to achieve reimbursement status from CMS. This puts an enormous financial strain on test developers who are forced to shoulder the costs of development, early marketing, and demonstration of a considerable degree of validity and utility all while bearing the significant risk that the test may not be granted reimbursement. Greater use of post-market processes that would allow for some period of cost recovery while this work is being completed would greatly support companies undertaking the risks of commercializing innovative new technologies.
 - b) A discussion of pre-market review and post-market controls should acknowledge that payers have shifted away from the very basis of FDA approval of diagnostics (i.e., analytical and clinical validity) towards a singular focus on clinical utility. This dichotomy renders this question moot unless there is some mechanism to align regulators with payers. Use of post-market controls might significantly reduce risk of bringing a new diagnostic to market if an FDA stamp of approval on validity somehow streamlined the process of getting reimbursed for running the 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?*
- a) Supplemental premarket submission for modifications is not practical with LDTs. Many modifications of these tests are market driven. The most efficient way to regulate this process is through a verified QMS and should not fall under FDA authority except when the LDT is also classified as a high-risk device (refer to answers to questions 2 & 3).
- 7) *We have heard a lot 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?*
- a) PCLS has no response to this question.
- 8) *The Section 1143 guidance documents raise important questions about the relationship between the FFDCA 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 regulations 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?*
- a) CLIA is mainly focused on the laboratory environment as defined by a collection of equipment, personnel, and procedures that constitute a suitable environment in which tests may be performed. The FDA is more focused on a specific test and whether or not it offers appropriate safety and efficacy to be used in a clinical environment. These two things are related but different. We believe they can live in accord if implemented intelligently. There exists significant potential peril in the simultaneous regulation/oversight of a test by both FDA and CMS, acting through MACs. This duplicative oversight complicates investment decisions with uncertainty.
- b) We believe some level of constraint on what the FDA can regulate by defining LDTs as medical devices, revision of CLIA rules to better control development of low-risk tests that are exempt from FDA oversight, and leadership from CMS on reimbursement decisions rather than delegation of these decisions to the MACs offers a way forward. These three factors define the crux of the problem being

described.

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. Ebola)?*

- a) One of the many shortcomings of the current program of regulatory oversight is the lack of agility that is in many cases demanded by rapidly emerging or changing threats to human health. Advanced diagnostics can increasingly be developed in a timely and highly directed fashion; however, there is no mechanism for providing regulatory approval at a commensurate pace. Regulations should include a streamlined path for high priority disease states.

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?*

- a) PCLS has no response to this question.

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

- a) Unfortunately, the dramatic changes to the approval and reimbursement process that CMS implemented in early 2013 (and that continue to evolve) have wreaked havoc on this nascent, yet potentially hugely important industry. Effective diagnostic testing technology promises to save, not cost, the U.S. healthcare system precious financial resources. As a technology class, advanced diagnostics can claim the credit for redrawing a number of clinical workflows that were previously far more subjective and opaque than they are today. While the annual costs of molecular diagnostic tests has increased significantly since 2007 when these tests were gaining early adoption, total molecular diagnostic spending totaled \$255 million in 2013, or 0.05% of total Medicare Part B spending.² Given the potential (and in many cases proven) beneficial impact of these technologies on the rest of the healthcare system, the extreme efforts to control costs in the diagnostics sector on behalf of CMS and its designees seem somewhat misguided.

² www.gpo.gov; CMS.



January 5, 2015

The Honorable Fred Upton
Chairman
House Energy and Commerce Committee
2183 Rayburn HOB
Washington, DC 20515

The Honorable Diana DeGette
Member
House Energy and Commerce Committee
2368 Rayburn House Office Building
Washington, DC 20515

Dear Chairman Upton and Representative DeGette:

On behalf of the American Association of Bioanalysts (AAB) and National Independent Laboratory Association (NILA), I am pleased to provide a response to the Committee's request for response on the *21st Century Cures Request for Feedback: A Modernized Framework for Innovative Diagnostic Tests*. AAB is a national professional association whose members include clinical laboratory directors, owners, managers, medical technologists, physician office laboratory technicians, and others. NILA's members are community-based laboratories that range in size from intra-state to multi-state regional laboratories. In addition to providing diagnostic laboratory services relied on by physicians across the country every day, a number of AAB and NILA members are engaged in the development of laboratory tests that provide patients and their physicians access to safe and effective testing options.

Since 1949, AAB has administered one of the nation's full-service proficiency testing programs approved by the Clinical Laboratory Improvement Amendments of 1988 (CLIA), Joint Commission on Accreditation of Healthcare Organizations (JCAHO), Centers for Medicaid and Medicare Service (CMS), and all state agencies to satisfy laboratory proficiency testing requirements.

In response to the Committee's white paper on diagnostic tests and outlined questions, AAB and NILA are pleased to issue the following response:

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?

Clinical laboratory practice and any testing conducted by a laboratory is not the practice of medicine. It does not matter if the clinical laboratory and testing services performed are led by a Ph.D. scientist, pathologist, oncologist, infectious disease specialist, or medical geneticist – clinical laboratory testing is a health care service utilized to support the practice of medicine broadly, and personalized medicine, specifically. A patient's treating physician utilizes testing performed by a laboratory along with a patient examination, review of patient/family medical history, and other factors to support the actual practice of medicine and establish a diagnosis on a patient's condition or decision on how to manage a patient's care. In a situation where a single clinical laboratory develops a new laboratory test, many of these tests are predictive in nature, using complex algorithms to ultimately provide predictive data on a patient's level of risk for a certain disease or condition. Again, these types of tests do not constitute the practice of medicine, as any decision in relation to the test results is the ultimate responsibility of a patient's treating physician.

The Committee must also understand that historically under CLIA and under judicial review, non-medical providers, including Ph.D. scientists are permitted to direct laboratories, including the overall technical and administrative responsibility for the laboratory. The training and expertise of these professionals has been essential at guiding the physician community on test results to support the practice of medicine, but the work of these scientists is not the practice of medicine itself.

Clinical laboratories are not manufacturers but health care providers who offer testing services, not products. These services include consultation with physicians to support the design of new tests, conducting of testing on patient samples, and the interpretation of test results to support physician understanding and decision making. These laboratory activities greatly differ from those of manufacturers who develop and produce in vitro diagnostic test kits, testing instruments, or durable medical equipment that is sold in the open commercial market.

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 (FDCA). 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?

Laboratory developed tests differ significantly from FDA-regulated medical devices in that LDTs are services – not device products or articles. They are proprietary professional interpretive services available to treating medical professionals. The services included through LDTs include the design, development, and validation of a test, and the interpretation of LDT results. Because LDTs are services and not devices, they require a separate regulatory pathway.

LDTs are not described in the Federal Food Drug and Cosmetic Act nor referenced in legislative history as being under the authority of the FDA as regulated devices.

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?

While AAB and NILA does not support the regulation of LDTs as medical devices under current statute, the AAB and NILA does support the regulation of these tests through a risk-based classification approach that ensures the analytic and clinical validity for all LDTs. The AAB and NILA believe that regulatory oversight should be under the FDA or CMS/CLIA, depending on the level of risk classification: high risk (FDA oversight); moderate risk (CMS/CLIA oversight); low risk (CMS/CLIA oversight). There is precedent for such an approach under FDA and CLIA, as CLIA certification for laboratories is based on the level of complexity of testing that a laboratory performs: waived (low); moderate; high complexity.

AAB and NILA also believes that because of the many challenges the federal agencies have currently had in defining risk in relation to LDTs, a formal process must be established to ensure stakeholder feedback is received and can be acted on. AAB and NILA urge Congress to establish a federal advisory committee and require a notice and comment rulemaking process to provide insight into the risk classification process and allow for interagency and outside expertise, including the FDA, CMS/CLIA, federal agencies, and professional organizations that represent clinical laboratories, physicians, consumers, and organizations with experience and expertise in proficiency testing and accreditation processes. CLIA must also be modernized, including improvement to its oversight structure, ability to assess clinical validity, and the need to modify proficiency testing programs to address changes in the complexity of laboratory testing and

where testing is proprietary and cannot currently be assessed using traditional proficiency testing processes.

The risk level for each test should be determined based on the potential for a misinterpreted test result to cause harm (death or disability) to a patient or have a significant adverse effect on public health. The risk assessment process must also consider the transparency of the test methodology utilized, including whether the laboratory utilizes complex and proprietary algorithms or software to establish a test result that could result in increased risk to a patient.

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?

AAB and NILA do not support the regulation of LDTs as medical devices under current statute, and therefore, does not support the establishment of current pre-market review standards for LDTs or on modifications to an existing FDA-cleared test kit utilized in the development of a LDT.

For those LDTs determined to be high risk upon a process that includes notice and comment rulemaking and a federal advisory committee(per question 3 above), AAB and NILA believe regulatory oversight should be under the jurisdiction of the FDA and that the agency must establish a separate regulatory approval process outside of the current device approval (e.g., PMA) process to assess the analytical and clinical validity, and therefore, the safety and effectiveness of high risk LDTs, including those that modify FDA-cleared test kits.

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

Yes, ensuring both the analytical validity and clinical validity of all LDTs, whether they undergo a pre-market review process by the FDA or CMS/CLIA is essential to ensuring the safety and quality of the test before it is utilized on patients. To do this will require a modernization of existing CLIA processes to require an assessment of clinical validity. To support the pre-market clinical validity review process, AAB and NILA believe the FDA or CLIA must work in tandem with outside accrediting agencies that currently require proof of clinical validity, including the College of American Pathologists (CAP), Joint Commission, and other accrediting organizations.

Post-market assessment is paramount to ensuring the safety and efficacy of LDTs available to patients. External quality control programs currently exist through the CLIA-based proficiency testing program and tell the agency how well traditional laboratory tests are performing out in the field, and over the years, this process has proven to not result in barriers to patient access to laboratory tests. However, the current proficiency testing program must be modified in order to adequately assess LDTs since LDTs are, by definition, only being conducted by a single laboratory and test result samples from the lab cannot be tested in comparison to samples from other laboratories. A modified proficiency testing program would need to ensure that the testing results from a single lab can be replicated and shown to be safe, effective, and reproducible. In addition, current CLIA requirements for proficiency testing for specific specialties and subspecialties (e.g., virology, chemistry, endocrinology) must be broadened to cover all categories of laboratory testing not currently included in CLIA's list (e.g., genetic testing).

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?

As stated in #4 above, AAB and NILA do not support the regulation of LDTs as medical devices under current statute, and therefore, does not support the establishment of current pre-market review standards/submissions for modifications to existing FDA-cleared test kits that are utilized in the development of a LDT. If a FDA-approved test kit is being altered for the purposes of developing a LDT, it is being used for the establishment of a new testing procedure that must be regulated through a separate FDA pathway. If a laboratory is forced to undergo a lengthy and expensive premarket submission process under current FDA requirements, it will hamper development of such LDTs and patient access to such tests.

7. We have heard a lot 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?

As stated in #1 above, clinical laboratory practice and any testing conducted by a laboratory is not the practice of medicine. Whether laboratory testing services are performed by a Ph.D. scientist, pathologist, oncologist, infectious disease specialist, or medical geneticist – laboratory testing is a health care service utilized to support the practice of medicine broadly, and

personalized medicine, specifically. At a minimum, AAB and NILA believe information should be accessible to patients and health care providers on which federal agency reviewed and approved any given test, the laboratory that performed the test, and how to access publicly available information of the analytic validity of the test results (e.g., proficiency testing results).

8. The Section 1143 guidance documents raise important questions about the relationship between the FDCA 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 regulations 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?

Both the FDA and CLIA share the same regulatory goal of ensuring correct laboratory test results, and as such, there is much overlap in what is being proposed within the FDA guidance and the current CLIA regulatory process. While the FDA is seeking to address the safety and effectiveness of the diagnostic test itself and the quality of the test and manufacture of the tests, CLIA is currently regulating the quality of the clinical testing process, the quality of the laboratory performing the testing, an assessing the performance of the tests themselves when "out in the field."

The FDA has not issued any information on how Quality Systems Regulation (QSR) applicable to devices under the FDA would interact with quality requirements under CLIA. CLIA already has an extensive quality control process that involves: proficiency testing, internal quality controls, and external quality controls. The FDA has demonstrated that regardless of current QSRs, it does not have external quality controls in place for how waived tests approved by the agency perform in the field. There have been numerous documented problems for tests approved by the FDA as waived, with little-to-no quality assessment.

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. Ebola)?

LDTs have resulted in promise for patients facing rare/orphan diseases, particularly where IVD manufacturers did not find it profitable to work toward development of a product for a limited population. Any new regulatory process for LDTs must not be so burdensome as to eliminate innovations for these vulnerable patient groups. The AAB and NILA recommend excluding LDTs for rare/orphan diseases from any regulatory process until such a time the tests meet a high-

volume threshold and are commonly used in the general market, where risk to public health could be substantially increased.

Likewise, any regulatory system for LDTs must not impose lengthy burdensome requirements on tests used for emergency purposes (e.g., Ebola). Where the public health is more greatly served by the availability of testing to support early diagnosis and treatment options during emergencies, the government must maintain an emergency system that allows for such flexibility and does not squander innovation. The AAB and NILA recommends excluding LDTs for emergency purposes (e.g., public health concerns) from any new regulatory process until such a time the tests may meet a high-volume threshold and are commonly used in the general market, where risk to public health could be substantially increased.

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?

It is important that any new regulatory system not be so burdensome that it eliminates innovation in laboratory testing. There should be a phase-in for current tests on the market, and such a phase-in would be required if a new advisory committee is to be established to support FDA-CMS/CLIA efforts to define test risk levels. The AAB and NILA do not believe that all current diagnostic tests should be grandfathered into the marketplace. All tests need to be assessed for analytical and clinical validity, and this will need to be done over an extended timetable, which could be as long as three-to-five years, given the volume of tests currently on the market.

The *Protecting Access to Medicare Act of 2014* also included a new statutory definition for some LDTs, called “Advanced Diagnostic Tests.” Any regulatory process for LDTs must also include these tests so that there is consistency across the market in terms of regulatory review and oversight.

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

Any regulatory process must fairly assess the analytical and clinical validity of all LDTs, but must not become so burdensome and economically challenging as to squander investment in the growth of LDTs, and as a result, patient access to needed diagnostic testing services.

One incentive would be to establish a regulatory process for moderate and high-risk LDTs that expands upon the 2011 FDA-CMS parallel review process for innovative medical devices, allowing the tests to be considered for coverage and regulatory approval, simultaneously.

AAB and NILA are committed to working with the Committee, the federal agencies, and the patient community to address these challenges. It is important that we collaborate to ensure that a fair and sustainable regulatory process is in place to assess the quality and safety of LDTs while allowing for continued innovation.

Conclusion

Thank you again for the opportunity to provide a response on these important issues. AAB and NILA applaud the Committee's focus and work on the 21st Century Cures Initiative. We look forward to continuing to work with you as you address issues related to the regulation of laboratory developed tests. Should you have any questions, or require additional information, please contact Julie Scott Allen, our Washington representative, at (202) 230-5126 or julie.allen@dbr.com.

Sincerely yours,

A black rectangular redaction box covering the signature of Mark S. Birenbaum.

Mark S. Birenbaum, Ph.D.
Administrator

January 5, 2015

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

The Honorable Diana DeGette
Member
House Energy & Commerce Committee
2125 Rayburn House Office Building
Washington, DC 20515

Sent via e-mail: Cures@house.mail.gov

Re: Request for Information Regarding 21st Cures – Request for Feedback: A Modernized Framework for Innovative Diagnostic Tests

Attachments:

1. AACR's Policy Statement on Reliable and Effective Diagnostics Are Keys to Accelerating Personalized Cancer Medicine and Transforming Cancer Care.
2. "21st Century Cures: Examining the Regulation of Laboratory Developed Tests." Testimony by Dr. Charles Sawyer before the Committee on Energy and Commerce, Subcommittee on Health, United States House of Representatives. September 9th, 2014.
3. AACR's comments to FDA on "Expedited Access for Premarket Approval of Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Disease or Conditions" Docket No. FDA-2014-D-0363.

Dear Chairman Upton and Representative DeGette:

Thank you for spearheading the 21st Century Cures initiative- an extraordinary, bipartisan initiative aimed at reviewing the steps that can be taken to accelerate the pace of medical innovation in America- from basic science discovery, to streamlining medical product development processes, as well as harnessing digital technologies to improve health-care delivery.

The American Association for Cancer Research (AACR) was honored to testify in front of the committee on September 9, 2014, in order to provide our perspective on the proposed framework by the Food and Drug Administration regarding the regulation of Laboratory Developed Tests (LDTs). We continue to be extremely engaged on this specific issue and welcome this additional opportunity to address specific concerns regarding the regulation of innovative diagnostic tests. We believe that the proposed framework for regulatory oversight will protect patients, instill physician confidence in the validity of the test results, incentivize innovation, and advance the practice of personalized or precision medicine.

The mission of the AACR is to prevent and cure cancer through research, education, communication, and collaboration. Founded in 1907, the AACR is the world's oldest and largest cancer organization dedicated to accelerating advances in cancer research to benefit patients. The AACR's membership includes more than 35,000 basic, translational, and clinical researchers, health care professionals, patients and patient advocates residing in the U.S. as well as 96 other countries. Since the AACR encompasses the entire continuum of cancer research and biomedical science – from the laboratory to the clinic including public policy – we are able to marshal the full spectrum of expertise in the cancer community to accelerate progress in the prevention, detection, diagnosis, and treatment of cancer.

Indeed, cancer researchers today are leading the way in the exciting area of personalized or precision medicine, where scientists are increasingly developing treatments that are precisely targeted to the unique molecular and genetic characteristics of an individual's cancer. However, the success of these personalized treatments depends in no small measure on diagnostic tests that are able to reliably detect specific molecular or genetic mutations necessary to ensure that a drug or treatment is ultimately effective.

We greatly appreciate the thoughtful questions in *A Modernized Framework for Innovative Diagnostic Tests* and are pleased to provide the following feedback to the Committee on this important issue.

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 AACR holds that while LDTs should be regulated by the FDA based on the level of risk posed by the test to the patient, the practice of medicine should NOT be regulated or overseen by the Agency. Therefore, it will be crucial to have clear and precise separation between what will constitute the development and manufacturing of diagnostic tests, which will be subject to oversight by the FDA, the actual conduct of the test in a laboratory that is regulated by the Centers for Medicare & Medicaid Services (CMS) through the Clinical Laboratory Improvement Amendments (CLIA)¹, and the practice of medicine which will continue to be the purview of professional medical associations that rely on the expertise of individual medical practitioners.
 - The AACR believes that it is important that both the diagnostic tests components, as well as the precise protocol for using the diagnostic test, are standardized to ensure consistency of test quality and test results. This particular recommendation applies to those diagnostic tests that are classified as high-risk, as well as certain moderate risk tests, regardless of origin and including instances wherein laboratories significantly modify a manufactured test kit. The current lack of oversight of LDTs by the FDA has led to discrepancies in testing procedures and results which could directly impact patient safety and treatment outcomes^{2,3}.
 - The interpretation of diagnostic test results relies on the judgment of qualified medical personnel and therefore, should continue to be considered the practice of medicine which is not and should not be subject to regulation by the FDA.

¹ Standards and Certification: Laboratory Requirements (42 CFR 493) <http://www.ecfr.gov/cgi-bin/text-idx?SID=1248e3189da5e5f936e55315402bc38b&node=pt42.5.493&rgn=div5>, Accessed on Dec. 16th, 2014

² Peikoff, Kara. December 30, 2013. I Had My DNA Picture Taken, With Varying Results. The New York Times. December 30, 2013 <http://www.nytimes.com/2013/12/31/science/i-had-my-dna-picture-taken-with-varying-results.html?pagewanted=all&r=0#commentsContainer>, Accessed on Dec. 16th, 2014

³ Daley, Beth. December 14th, 2014. Oversold prenatal tests spur some to choose abortions. The Boston Globe. <http://www.bostonglobe.com/metro/2014/12/14/oversold-and-unregulated-flawed-prenatal-tests-leading-abortions-healthy-fetuses/aKFAOCP5N0Kr8S1HirL7EN/story.html?event=event25>, Accessed on Dec. 16th, 2014

- For example, in the case of an LDT that utilizes the ImmunoHistoChemical (IHC) staining technique protocol for a companion diagnostic test, which would be categorized as a high-risk test, the equipment, reagents and precise protocol (e.g. sample collection and storage protocols, antigen retrieval procedure, incubation time) used to stain a sample should be subject to FDA regulation. The implementation of the test protocol should continue to be subject to CLIA oversight, while the pathologist's interpretation of the test results and expert opinion would continue to not be subject to FDA's oversight since it constitutes the practice of medicine.
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?
- The AACR applauds the FDA's proposal to phase-in a risk-based approach to regulating LDTs as medical devices and agrees that in the absence of a marketed test kit, the exact constituents of a "device" may lead to confusion.
 - The diagnostic test should be considered the regulated device, including the test protocol and any and all equipment including software, General Purpose Reagents (GSRs), and Analyte-Specific Reagents (ASRs) used to perform the test.
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?
- The AACR believes that risk classification should be based on the overall risk to patient safety from an erroneous test result or the risk posed to patients from an invasive test procedure. Further, we believe that the current risk classification system used by the FDA for devices and *In Vitro* Diagnostics (IVDs) is appropriate and applicable to LDTs as well since the types of risks posed by diagnostic tests do not differ based on the origin of the diagnostic test.
 - Therefore those LDTs in which erroneous test results pose the greatest threat to patient safety should be designated Class III or the highest risk category tests. For example, LDTs that are offered *in lieu* of FDA approved companion diagnostic tests and used to

directly determine a patient's course of treatment (or non-treatment) should be classified as Class III or high-risk diagnostic tests. In addition, other LDTs such as prognostic tests, which are used to predict a patient's disease risk or the risk of disease recurrence may be classified as Class II (moderate risk) or Class III (high risk) depending on the specific intended uses, claims and limitations of the individual tests, and the availability of other clinical or informational evidence to assist in the determination addressed by the LDT.

- The AACR believes that risk should not be defined based on the technical or technological complexity of the test, but should be based on the risk posed to patients. For example; all diagnostic tests utilizing a complex technology or technique such as Next Generation Sequencing (NGS) should not be classified under the same risk designation if they confer different risks to patient safety. Rather, the safety and efficacy of each individual test should be considered independently.
 - The AACR agrees with the FDA that the risk posed to patients by tests does not differ based on the origin of tests- LDTs are *in vitro* diagnostics (IVDs) and should therefore be subject to the same regulatory risk guidelines as all medical devices.
 - The types of risks to patients from inaccurate diagnostic tests are akin to those posed by faulty therapeutic medical devices. For example, an erroneous test result could lead to misdiagnosis leading to unnecessary or over-treatment. Likewise, an erroneous test result could lead to a failure to diagnose a disease or condition leading to the patient not being treated. Both of these situations would be equally unacceptable. Therefore, we believe that the FDA's current risk classification system for medical devices is appropriate and sufficient to be applied to LDTs.
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?
- The same safety and effectiveness standards should apply to both LDTs and test kits because they are both IVDs, which section 210(h) of the Federal Food, Drug, and Cosmetic Act (FFDCA) classifies as medical devices⁴.

⁴ Federal Food, Drug, and Cosmetic Act.

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?FR=809.3>, Accessed on Dec. 16th, 2014

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?
- The AACR believes that premarket review of high risk and certain moderate risk LDTs is important to ensuring patient safety. CLIA validation of LDTs, which is limited to analytic validation, occurs only after the test is available to the public (post-market).
 - The FDA has released draft guidance on Expedited Access PMA, which would serve to hasten the pre-market approval for medical devices, including diagnostic tests, for unmet medical needs by relying on some level of post-market data for assessing safety and effectiveness⁵. The AACR welcomed this proposal and offered comments in response to the draft guidance document (attached).
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?
- One of the hallmarks of LDTs is their adaptability- they can be easily experimentally modified by laboratories, often leading to the development of a better diagnostic. However, *significant changes* to existing LDTs and marketed test kits, including significant changes to the protocol could alter the outcome of the test. Therefore, we believe supplemental pre-market submissions would be warranted in these situations.
 - The requirements for submission and approval of supplemental clearance should be the same for both high risk and certain moderate risk LDTs and distributed test kits because they are both IVDs.
7. We have heard a lot 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

⁵ U.S. Food and Drug Administration. Draft Guidance for Expedited Access for Premarket Approved Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions. <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm393879.htm>
Accessed on Dec. 16th, 2014

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?

- The AACR agrees that medical product “labeling” regulations present a challenge with regard to LDTs.
 - The standards for dissemination of scientific information should apply to diagnostic tests based on the level of risk they pose to patients. For example, a Class III test should have different standards in the test-specific information conveyed to the ordering physician compared to a Class I test.
 - There should be regulatory oversight in determining whether information pertinent to the test itself is provided to patients and health care providers. For example, it is appropriate to require that information on the limitations or caveats for high risk and certain moderate risk LDTs, especially information that would affect the interpretation of the test results, be provided to the ordering physician. However, the considered opinion of a pathologist and his/her interpretation of the test result is part of the practice of medicine and should continue to not be regulated by the FDA.
8. The Section 1143 guidance documents raise important questions about the relationship between the FFDCA 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 regulations 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?
- The AACR views CLIA and FDA guidelines as complementary systems of regulation, both integral and important for patient safety. CLIA guidelines ensure that LDTs are performed in the appropriate laboratory conditions, but do not ensure the clinical relevance or validity of the tests.
 - The AACR agrees with the FDA’s assessment that CLIA regulations might be sufficient for certain LDTs, such as those tests designated as “*Traditional LDTs*”, and for which the FDA will “*exercise enforcement discretion.*” However, for high risk and certain moderate risk LDTs it is essential to have active FDA oversight of tests to ensure patient safety and product efficacy.

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. Ebola)?
- The Humanitarian Use Devices (HUD)/Humanitarian Device Exemption (HDE) provisions (FFDCA) regulations (21 CFR 814, Subpart H) provide an expedited regulatory pathway for the development of IVDs for rare diseases (fewer than 4000 patients per year tested).
 - The AACR agrees with the FDA that LDTs that would test greater than 4,000 patients per year do not qualify as HUDs, even if prevalence of that disease is below 4,000 patients per year.
 - Section 564 of the FFDCA (21 U.S.C. 360bbb-3) permits the FDA to authorize the use of an unapproved medical device in the case of an emergency. The FDA recently issued an Emergency Use Authorization (EUA) for unapproved IVDs in diagnosing Ebola this past August. The AACR believes that the EUA policy works well for IVDs including LDTs that are needed for emergency needs.
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 AACR acknowledges that there will be challenges in implementing the new guideline for LDTs, but believes that the phased-in implementation plan proposed by the FDA, with initial action directed toward high-risk tests, is appropriate and reasonable.
 - The AACR does not believe that all current diagnostic tests should be “grandfathered” into the marketplace because of concerns involving clinical efficacy and patient safety.
 - Further, the AACR acknowledges the FDA’s efforts at ameliorating the challenges for laboratories during the transition period by proposing that laboratories will continue to be allowed to offer current LDTs during the pre-market review process, at least until the FDA completes its review of applications.
 - New LDT products should follow the IVDs pre-market guidelines⁶.

⁶ U.S. Food and Drug Administration. In Vitro Diagnostic (IVD) Device Studies – Frequently Asked Questions. <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM071230.pdf> Accessed Dec. 16th, 2014

11. What incentives can be put in place to encourage the development of new, more accurate or more efficient diagnostic tests?
- Ensuring the safety, reliability and accuracy of diagnostic tests is vital to safeguard patients, instill physician confidence in the validity of test results, advance personalized medicine and promote innovation.
 - Having a predictable and reliable regulatory environment is important to encourage an innovative biomedical ecosystem in the United States.
 - Implementing a single, strict regulatory pathway through the FDA will help reassure clinicians, patients and the public that the tests used to make treatment decisions are safe, accurate and effective.
 - Implementation of a risk-based framework by the FDA that would provide for the evaluation of all high risk and certain moderate risk molecular diagnostic tests would balance the importance of encouraging innovative medical product development with the need for ensuring patient safety.

We would like to take this opportunity to once again thank the subcommittee for recognizing the importance of LDTs in our health care system, especially in the delivery of modern cancer care, and for taking the initiative to examine the FDA's proposal to phase-in a risk-based oversight framework for LDTs. The AACR is pleased to extend its resources and broad expertise to you and your colleagues as you consider further action on this matter. If you have any further questions or require follow up, please contact Rasika Kalamegham, PhD, Director, Regulatory Science and Policy at 267-765-1029 or rasika.kalamegham@aacr.org.

Sincerely,



Margaret Foti, PhD, MD (hc)

Chief Executive Officer

American Association for Cancer Research

Clinical Cancer Research



Reliable and Effective Diagnostics Are Keys to Accelerating Personalized Cancer Medicine and Transforming Cancer Care: A Policy Statement from the American Association for Cancer Research

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Policy Statement

Reliable and Effective Diagnostics Are Keys to Accelerating Personalized Cancer Medicine and Transforming Cancer Care: A Policy Statement from the American Association for Cancer Research

Charles L. Sawyers¹ and Laura J. van 't Veer²

Diagnostics are enabling physicians to make more informed treatment decisions by tailoring treatments based on each patient's unique molecular profile. Diagnostics are also an increasingly vital tool for translating the state-of-the-art advances made in basic research into improved clinical outcomes for patients. Some of the most exciting scientific advances of our time—genomics, proteomics, and other "omics" technologies—are propelling the development of novel, rapid, sensitive, less invasive, and more accurate molecular diagnostic tests, which in turn is dramatically improving our ability to detect and treat various cancers earlier and with greater precision.

Diagnostics Are Integral to the Practice of Personalized Medicine

The goal of personalized medicine is to customize healthcare to fit the needs of the individual—with medical decisions, practices, and products tailored to the specific patient. Personalized therapies for cancer are rapidly increasing in number, as exemplified by drugs such as crizotinib (1) for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a specific rearrangement of the *ALK* gene, and vemurafenib (2) for patients with late-stage melanoma whose tumors carry the V600E mutation in the *BRAF* protein. These new drugs, sometimes referred to as targeted therapies, are designed to target specific mutations or genes in a patient's tumor.

The success of personalized medicine treatments, therefore, depends on accurately identifying patients with a particular mutation before treating them. In fact, the U.S. Food and Drug Administration (FDA) approves targeted therapies along with a diagnostic tool (called a *companion diagnostic*), which provides physicians with information that is essential for the safe and effective use of the therapy (3). More specifically, drugs that are effective in a specific subpopulation of patients are approved with the stipulation that the corresponding diagnostic test must be used to identify the appropriate patients for treatment. Thus, it follows that the diagnostic tools used to detect the

molecular alterations that form the basis of tailored cancer treatments are crucial for the safe and effective practice of personalized medicine. This further underscores the importance of ensuring the accuracy and reliability of these diagnostic assays that physicians and clinicians utilize when making medical decisions.

Recognizing the central role of diagnostics tests to current cancer care, on October 29, 2013, the American Association for Cancer Research (AACR) and AdvaMedDx (4) organized a symposium on "*Transforming Cancer Care through Diagnostics and Personalized Medicine* (5)". The purpose of the symposium was to highlight the importance of diagnostics in improving care for cancer patients and to call attention to some of the scientific, regulatory, and policy issues that are central to ensuring a thriving molecular diagnostics industry (see box). The audience of more than 300 people comprised a diverse group of stakeholders, including researchers, clinicians, patients and patient advocacy leaders, drug and diagnostic industry representatives, regulators, and policymakers.

FDA Regulation to Ensure the Reliability and Safety of Molecular Diagnostics

It is widely recognized that the process of seeking approval from the FDA for a diagnostic test is grounded in sound scientific evidence that physicians can rely on for clinical decision-making. Tests developed by a manufacturer and sold to laboratories (often referred to as test "kits") must go through rigorous pre-market analysis, evaluation of its safety and effectiveness, and an approval or clearance process from the FDA before it can be marketed. These test kits are also subject to post-market oversight, including mandatory adverse event reporting and the FDA's recall authority.

The FDA typically assesses and evaluates diagnostic tests on the following three measures (6):

- *analytic validity* to ensure the accuracy, sensitivity, specificity, and reproducibility of the test;
- *clinical validity* to demonstrate that the results of the test are linked to a biological function or a specific disease state of interest (e.g., presence of the V600E mutation in the *BRAF* gene is associated with aggressive melanoma); and
- *clinical utility*, if applicable, to demonstrate whether use of the information obtained from the test improves patient

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Highlights from the October 29, 2013, AACR-AdvaMedDx symposium "Transforming Cancer Care through Diagnostics and Personalized Medicine"

- AACR president and chair of the symposium planning committee, Charles L. Sawyers, MD, noted that the goal for the day was to discuss how to most effectively utilize and speed the translation of information gleaned from investments in basic research into commercial diagnostic products that result in more tailored treatments and better patient outcomes for cancer patients.
- In his opening keynote, National Cancer Institute Director and Nobel laureate Harold E. Varmus, MD, talked about the importance of molecular diagnostics and noted how crucial they are to tailoring therapies to patients based on the unique molecular signatures of their cancers. He stressed the need to incentivize development of validated and accepted diagnostics in order to keep pace with the explosion of new, targeted cancer drugs that are in the pipeline.
- During a special lunchtime conversation, National Institutes of Health Director, Francis S. Collins, MD, and Commissioner of the U.S. Food and Drug Administration, Margaret A. Hamburg, MD, were enthusiastic about the promise of new "omics"-based technologies to comprehensively examine the entire genome of patients, leading to improvements in patient care. They also emphasized the need to optimize and align the scientific enterprise and the regulatory framework for these technologies of the future.
- Commissioner Hamburg stressed that regulating these complex medical products (including companion diagnostics) and coordinating their review and oversight in a manner that efficiently incorporates current regulatory science standards while upholding patient safety present unique challenges, such as requiring the Agency to rethink its approach to clinical trial design; scientific computing; data mining etc. The Agency's new approach to regulating these products cuts across regulatory frameworks and involves multi-disciplinary, cross-collaborative review, she said.
- Dr. Collins predicted that the coming era of whole genome sequencing would soon eclipse our current system of examining just one or a few genes at a time to decide on a treatment course for a patient. He cautioned, however, that whole-genome sequencing presents new ethical and regulatory challenges, such as defining risk and addressing how health care providers should approach incidental findings, which is genetic information discovered unintentionally.
- The Director of the Coverage and Analysis Group at the Centers for Medicare and Medicaid Services, Louis B. Jacques, MD, stressed the need for transparency and unbiased review of tests and mentioned that having a third-party reviewer like the FDA's stamp of approval reassures payors of the utility of tests. During a discussion about valuation of these tests, he suggested that superior tests could realize better value if reimbursement decisions were linked to evidentiary standards that recognize meaningful performance differences between tests.

treatment and management of the disease and how well it relates to the clinical outcome of interest, such as increased survival or a positive response to the drug (e.g., melanoma patients with the BRAF V600E mutation are more likely to benefit when treated with the drug vemurafenib).

Laboratory-Developed Tests—A Vastly Different Regulatory Standard for Molecular Diagnostics

There are also many molecular diagnostic tests that are currently available to physicians but have not undergone an FDA review and approval process. This is because molecular diagnostic tests can ultimately reach the marketplace (and be utilized by the physician and patient) through an alternative to the FDA review and approval process.

This alternative involves laboratory-developed tests or LDTs, which are tests that are designed, manufactured, and offered within a single laboratory. Currently, LDTs are not required to obtain FDA approval before marketing as long as they are designed, manufactured, and used in a single laboratory that meets the Clinical Laboratory Improvement Amendments (CLIA) certification requirements (7). The standards for CLIA certification of a laboratory and CLIA

requirements for offering a non-FDA approved test are very different from FDA approval of a test, particularly because CLIA oversight does not assess or evaluate the safety and/or clinical efficacy of a test. Therefore, an LDT developed in a CLIA-certified laboratory can be utilized by a physician to make treatment decisions without any independent verification of the test's clinical validity or utility.

The FDA's Evolving Position on Exercising Enforcement Discretion over LDTs

While the FDA has authority over all diagnostic tests, the agency had historically chosen not to enforce its authority in the case of LDTs (8). The FDA chose not to exercise its regulatory authority in the past largely because LDTs were typically well-established diagnostic test procedures [e.g., urine analysis, microbiology cultures, blood analysis. (9)]. However, some LDTs being developed today run the risk of being ineffective and exposing patients to inappropriate clinical decision-making if they are not subject to the same scrutiny given to FDA-approved tests (10). Examples include germline DNA tests that claim to predict the likelihood for developing certain cancers or their clinical outcome, and LDTs offered and used *in lieu* of FDA-

approved companion diagnostic tests to identify specific tumor mutations and channel patients toward treatment with targeted therapies. Tests are typically classified as "high-risk" if the test result will directly determine the course of treatment offered (or not) to the patient. Yet these LDTs are widely considered as equivalent to FDA-approved diagnostic tests, and physicians, patients, and payors are often unaware of the regulatory review status of the specific test (FDA-approved test or LDT) being used. The FDA has recently informed Congress of its intent to regulate LDTs using a risk-based, phased-in approach to ensure the safety, accuracy, and reliability of test results used to make treatment decisions by physicians and patients (9).

AACR Policy Statement—Balancing Innovation with Safety by Adopting a Risk-Based Regulatory Framework

In vitro diagnostic tests can be used to determine the likelihood of developing cancers, screen for cancers, gain information about existing cancers, predict the likelihood of recurrence of certain cancers, predict a patient's response and tolerance for treatments, predict patient benefit, estimate side effects, and monitor patients while they undergo treatment. Therefore, the AACR believes it is imperative that all diagnostic tests used to make high-risk treatment decisions, including the tailoring of an individual's cancer treatment regimen, must be FDA-approved to ensure that these diagnostic tests are held to the highest regulatory and approval standards. Having a single, strict, regulatory approval standard would reassure the public that the tests used in high-risk health care decision-making, whether developed by a laboratory or other manufacturer, are safe, accurate, and effective.

Diagnostic tests are evolving to become more complex. These tests are not only technically challenging to perform, but also return results that are complicated to interpret. Further, clinicians are increasingly relying on these complex test results to make treatment decisions. Therefore, patients and physicians should be able to rely on the test results that are forming the basis of high-risk treatment decisions, whether these tests are developed as an LDT or are kits

approved by the FDA. Implementation of a risk-based framework by the FDA that would provide for evaluation of all high-risk molecular diagnostic tests would balance the need for encouraging innovative medical product development with the need for ensuring patient safety. A focus on high-risk tests would also help channel the FDA's limited resources toward those products that pose the greatest health risks for patients. Having a predictable and reliable regulatory environment is important for patients and for diagnostic and drug developers, since the success of a targeted therapy is inextricably linked to the successful development of its companion diagnostic test. Therefore, a single regulatory standard for high-risk diagnostic tests is key to ensuring the safety and efficacy of molecular diagnostic tests.

Recognizing the importance of reliable and safe diagnostics to propel continued innovation of personalized cancer treatments, the AACR has convened a diagnostics guiding principles committee that includes stakeholders from academia and industry to offer policy proposals that will accelerate development of innovative diagnostics by advocating for a more predictable regulatory (and investment) climate for the industry, while simultaneously ensuring patient safety. When a test provider claims that evidence-based information can be used to associate a patient's tumor biomarker status to treatment agents with potential clinical benefit (or lack thereof), physicians and patients should be able to proceed with confidence.

Disclosure of Potential Conflicts of Interest

L.J. van 't Veer is a co-founder, stockholder, and part-time employee of Agendia Inc. C.L. Sawyers is a co-inventor of patents on drug resistance mutations in BCR-ABL, filed by the University of California Los Angeles and licensed to Housey Pharmaceuticals.

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July 22, 2014
Division of Dockets Management
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2014-D-0363 "Expedited Access for Premarket Approval Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Disease or Conditions"

To whom it may concern:

On behalf of the American Association for Cancer Research (AACR), the oldest and largest scientific organization in the world dedicated to the prevention and cure of cancer through research, education, communication and collaboration, we sincerely thank the U.S. Food and Drug Administration (FDA) for the opportunity to provide comments in response to the April 2014 draft guidance on "Expedited Access for Premarket Approval Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Disease or Conditions."

The AACR applauds the FDA for developing a draft guidance outlining a new, voluntary program to help patients have more timely access to life-saving medical devices including *in-vitro* diagnostic devices. There are, however, a few areas in which we believe additional guidance would be beneficial. Specifically, the AACR requests FDA to provide greater clarity and detail on the definition of "breakthrough technologies", acceptable post-approval studies, alternative mechanisms of evidence gathering, use of surrogate end points, use of the EAP pathway in conjunction with other expedited pathways for medical products and the logistics of implementing this ambitious new program in a potentially resource constrained environment among other issues. We have elaborated on these concerns below.

With these additions, we believe the guidance document will clarify the pathway to expedite development and approval of novel medical devices intended to fulfill an unmet medical need for life threatening diseases like cancer and create new hope for cancer patients worldwide.

Pathway nomenclature

The pathway as currently named is the “Expedited Access PMA” or EAP pathway. We would like to draw the Agency’s attention to an existing pathway that shares this exact acronym namely the “**E**xpanded **A**ccess **P**rogram” (EAP) which allows patient access to experimental drugs outside a clinical trial through a single patient Investigational New Drug (IND) mechanism. To avoid confusion, we suggest the Agency rename the pathway the “**Accelerated Access Pathway**” or AAP. As the draft states, the proposed new pathway is based in part on existing expedited development programs at the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), namely the Accelerated Approval pathway for drugs and biologics. Thus, we urge the Agency to consider AAP as a viable alternate name for the pathway since it would be parallel and analogous to the mechanism and nomenclature of the existing pathway for drugs and biologics and would help avoid confusion.

Explicitly define “breakthrough technology”

The draft guidance states that a product may qualify for the Expedited Access PMA or EAP designation if “*The device represents a breakthrough technology that provides a clinically meaningful advantage over existing technology*”.

It would be helpful if the Agency could clarify what it means by a “breakthrough technology”. For example, could an assay based on existing and commonly used technology (such as immunohistochemistry) be considered breakthrough if it provided a clinically meaningful advantage when used with a highly effective therapeutic?

Multiple *in vitro* diagnostic devices or IVDs could be developed using a breakthrough technology such as next generation sequencing or NGS technology. In such a case, the Agency should clarify whether all IVDs that utilize the same underlying cutting-edge technology, such as NGS, could qualify for the EAP designation or whether the designation could only be given to the first application of the technology.

Further technology is constantly evolving and what is considered innovative today will eventually become a routine and common procedure. Therefore, it would help if the Agency could provide some broad, high-level guidelines on its thinking about how it would define and designate a “breakthrough technology”.

Provide clarity on the implementation of the EAP pathway

The draft states that “*FDA may approve more than one EAP device for the same condition because of the possibility that the data from the post-approval study may not*

confirm certain safety or effectiveness aspects of the device under the conditions of use. FDA may therefore consider devices as offering a “significant, clinically meaningful” advantage over existing approved alternatives, notwithstanding the availability of an EAP Device approved on the condition of a post-approval study.”

It would be helpful if the Agency could elaborate on how it would interpret and implement this section of the guidance. For example, a plausible scenario is as follows: two products receive EAP designation for the same condition and one product gains approval before the other.

This above situation raises several questions including but not limited to the following:

- Would the second EAP designated product subsequently have to demonstrate evidence of “*significant, clinically meaningful advantage*” over the first EAP designated product?
- Would the details of the data development plan change for the second EAP designated product, even if previously agreed upon by both the sponsor and the Agency?
- If so, would the Agency continue to work with the sponsor to aid in revising the data development plan? and
- Would the burden of proof for demonstrating *significant, clinically meaningful advantage* differ from proving safety and effectiveness?

With respect to the concern that the “...*data from the post-approval study may not confirm certain safety or effectiveness aspects of the device...*”, it would be helpful if the Agency could clarify whether this would result in a “revision” to a specific aspect of the device in question or whether it would entail something more. For example, perhaps a cutoff value for a biomarker based *in vitro* diagnostic assay would change based on data obtained in the post-marketing setting which may necessitate recalibration of the device. It would also help if the Agency could elaborate on how the data obtained from post-approval studies would be used to refine or revise the product in the post-marketing setting including the logistics of informing the sponsor of changes to the product, ensuring implementation of these changes while the product is on market, timeline for implementation of changes etc.

Clarify use of EAP pathway in conjunction with existing expedited pathways for approval of drugs and biologics

The EAP draft guidance states that “...*certain companion diagnostics, when appropriate, and with consultation from CDER or CBER, may be considered for the Expedited Access PMA. For example, if a drug is reviewed via the accelerated drug approval pathway based on a surrogate endpoint, the companion diagnostic may be considered for the Expedited Access PMA.*”

We welcome the Agency’s willingness to consider a companion diagnostic for the EAP designation if its corresponding therapeutic partner is granted expedited review via the accelerated approval pathway. However, the Agency should clarify the status of the companion diagnostic in a situation wherein the therapeutic product fails its confirmatory study since an investigational drug or biologic is granted accelerated approval on the condition that the sponsor will conduct post-market confirmatory studies and with the understanding that the Agency has authority to withdraw approval for the drug or biologic if the confirmatory studies fail to meet the appropriate clinical end point. We also request that the Agency provide more details on the processes and procedures whereby sponsors can coordinate filing requests for accelerated approval of the therapeutic product and the EAP designation for its companion diagnostic.

Given that the recent “Breakthrough Therapy designation” has provided a great opportunity to expedite approval of therapies especially in oncology, the Agency should clearly state whether companion diagnostics to Breakthrough Therapy designated products may also be considered for the Expedited Access PMA. Further, given that most oncology therapies under current development are targeted therapies with a companion diagnostic, the Agency may want to consider automatically granting EAP designation to the companion diagnostic of breakthrough designated and accelerated approval pathway products.

Provide greater details on acceptable post-marketing studies

The EAP program will rely heavily on post-marketing studies to provide additional evidence of the safety and efficacy of the device. However, the guidance fails to give details of situations or examples of post-market studies that may be appropriate. We note that the Agency has released draft guidance on *Balancing Premarket and Postmarket*

Data Collection for Devices Subject to Premarket Approval¹ in which there is one example of a situation where postmarket data collection may be appropriate for an IVD.

“Example: HPV testing devices have two distinct intended use populations with inherently different risk levels for cervical pre-cancer and cancer. Approval for both populations was based on full analytical data and agreement of clinical samples against a valid comparator, and clinical evidence of safety and effectiveness for the high risk population. A post-approval study assessed the longitudinal risk of cervical cancer in the population with lower risk.”

However, given the diversity of IVD products it would be helpful for the Agency to give more examples of situations where post-market data studies would be appropriate for an IVD seeking EAP approval. It would also be helpful if the Agency could provide details on what kinds of information can be relegated to post-market studies by sponsors who are planning to file for an EAP designation. In other words, it would be helpful if the Agency could clarify whether they are primarily interested in collection of serious adverse effects or long-term safety or product effectiveness etc.

The draft states that “...FDA may require a bridging study to evaluate the potential impact of various changes (e.g., specimen processing or storage, device or software modifications) on analytical and clinical performance.”

The Agency should clarify whether these bridging studies should be conducted in the pre or post marketing setting. We also refer the Agency to our concerns about interpretation of data from post-approval studies not confirming certain safety or effectiveness aspects of the device detailed earlier in this comment letter. We request the Agency to clarify whether bridging studies can be carried out and/ or may suffice in cases where post-approval studies raise concerns about the quality of a product.

Establishing safety and efficacy of IVDs requires establishing not just analytic and clinical validity, but most importantly clinical utility. Collecting clinical utility data often involves conducting clinical studies which can be expensive and time consuming. The

¹ Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval: FDA Draft Guidance issued on April 23, 2014.
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM393994.pdf>

draft guidance, however, does not mention collection of clinical utility data. Therefore, it would be helpful if the Agency could clarify whether clinical utility data may be collected in the post-market setting if the IVD qualifies for an EAP designation and elaborate on how data collection in the post-market setting should be implemented.

Provide greater detail on acceptable evidence

The draft states that *“In the absence of a new prospective clinical study, FDA may in some cases accept alternative experimental designs unique to diagnostics to generate evidence demonstrating the analytical and clinical validity of an IVD for premarket approval.”* One of the examples given is: *“In cases where the clinical validity of a biomarker test may be fully established in the literature, only analytical data that demonstrate a genetic test can accurately detect the variant may be necessary.”*

Given that studies in literature span the gamut from early observational studies to studies in validated animal models to reports of clinical trials, it would be helpful if the Agency could clarify, detail and elaborate on what level of evidence and what methodology of study constitutes *“fully established clinical validity of a biomarker test”* in the literature.

With respect to Companion Diagnostics, the draft states that *“In some situations (e.g. a test that combines multiple analytes into a score), a reference method may not exist for direct analytical comparison. In these instances, alternative approaches to address analytical performance may be appropriate.”*

We commend the Agency for including this forward-looking concept in the draft. However, it would be helpful if the Agency could provide concrete examples of methodologies and/or kinds of studies that would be acceptable “alternate approaches” to address analytical performance of IVDs and companion diagnostics. We acknowledge the difficulty of providing such comprehensive information *a priori*, therefore, we urge the Agency to provide as much detail and clarity as possible on this issue which is of great importance and concern to the field.

Clarity on the use of surrogate end points

The draft states: *“FDA may, as a basis for PMA approval, rely on assessments of a device’s effect on an intermediate or surrogate endpoint that is reasonably likely to predict clinical benefit...”*

As an example, the draft provides the following: *“Early pathophysiologic analysis of biopsied breast lesions is not a direct measure of clinical benefit but has been shown to correlate with and predict morbidity and mortality associated with breast cancer. Pathophysiological analysis of biopsied breast lesions could serve as a surrogate endpoint for device trials, provided there is sufficient evidence of a known or reasonably likely predictive relationship with clinical benefit such as survival.”*

It would be helpful if more examples of acceptable surrogate and intermediate endpoints could be provided. It would also be helpful if the Agency could provide details of currently accepted surrogate and/or intermediate endpoints for approval of IVDs and companion diagnostics especially in oncology. The Agency should also clarify the conditions as well as the process by which a sponsor could use a novel surrogate or intermediate end point to provide evidence of a device’s efficacy and/or safety.

An important consideration for researchers and developers of oncology products is the use of surrogate end points to qualify a therapeutic and its companion diagnostics. We request the Agency to clarify whether the “clinical benefit” of a companion diagnostic demonstrated using a surrogate end point or otherwise, will be judged or considered independently of its corresponding therapeutic product.

Logistics of implementing the EAP program

The draft states that *“As part of this EAP program, FDA intends to provide, **as resources permit**, more interactive communications during device development and more interactive review of Investigational Device Exemption (IDE) applications and PMA applications. In addition, FDA intends to work interactively with the sponsor to create a data development plan specific to the device (“Data Development Plan”). This Data Development Plan should outline all data the sponsor intends to collect in support of device approval, including what data will be collected premarket and postmarket.”*

We enthusiastically welcome the Agency’s willingness to consider a pathway to expedite development of life-saving medical devices. However, it is concerning that the Agency uses the phrase **“as resources permit”** to qualify its ability to provide more interactive communications. It would be helpful if the Agency could elaborate on its thinking around how it plans to implement this exciting new, albeit potentially resource intensive program. We specifically request that the Agency clarify the meaning and intent behind the phrase **“as resources permit”** and elaborate on how it plans to determine whether it has adequate resources to man the program and further whether and how it plans to

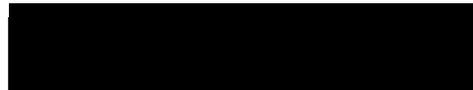
communicate its resource availability to researchers and developers who wish to avail themselves of the EAP program. Of concern to us is, whether the Agency can deny a potential EAP designation to a product that fully merits the designation, solely on the basis of a lack of Agency resources. This also leads to a concern that EAP designations will be limited by the Agency's resource constraints or EAP designations will only be considered when and if the Agency decides it can spare adequate resources, which we acknowledge may fluctuate from time to time. The question of resource availability also poses concerns about the Agency's ability to work with sponsors on the "data determination plan" which is a central and crucial component of obtaining the EAP designation. Since the main advantage to sponsors granted the EAP designation is the ability to work with the Agency to create the Data Development Plan and have interactive communications during product development, it is unclear how a sponsor may benefit from the EAP designation if the Agency grants the designation, but subsequently decides it is resource constrained and therefore cannot offer the above benefits to the sponsor.

The AACR commends the FDA for its commitment to incorporating scientific advances into its regulatory framework. The AACR is pleased to extend its resources and broad expertise to the FDA as the Agency further considers revisions to the April 2014 draft guidance on "Expedited Access for Premarket Approval Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Disease or Conditions". If you have any further questions or require follow up, please contact Rasika Kalamegham, PhD, Director, Regulatory Science and Policy at 267-765-1029 or rasika.kalamegham@aacr.org.

Sincerely,



Frank McCormick, PhD, FRS
Chair, Regulatory Science & Policy
Subcommittee



Margaret Foti, PhD, MD (h.c.)
Chief Executive Officer



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

**Testimony Before
Committee on Energy and Commerce
Subcommittee on Health
United States House of Representatives**

Charles L. Sawyers, MD

Immediate Past President of the AACR

Chair, Human Oncology and Pathogenesis Program

Memorial Sloan Kettering Cancer Center

New York, NY

September 9, 2014

21st Century Cures: Examining the Regulation of Laboratory

Developed Tests

Testimony of Charles L. Sawyers, MD, Chair, Human Oncology and Pathogenesis

Program, Memorial Sloan Kettering Cancer Center

Good morning, Mr. Chairman and distinguished Members of the Subcommittee. I am the immediate past president of the American Association for Cancer Research (AACR), and serve as Chair of the Human Oncology and Pathogenesis Program at Memorial Sloan Kettering Cancer Center. I am honored to appear before you today to provide you with a perspective from the AACR on the recent notification offered by the Food and Drug Administration regarding the regulation of Laboratory Developed Tests (LDTs). Specifically, I will address the ways in which we believe this potential framework for regulatory oversight will protect patients, incentivize innovation, and advance the practice of personalized or precision medicine.

The mission of the AACR is to prevent and cure cancer through research, education, communication, and collaboration. Founded in 1907, the AACR is the world's oldest and largest cancer organization dedicated to accelerating advances in cancer research to benefit patients.

The AACR's membership includes more than 35,000 basic, translational, and clinical researchers, health care professionals, patients and patient advocates residing in the U.S. as well as 96 other countries.

Because the AACR encompasses the entire continuum of cancer research and biomedical science – from the laboratory to the clinic including public policy – we are able to marshal the full

spectrum of expertise in the cancer community to accelerate progress in the prevention, detection, diagnosis, and treatment of cancer.

Cancer researchers today are leading the way in the exciting area of personalized or precision medicine, where scientists are increasingly developing treatments that are precisely targeted to the unique molecular and genetic characteristics of an individual's cancer. However, the success of these personalized treatments depends in no small measure on diagnostic tests that are reliable.

The Promise of Personalized or Precision Medicine

The knowledge of cancer's underlying biological causes, enabled through sustained investment by the federal government, primarily through the National Institutes of Health, has catalyzed a shift from the classification of cancer by site of origin, like lung or breast cancer, to classification by molecular subtype. This means that we are rapidly moving away from the era of one-size-fits-all cancer treatments that involve surgery, radiation, and chemotherapy, and are instead utilizing more sophisticated and highly innovative DNA sequencing technologies to provide patients with more opportunities for targeted treatments and personalized or precision medicine. More and more, we are treating cancer patients based on the specific molecular characteristics of his or her tumor(s), which is increasingly determined using highly complex DNA sequencing technologies. The promise of this approach is immense, and we are now ensuring that these advances are being applied to various forms of cancer with increasing speed and success.

I know the impact of molecularly targeted cancer therapy from firsthand experience, having led the first clinical trial of a drug called Gleevec that is highly effective in a form of blood cancer known as chronic myeloid leukemia. Patients with this formerly devastating disease now live for decades simply by taking a pill once a day that precisely targets the cancer cells. In fact, many of the patients I treated on the first clinical trial in 1999 are still alive and well today.

Since the approval of Gleevec in 2001, many additional targeted therapies have been developed and approved for a range of cancers; including previously deadly cancers -45 such personalized or precision medicines have gained FDA approval as of July 31 this year¹. The benefit of targeted cancer therapy is that we are able to hone in on specific mutations that drive the growth of a patient's tumor cells, thereby enhancing the chance of a successful treatment response without the side effects of chemotherapy or radiation. However, this sophisticated mechanism of action also means that these drugs are only effective in those patients whose tumors carry these mutations. Therefore, the success of these personalized or precision medicine treatments depends on accurately identifying patients with a particular mutation before treating them with the appropriately matched drug. This is why the sophisticated new diagnostic tests that enable physicians to match the right drugs to the right patients play such a critical role in cutting-edge cancer care.

Importance of Accurate and Effective Diagnostics in Cancer Care

That over 40 targeted cancer therapies have gained FDA approval over the past 10 years is a testament to the fact that we have a streamlined and effective regulatory process in the U.S. To ensure that the right patients receive a targeted drug, the FDA approves targeted therapies in

¹ US Food and Drug Administration. Hematology/Oncology (Cancer) Approvals; accessed on Sep. 5, 2014 <http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm>

conjunction with a diagnostic tool called a *companion diagnostic*, which provides physicians and patients with information that is essential for the safe and effective use of the therapy². Drugs that are effective in a specific sub-population of patients are approved with the stipulation that the corresponding diagnostic test must be used to identify the appropriate patients for treatment. Thus, it follows that the diagnostic tools used to detect the molecular alterations that form the basis of tailored or personalized cancer treatments are crucial for the safe and effective practice of personalized medicine. A safe, reliable, accurate, and sensitive diagnostic test is as important as a safe, reliable, and effective drug.

Different Paths to Market for Diagnostics

In contrast to the single regulatory path to market for drugs, there are two very different paths to market for a diagnostic³. The first path is by gaining approval or clearance from the FDA which requires a sponsor to demonstrate proof of analytic and clinical validity as well as clinical utility of the test in some cases. *This is the path by which companion diagnostics are currently approved, in conjunction with approval of a targeted therapy.* The second path to market is when a test developer designs, manufactures and offers the test within a single laboratory as a laboratory developed test or an LDT. Because LDTs are not subject to the same level of scrutiny as diagnostics approved through the first regulatory path, there is less certainty and confidence in the accuracy of these products. This is particularly relevant for the highly sophisticated DNA sequencing technology based tests that generate the information from tumor cells that form the basis for many companion diagnostic tests.

² US Food and Drug Administration. List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools); accessed on Sep. 5, 2014

³ Sawyers CL, and van 't Veer, LJ. Reliable and Effective Diagnostics Are Keys to Accelerating Personalized Cancer Medicine and Transforming Cancer Care: A Policy Statement from the American Association for Cancer Research. Clin Can Res; Published Online First September 9, 2014; doi: 10.1158/1078-0432.CCR-14-2295.

For a cancer patient, the consequences of an incorrect treatment recommendation made on the basis of a faulty diagnostic test are unacceptable, since the patient may lose the opportunity to receive an effective treatment or may be exposed to side effects from a treatment that has little to no chance of benefit. Physicians and patients must be able to trust the claims made by developers of health care products, especially products that determine the treatment regimen for a cancer patient.

A Single Regulatory Standard to Ensure Patient Safety and Reliability of Diagnostics

Given the importance of diagnostic tests to personalized cancer treatments, the AACR believes it is imperative that all diagnostic tests used to make high-risk treatment decisions, including the tailoring of an individual's cancer treatment regimen, must be FDA-approved to ensure that these diagnostic tests are held to the highest regulatory and approval standards⁴. Having a single, strict regulatory approval standard will reassure the American public that the tests used in high-risk health care decision-making, regardless of origin, are safe, accurate, and effective.

The FDA's Proposed Framework for Regulatory Oversight of LDTs

The AACR welcomes the recent notification to Congress by FDA of its intent to phase-in a risk-based framework for regulatory oversight of laboratory developed tests⁵. We commend the FDA for taking a regulatory approach that puts patients first by proposing a classification of LDTs

⁴ Sawyers CL, and van 't Veer, LJ. Reliable and Effective Diagnostics Are Keys to Accelerating Personalized Cancer Medicine and Transforming Cancer Care: A Policy Statement from the American Association for Cancer Research. Clin Can Res; Published Online First September 9, 2014; doi: 10.1158/1078-0432.CCR-14-2295.

⁵ US Food and Drug Administration. Notification to Congress and Anticipated Details of the Draft Guidance for Industry, Food and Drug Administration Staff and Clinical Laboratories; Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs); accessed on Sep 5, 2014
<http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407409.pdf>

based on the risk posed by the test to the *patient*. We also note that the FDA plans to focus its efforts and appropriately utilize its resources by continuing to exert its policy of enforcement discretion over low-risk and routine laboratory procedures such as blood and urine analysis. As an organization of cancer scientists and physicians, we strongly support efficient and evidence-based regulatory policy making, and we look forward to doing the same with this proposal.

The proposed framework strikes a thoughtful balance between protecting patient safety while promoting research and innovation in this rapidly evolving field in the following ways:

- By prioritizing FDA's initial oversight efforts to ensure that high-risk LDTs undergo pre-market review to assess the accuracy and safety of the test especially when there is an FDA-approved/cleared equivalent currently on the market;
- By ensuring that this proposal will not adversely affect the ability of researchers at academic medical research centers to develop new tests or conduct clinical research;
- By ensuring that patient access to tests that have not yet undergone FDA review will not be obstructed in cases where there is not an equivalent FDA-approved or cleared test
- By requiring adverse event reporting of LDTs and
- By providing adequate time for laboratories and providers to be in compliance by phasing in the requirements over a period of nine years after the guidance is finalized.

Conclusion

Diagnostic tests are evolving to become more technically complex, and the complexity of these tests will only grow with the increasing use of next-generation sequencing or NGS-based tests. Further, clinicians are increasingly relying on these complex test results to make treatment

decisions. Therefore, patients and physicians should be confident in the test results that are forming the basis of high-risk treatment decisions, whether these tests are developed as an LDT or are kits approved by the FDA. Implementation of a risk-based framework by the FDA that would provide for evaluation of all high-risk molecular diagnostic tests would balance the need for encouraging innovative medical product development with the need for ensuring patient safety. Having a predictable and reliable regulatory environment is important for patients and for developers of diagnostic and drugs, since the success of a targeted therapy is inextricably linked to the successful development of its companion diagnostic test. Therefore, a single regulatory standard for high-risk diagnostic tests is crucial to ensuring the safety and efficacy of molecular diagnostic tests and the key to advancing personalized medicine. We are in the midst of an extremely promising age of innovative new cancer treatments. Genome sequencing and targeted treatments are revolutionizing the way we treat cancer patients and the way we develop cancer treatments. A robust, predictable, and reliable evidence-based regulatory framework will ensure that these 21st century cures will reach patients in an efficient and expeditious manner.

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About the American Association for Cancer Research

Founded in 1907, the American Association for Cancer Research (AACR) is the world's oldest and largest professional organization dedicated to advancing cancer research and its mission to prevent and cure cancer. AACR membership includes more than 35,000 laboratory, translational, and clinical researchers; population scientists; other health care professionals; and cancer advocates residing in more than 90 countries. The AACR marshals the full spectrum of expertise of the cancer community to accelerate progress in the prevention, biology, diagnosis, and treatment of cancer by annually convening more than 20 conferences and educational workshops, the largest of which is the AACR Annual Meeting with more than 18,000 attendees. In addition, the AACR publishes eight peer-reviewed scientific journals and a magazine for cancer survivors, patients, and their caregivers. The AACR funds meritorious research directly as

well as in cooperation with numerous cancer organizations. As the scientific partner of Stand Up To Cancer, the AACR provides expert peer review, grants administration, and scientific oversight of team science and individual grants in cancer research that have the potential for near-term patient benefit. The AACR actively communicates with legislators and policymakers about the value of cancer research and related biomedical science in saving lives from cancer. For more information about the AACR, visit www.AACR.org.



January 5, 2015

The Honorable Fred Upton
Chairman
Energy and Commerce Committee
U.S. House of Representatives
2125 Rayburn Building
Washington, DC 20515

The Honorable Diana DeGette
Member
Energy and Commerce Committee
U.S. House of Representatives
2125 Rayburn Building
Washington, DC 20515

Dear Chairman Upton and Representative DeGette:

The American College of Medical Genetics and Genomics (ACMG) welcomes the opportunity to comment on the questions and issues raised in the course of your work on the 21st Century Cures Initiative, and specifically how to ensure access to innovative clinical tests. Our primary interest relates to the rapidly evolving capabilities in genetic and genomic testing that are going to continue to transform health care over the next decade. In the eyes of many consumers—and your constituents—the genetic and genomic revolutions are here and they have captured great interest and enthusiasm in the promises of personalized medicine. As such, we request that any proposals put forward by the Committee distinguish between genetic from other testing, allow for the development of innovative solutions in the genetic testing arena, and not subject genetic testing to any Laboratory Developed Test (LDT) requirements that the Committee may be considering.

About ACMG: ACMG is the only nationally recognized medical organization dedicated to improving health through the practice of medical genetics and genomics. ACMG has over 1750 members, nearly 80% of which are board certified clinical and laboratory geneticists and genetic counselors. The College's mission includes the following major goals: 1) to define and promote excellence in the practice of medical genetics and genomics and to facilitate the integration of new research discoveries into medical practice; 2) to provide medical genetics and genomics education to fellow professionals, other healthcare providers, and the public; 3) to improve access to medical

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genetics and genomics services and to promote their integration into all of medicine; and 4) to serve as advocates for providers of medical genetics and genomics services and their patients.

A Misalignment of Incentives— Genetic Tests are Different from LDTs: Very few genetic testing products have been cleared by FDA for clinical use, though some critical components of testing have been cleared as analyte specific reagents (ASRs). In fact, it is unusual for there to be an FDA cleared diagnostic genetic test. The great majority of guidance to providers and laboratories has been through the promulgation of standards and guidelines for testing and the development of educational programs by professional organizations, such as ACMG. Central influences leading to the limited role of manufacturers in the development of genetic testing have been the speed at which the field has grown, the vast amount of complex information underlying genetic and genomic medicine, and the limited experience and training of the great majority of clinical service providers. To the extent that there has been “regulation”, it has largely been through payer coverage policies for the past 30 years.

Getting Testing to Those in Need—The Challenges: The individual rarity of the 5,000 – 7,000 conditions with strong to moderately-strong genetic influences has largely been limited due to an imbalance between the incentives that drive industry to develop products for the diagnosis of rare diseases and their expected return on that investment. This is best highlighted by the contrasting outcomes of the Orphan Drug Act that protected and incentivized the development of treatments for rare diseases, and the impact of the Humanitarian Device Exemption that was directed at traditional device manufacturers and resulted in clinical laboratories developing Laboratory Developed Procedures that for 30 years have been the only means of ensuring access to rare disease diagnostics in the U.S. *Even designating genetic and genomic testing laboratories as manufacturers is more likely to result in limiting access to these innovative diagnostic tests than it is to ensuring their safe and effective use.* We urge the Committee to distinguish between LDTs and genetic testing, which warrants separate treatment to foster innovation, incentivize entrepreneurial focus and expand access to cures.

The ACMG is committed to ensuring that:

- Patients will have appropriate access to genetic tests available to diagnose the condition associated with their signs and symptoms.
- Physicians/clinicians will be able to order genetic tests that are medically indicated in their patients.
- Patients with genetic disorders will have access to clinical trials, which are promoted by clinicaltrials.gov and which typically require a patient to have genetic test results that confirm and characterize their disorder.

In light of this background, our responses to the Committee’s questions follow:

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 integration of genetic and genomic information into the clinical context of individuals or their families is complex and requires a unique base of knowledge and training. In 1992, the American Board of Medical Specialties (ABMS) recognized this by designating that the American Board of Medical Genetics and Genomics, as the only certification body for clinical and laboratory geneticists, be recognized as the 24th primary medical specialty board of medicine.

Most of the laboratory tests that are used in medicine produce results that stand on their own, without the need for expert interpretation to ensure their safe and effective use by providers. *Genetic and genomic tests fall into a group of high complexity tests based on recently acquired and rapidly evolving knowledge.* Furthermore, genetic testing is a process that includes not only the analytical phase but also pre-analytical and post-analytical components. Patient harms can occur in the pre-analytical phase (e.g., lack of education/counseling, disregard for the informed consent process, wrong test ordered) as well as post-analytically in the delivery of results and subsequent clinical follow-up. The pre- and post analytic phases of the genetic testing process are generally considered a part of the practice of medicine.

While genetic diagnostic laboratories have developed tests for several decades, to date, they have not been considered manufacturers or regulated as such. We support the status quo for this unique set of tests, urge Congress to clearly delineate general LDTs from genetic tests, and strongly recommend that the Committee decline to regulate genetic testing. To do otherwise would have extreme consequences for the laboratories and the patient care services they provide. Genetic tests are not typical testing devices and the current system for FDA regulation of devices cannot be applied to these tests. Instead, the majority of genetic tests are Laboratory Developed Procedures (LDPs), which should be the subject of a separate initiative outside the LDT process.

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?*

Many types of genetic tests that reflect the evolution of genetic information and new technologies are currently in use. They are used in germline genetic testing and somatic cancer based testing, and include tests that target specific types of variation for conditions like Down syndrome or acute leukemias to more open test platforms such as tandem mass spectrometry and genetic/genomic sequencing that provide a comprehensive look at potential contributors to a disease. What distinguishes genetic testing is that all tests are highly complex, particularly at the clinical level, and are overlaid on a rare disease backdrop in a system in which most non-genetics trained providers lack the training to independently manage genetic information.

The information gleaned from genetic tests can range from well-documented genetic variations to a private variation that is seen in only a single patient/family, requiring professionals to integrate gene and gene product laboratory data with clinical results in

order to interpret the final test result. The significant need for professional input to both the intended use of the platform or equipment used to perform the test and the clinical interpretation of the results of a disease/phenotype-specific test points to the need for the professional role in delivery of genetic tests.

Moreover, the field is undergoing rapid change in technologies from “traditional” targeted LDPs to genome-scale sequencing. Traditional LDPs are validated against disease/phenotype associations and the biological and pathological implications of the genetic change while newer technologies allow for the variation to be identified and subsequently evaluated to determining its likelihood of being associated with the disease/phenotype. For example, next generation sequencing (NGS) is performed by complex machines but must be interpreted by a medical genetics expert. This is analogous to medical imaging, where the equipment is regulated, but a physician interprets the images.

These examples clearly specify the importance of recognizing that genetic tests have a technical and a clinical component; and, while these are intrinsically linked, ACMG believes that FDA regulation of genetic tests as LDTs is inappropriate.

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?*

There are two types of risks to consider. Medical risks associated with a test involve the interventions to be pursued based on the test result and are relatively straightforward. However, in genetics, risks can be to individuals or families; prenatal or postnatal; germline or somatic. There are also non-medical risks that arise from the information itself and other risks that arise from the unknowns of new technologies and tests.

Our view is that laboratories must continue to innovate to bring new tests forward and that our current models of comparing the performance of the new technologies against the predicate technologies in a way that is specific to their intended use remains appropriate. As with all predicate technologies in genetics and genomics, the more difficult problem arises when information not previously available comes into play. It is critical that practice standards continue to evolve to guide development.

As to risk classifications, ACMG has a well-developed position. “We recommend that all clinical molecular genetic tests fall into either the moderate-risk or high-risk category. Tests that (i) do not utilize proprietary methods or algorithms, (ii) are amenable to inter-laboratory comparisons, and (iii) are evaluated by external proficiency testing should be categorized as moderate risk. Due to the potentially serious implications of an incorrect result or interpretation for the patient and the patient’s blood relatives, we recommend that all clinical molecular genetic test results be reviewed and interpreted by an individual certified in either Clinical Molecular Genetics (American Board of Medical Genetics and Genomics, ABMGG) or Molecular Genetic Pathology (American Board of Pathology/ABMGG). The professional interpretation of test results should be provided by

an individual certified in clinical genetics (ABMGG), clinical cytogenetics (ABMG), clinical molecular genetics (ABMGG), or molecular genetic pathology (American Board of Pathology/ABMG). In addition, we recommend that an ABMGG-certified clinical geneticist and/or American Board of Genetic Counseling/ABMGG-certified genetic counselor provide pre- and post-test counseling to patients, as necessary.”¹

In sum, we recommend that the Committee, and the FDA, recognize the distinct risk-based aspects of genetic testing, and that a new paradigm specific to such testing (and distinct from general LDT testing) be developed that both preserves both incentives for innovation an access to treatments while protecting against harms or risks.

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?*

All medical tests and procedures should be safe and effective whether they are through FDA cleared products, LDTs or LDPs, but how they are overseen must be different. Genetic and genomic tests have a distinct set of checks and balances in the existing oversight of the products used in testing that reduces the need for extensive oversight of the laboratory and clinical practices associated with testing. Particularly given that most genetic tests require professional clinical interpretation that ranges from associating the test result with the indications for testing to putting that result into the direct context of the medical and family history of the individual who is tested, a different paradigm from that applicable to LDTs is warranted. Aside from the medical risks, most other potential harms are best managed through professional responsibilities in the pretest and posttest environments. Decisions about which test to order and what the result means in an individual patient's context are clearly within the practice of medicine.

5. *Are there areas where the balance between pre-market review versus post-market controls should be reconsidered?* Premarket FDA review of genetic/genomic tests in the high-risk category remains appropriate, particularly when the results cannot be independently confirmed by a physician or when the actions to be taken based on the test results impart high medical risks. However, the biggest gap in genetic testing has been the over emphasis on privacy issues—particularly in the rare disease arena—which can harm patient access to cures, instead of prioritizing quality improvement (which requires bringing data together about those tested in order to improve interactions with future patients). Programs such as NIH’s ClinGen Resource Project aim to fill this void.

FDA, in partnership with CMS, should focus its efforts on developing “special” genetic testing controls by setting high standards for 1) the training, experience, and certification of personnel, 2) quality management of laboratories, and 3) collection of data that allows continuous quality improvement. Some aspects of this are already occurring under the CLIA and the CAP Proficiency Testing programs. However, we emphasize that the standards are completely different from those applicable to standard LDTs. We urge Congress to recognize the distinction in whatever policy recommendations it proposes.

How can post market processes be used to reduce barriers to patient access to new diagnostic tests?

Unlike LDTs in general, in the genetic testing arena the rarity and diversity of abnormal test results can often confound test interpretation and the development of clear treatment methods. The only remedy for this problem is to develop an organized approach to robust collection and aggregation of data about patients with similar results to inform test result interpretation. Directly put, only through the creation of large data sets will the best information be available to guide and improve clinical practices. Unfortunately, the very strict privacy laws in effect today have impeded the needed data collection efforts, resulting in deficiencies in the data that have led to ill-informed decisions (including those related to coverage). A system that utilizes third party review should be sufficiently nimble to move quickly as needs arise. Recognition by FDA of tests evaluated through third party review should facilitate payer coverage decisions.

The imposition of new “post-market” processes for genetic testing LDPs run the risk of increasing barriers to patient access. Of course, barriers such as workforce maldistribution, workforce pipeline issues, lack of physician and health professional proficiency in the application of genetic and genomic tests to patient care, and lack of reimbursement are the biggest hurdles to patient access. These are unrelated to FDA regulation, but remain under the jurisdiction of this Committee and worthy of further exploration and attention.

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?*

Genetic testing for rare diseases requires highly complex laboratory tests, and these tests should be held to high and specific standards that bring the experiences of all who care for these patients. As such, oversight bodies will need to consider how best to interface with information systems such as ClinGen that aggregate wide experience from the field. The industry has the ability to interpret test results (genetic variants) and will continue to improve with increased knowledge and databases like ClinGen.

7. *We have heard a lot about the practice of medicine and its relationship with medical product “labeling.” What should comprise “labeling” for diagnostic tests?*

An LDP is not a manufactured product. However, the platform on which testing takes place is. Labeling should address the analytical uses and the technical capabilities and limitations of the testing platform.

Should different standards for dissemination of scientific information apply to diagnostic tests versus traditional medical devices?

Most of the traditional medical devices used in genetics and genomics are LDPs which are also used in diagnosis and screening. Ultimately, national level databases are needed to inform clinical practice. Such databases have been developed in other contexts by HHS agencies, such as NIH. Rather than replicating this shared investment, FDA should develop mechanisms to tap into this rich public resource, already designed to aggregate

data and being continuously refined by the scientific community through their contributions and continuous, dedicated use.

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?

There are many types of devices and associated LDTs used in genetic and genomic testing. Information dissemination about the clinical uses and their potential harms and benefits are a part of the informed consent process done in the pretest phase and that communication is considered to be within the practice of medicine. We recommend against FDA regulatory oversight of the information that is provided to patients, although we strongly recommend that the genetic information provided to patients be appropriately masked and aggregated to expedite cures for rare and other diseases.

8. *The Section 1143 guidance documents raise important questions about the relationship between the FFDCRA 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 regulations 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?*

The great majority of the differences between quality systems regulations promulgated by FDA and aimed at classical manufacturers relate to the cost of the requirements. Good manufacturing practices requirements for manufacturers that are predicated on a company having found a business case to justify its development of products in a particular area allow companies to determine whether that business case justifies their entering a particular market. This leaves the obvious question of how clinical laboratories would be able meet such a standard. A diagrammatic representation of ACMG's proposed framework for the shared FDA/CLIA/Practice of Medicine oversight of genetic and genomic tests is attached as Figure 1. It highlights the need for a broad partnership to address the complexities of genetic and genomic medicine and its safe and effective delivery.

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. Ebola)?

We believe that rare disease applications of genetic testing should be considered procedures performed in clinical laboratories. The overwhelming majority of the 3,000+ genetic tests currently in use were developed in clinical laboratories, both private and academic. Clear exemptions to or latitude in regulatory requirements to protect innovation and rapid translation of new tests are necessary. For that reason, we urge the Committee to distinguish between general LDTs and genetic testing.

9. *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?*

Tests are services, not devices; a device (such as testing equipment or a platform) may be part of the service. As with prior changes to FDA oversight, existing “traditional” LDTs (low- to moderate-risk) would be ‘grandfathered’ into continued use. New targeted tests would be subject to premarket review through a third party review body that is jointly administered by FDA and CLIA. New genomic/proteomic/metabolomic technologies can be subjected to platform oversight by FDA and clinical oversight through CLIA rules and under the practice of medicine, but a separate regulatory oversight regime is needed to distinguish genetic testing from general LTD use.

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

Today’s health care system has not been well aligned with the needs of a learning health system that requires as much data as possible to drive improvement and monitoring. Current rapid movement from genetic testing (for single genes and mutations) to clinical genome-based testing will mitigate this issue because of the universal applicability of the platforms used.

Incentives to drug manufacturers have included tax breaks for R&D activities, acceptance of the limited test clinical performance data that can be provided, time-limited marketplace advantages, and exemption from LDT post-registration oversight rules. Incentives to support the clinical practice of genetic and genomic testing should be included in the Committee’s proposal, such as support of projects that seek to aggregate data from genetic testing to inform safety and clinical interpretation of test results.

The ACMG appreciates this opportunity to provide input to the 21st Century Cures Initiative of the U.S. House of Representatives’ Committee on Energy and Commerce, Health Subcommittee on these crucial issues. We would welcome the opportunity to discuss them in more detail with members of the Subcommittee and its staff. A copy of ACMG’s published risk categorization for oversight of laboratory-developed tests for inherited conditions is also attached.

Sincerely,



Michael S. Watson, PhD, FACMG
Executive Director

¹Monaghan KG, Benkendorf J, Cherry AM, Gross SJ, Richards CS, Sutton VR, and Watson MS; a joint working group of the Laboratory Quality Assurance and the Professional Practice and Guidelines Committees of the American College of Medical Genetics and Genomics. Risk categorization for oversight of laboratory-developed tests for inherited conditions. *Genet Med* 15 (4):314-315 (April 2013)

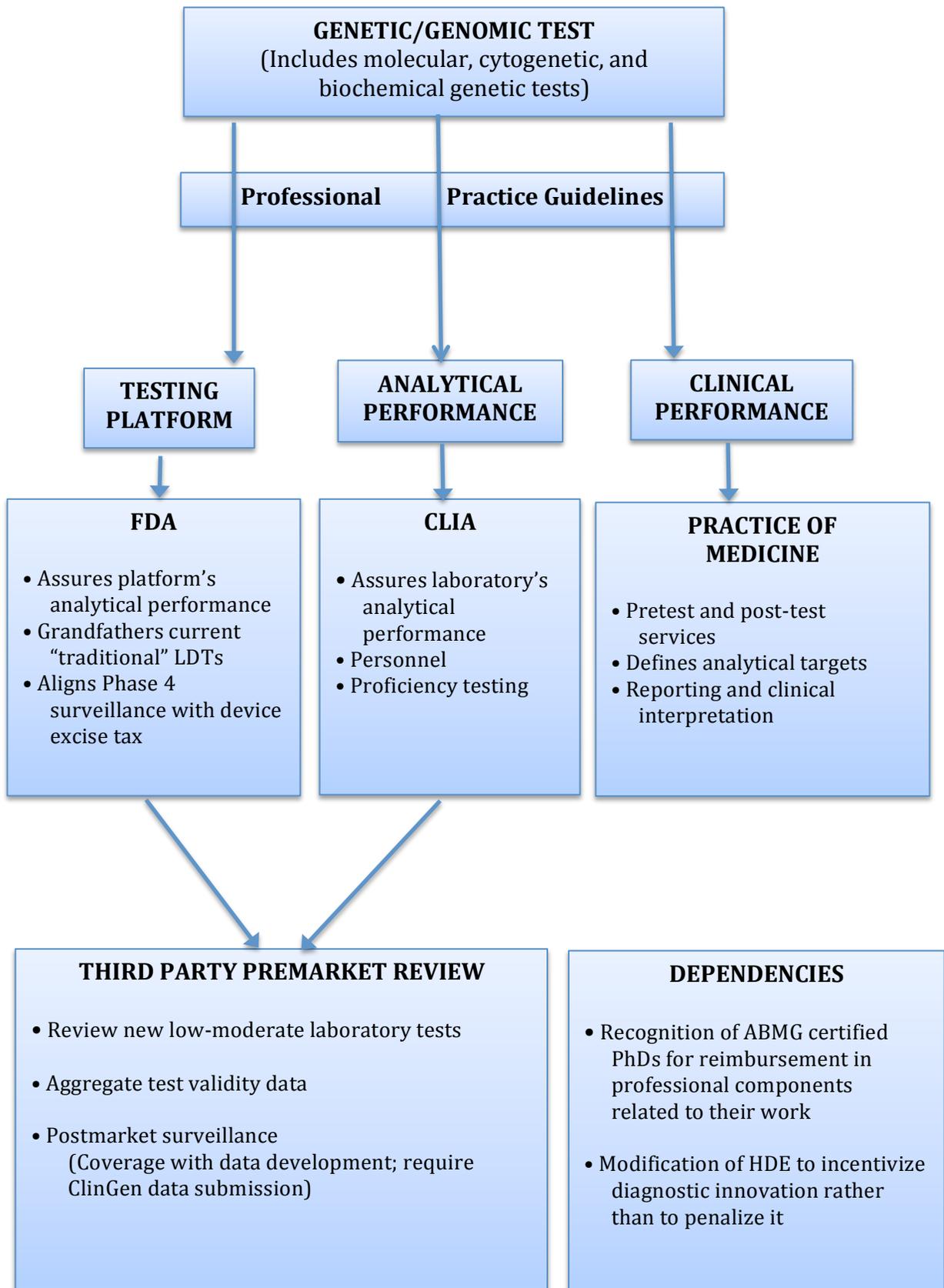


Figure 1: Proposed Framework for Oversight of Genetic and Genomic Testing

Risk categorization for oversight of laboratory-developed tests for inherited conditions

Kristin G. Monaghan, PhD¹, Judith Benkendorf, MS², Athena M. Cherry, PhD³, Susan J. Gross, MD⁴, C. Sue Richards, PhD⁵, Vernon Reid Sutton, MD⁶ and Michael S. Watson, PhD²; a joint working group of the Laboratory Quality Assurance and the Professional Practice and Guidelines Committees of the American College of Medical Genetics and Genomics

This document represents the proposed approach of the American College of Medical Genetics and Genomics (ACMG) to classify laboratory-developed tests for inherited conditions. Risk classification has been the determinant of whether or not medical tests are overseen and regulated by the US Food and Drug Administration (FDA). Therefore, because laboratory-developed tests for germline mutations continue to proliferate without sound regulatory frameworks in place, an

ACMG-appointed workgroup of laboratorians and clinicians considered the medical risks and implications resulting from germline mutation analysis in a variety of contexts to develop the proposed approach. It is expected that the expert opinion represented in this proposed classification system will be used to guide federal agencies, policymakers, and other stakeholders.

The ACMG has categorized testing for inherited conditions by utilizing the three-tiered risk-based system (Table 1), as

Table 1 ACMGs proposed approach to risk classification and oversight of laboratory developed tests for inherited conditions

Classification	Determining factors	Oversight recommendations
Low risk: the consequence of an incorrect result or interpretation is unlikely to lead to serious morbidity or mortality for patients or their offspring.	The test result is typically used in conjunction with other clinical findings to establish or confirm diagnosis; no claim that the test result alone determines prognosis or direction of therapy.	The laboratory internally performs analytical validation and determines adequacy of clinical validation before offering for clinical testing; the accretor during the normally scheduled inspections will verify that the laboratory performed appropriate validation studies.
Moderate risk: the consequence of an incorrect result or interpretation may lead to serious morbidity or mortality for patients or their blood relatives; the test methodology is well understood and independently verifiable; and interlaboratory comparisons can be performed or external proficiency testing is available.	The test result may be used for predicting disease progression or identifying whether a patient is eligible for a specific therapy. It includes diagnostic, presymptomatic, and predisposition genetic testing; carrier screening; preimplantation genetic diagnosis and prenatal testing, in which the confirmatory procedure may incur significant morbidity or mortality to the patient or fetus (including but not limited to invasive prenatal diagnostic procedures that may directly affect pregnancy management, outcome, and reproductive decision making).	Test results require expert interpretation by an appropriately trained board-certified (ABPath/ABMG or ABMG) MD or PhD. The laboratory must submit validation studies to the CMS-deemed accretor for review, and the accretor must make a determination that there is adequate evidence of analytical and clinical validity before the laboratory may offer the test clinically. A system needs to be developed by the American College of Medical Genetics and Genomics in conjunction with a CMS-deemed accretor to create an algorithm for the test validation review process. The laboratory should submit validation studies demonstrating analytical and clinical validity to the CMS-deemed accretor. Because of rapidly expanding knowledge and new techniques that improve clinical molecular testing, a rapid turnaround time for the accretor review is necessary.
High risk: the consequence of an incorrect result or interpretation could lead to serious morbidity or mortality; and the test methodology is based on a unique algorithm or proprietary method or is not independently verifiable.	The test is used to predict risk of, progression of, or patient eligibility for a specific therapy to treat a disease associated with significant morbidity or mortality; and/or the test result cannot be tied to the methods used or interlaboratory comparisons cannot be performed.	Test results require expert interpretation by an appropriately trained, board-certified (ABPath/ABMG or ABMG) MD or PhD. The laboratory must submit test to the FDA for review before offering the test clinically. The CMS and accretor determine compliance.

ABMG, American Board of Medical Genetics; ABPath, American Board of Pathology; FDA, US Food and Drug Administration; CMS, Centers for Medicare and Medicaid Services.

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recommended by the College of American Pathologists¹ and consistent with the usual FDA determination of testing-associated risk, whereby the FDA aligns risk with the medical decision made on the test results. The proposed risk categorization model of the ACMG is based on how an incorrect result might have an impact on patients and their blood relatives (including offspring). The risk model specifies determining factors for categorization and oversight recommendations for each level of risk. It should be recognized that genetic testing is a process including not only the analytical phase addressed in this document, but also preanalytical and postanalytical components, which are beyond the scope of this document. Patient harms can occur in the preanalytical phase (e.g., lack of education/counseling, disregard for the informed consent process, wrong test ordered) as well as postanalytically in the delivery of results and subsequent clinical follow-up.

Although the ACMG is in agreement with the features that the College of American Pathologists recommends to be included in the oversight framework for laboratory-developed tests, we recommend additional considerations for germline genetic testing. We recommend that all clinical molecular genetic tests fall into either the moderate-risk or high-risk category. Tests that (i) do not utilize proprietary methods or algorithms, (ii) are amenable to interlaboratory comparisons, and (iii) are evaluated by external proficiency testing should be categorized as moderate risk.

Due to the potentially serious implications of an incorrect result or interpretation for the patient and the patient's blood relatives, we recommend that all clinical molecular genetic test results be reviewed and interpreted by an individual certified in either Clinical Molecular Genetics (American Board of Medical Genetics, ABMG) or Molecular Genetic Pathology (American Board of Pathology/ABMG). The professional interpretation of test results should be provided by an individual certified in clinical genetics (ABMG), clinical cytogenetics (ABMG), clinical molecular genetics (ABMG), or molecular genetic pathology (American Board of Pathology/ABMG). In addition, we recommend that an ABMG-certified clinical geneticist and/or American Board of Genetic Counseling/ABMG-certified genetic counselor provide pre- and posttest counseling to patients, as necessary.

DISCLOSURE

The authors declare no conflict of interest. However, please note that all authors (except J.B. and M.S.W.) direct clinical testing laboratories.

REFERENCE

1. College of American Pathologists. Proposed Approach to Oversight of Laboratory Developed Tests draft proposal (4/28/2010). http://www.cap.org/apps/docs/advocacy/ldt/oversight_model.pdf Accessed 25 July 2012.



January 5, 2015

The Honorable Fred Upton
Chairman
Energy and Commerce Committee
U.S. House of Representatives
2125 Rayburn Building
Washington, DC 20515

The Honorable Diana DeGette
Member
Energy and Commerce Committee
U.S. House of Representatives
2125 Rayburn Building
Washington, DC 20515

Dear Chairman Upton and Representative DeGette:

The American College of Medical Genetics and Genomics (ACMG) welcomes the opportunity to comment on the questions and issues raised in the course of your work on the 21st Century Cures Initiative, and specifically how to ensure access to innovative clinical tests. Our primary interest relates to the rapidly evolving capabilities in genetic and genomic testing that are going to continue to transform health care over the next decade. In the eyes of many consumers—and your constituents—the genetic and genomic revolutions are here and they have captured great interest and enthusiasm in the promises of personalized medicine. As such, we request that any proposals put forward by the Committee distinguish between genetic from other testing, allow for the development of innovative solutions in the genetic testing arena, and not subject genetic testing to any Laboratory Developed Test (LDT) requirements that the Committee may be considering.

About ACMG: ACMG is the only nationally recognized medical organization dedicated to improving health through the practice of medical genetics and genomics. ACMG has over 1750 members, nearly 80% of which are board certified clinical and laboratory geneticists and genetic counselors. The College's mission includes the following major goals: 1) to define and promote excellence in the practice of medical genetics and genomics and to facilitate the integration of new research discoveries into medical practice; 2) to provide medical genetics and genomics education to fellow professionals, other healthcare providers, and the public; 3) to improve access to medical

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genetics and genomics services and to promote their integration into all of medicine; and 4) to serve as advocates for providers of medical genetics and genomics services and their patients.

A Misalignment of Incentives— Genetic Tests are Different from LDTs:

Very few genetic testing products have been cleared by FDA for clinical use, though some critical components of testing have been cleared as analyte specific reagents (ASRs). In fact, it is unusual for there to be an FDA cleared diagnostic genetic test. The great majority of guidance to providers and laboratories has been through the promulgation of standards and guidelines for testing and the development of educational programs by professional organizations, such as ACMG. Central influences leading to the limited role of manufacturers in the development of genetic testing have been the speed at which the field has grown, the vast amount of complex information underlying genetic and genomic medicine, and the limited experience and training of the great majority of clinical service providers. To the extent that there has been “regulation”, it has largely been through payer coverage policies for the past 30 years.

Getting Testing to Those in Need—The Challenges: The individual rarity of the 5,000 – 7,000 conditions with strong to moderately-strong genetic influences has largely been limited due to an imbalance between the incentives that drive industry to develop products for the diagnosis of rare diseases and their expected return on that investment. This is best highlighted by the contrasting outcomes of the Orphan Drug Act that protected and incentivized the development of treatments for rare diseases, and the impact of the Humanitarian Device Exemption that was directed at traditional device manufacturers and resulted in clinical laboratories developing Laboratory Developed Procedures that for 30 years have been the only means of ensuring access to rare disease diagnostics in the U.S. *Even designating genetic and genomic testing laboratories as manufacturers is more likely to result in limiting access to these innovative diagnostic tests than it is to ensuring their safe and effective use.* We urge the Committee to distinguish between LDTs and genetic testing, which warrants separate treatment to foster innovation, incentivize entrepreneurial focus and expand access to cures.

The ACMG is committed to ensuring that:

- Patients will have appropriate access to genetic tests available to diagnose the condition associated with their signs and symptoms.

- Physicians/clinicians will be able to order genetic tests that are medically indicated in their patients.
- Patients with genetic disorders will have access to clinical trials, which are promoted by clinicaltrials.gov and which typically require a patient to have genetic test results that confirm and characterize their disorder.

In light of this background, our responses to the Committee's questions follow:

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 integration of genetic and genomic information into the clinical context of individuals or their families is complex and requires a unique base of knowledge and training. In 1992, the American Board of Medical Specialties (ABMS) recognized this by designating that the American Board of Medical Genetics and Genomics, as the only certification body for clinical and laboratory geneticists, be recognized as the 24th primary medical specialty board of medicine.

Most of the laboratory tests that are used in medicine produce results that stand on their own, without the need for expert interpretation to ensure their safe and effective use by providers. *Genetic and genomic tests fall into a group of high complexity tests based on recently acquired and rapidly evolving knowledge.* Furthermore, genetic testing is a process that includes not only the analytical phase but also pre-analytical and post-analytical components. Patient harms can occur in the pre-analytical phase (e.g., lack of education/counseling, disregard for the informed consent process, wrong test ordered) as well as post-analytically in the delivery of results and subsequent clinical follow-up. The pre- and post analytic phases of the genetic testing process are generally considered a part of the practice of medicine.

While genetic diagnostic laboratories have developed tests for several decades, to date, they have not been considered manufacturers or regulated as such. We support the status quo for this unique set of tests, urge Congress to clearly delineate general LDTs from genetic tests, and strongly recommend that the Committee decline to regulate genetic testing. To do otherwise would have extreme consequences for the

laboratories and the patient care services they provide. Genetic tests are not typical testing devices and the current system for FDA regulation of devices cannot be applied to these tests. Instead, the majority of genetic tests are Laboratory Developed Procedures (LDPs), which should be the subject of a separate initiative outside the LDT process.

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?*

Many types of genetic tests that reflect the evolution of genetic information and new technologies are currently in use. They are used in germline genetic testing and somatic cancer based testing, and include tests that target specific types of variation for conditions like Down syndrome or acute leukemias to more open test platforms such as tandem mass spectrometry and genetic/genomic sequencing that provide a comprehensive look at potential contributors to a disease. What distinguishes genetic testing is that all tests are highly complex, particularly at the clinical level, and are overlaid on a rare disease backdrop in a system in which most non-genetics trained providers lack the training to independently manage genetic information.

The information gleaned from genetic tests can range from well-documented genetic variations to a private variation that is seen in only a single patient/family, requiring professionals to integrate gene and gene product laboratory data with clinical results in order to interpret the final test result. The significant need for professional input to both the intended use of the platform or equipment used to perform the test and the clinical interpretation of the results of a disease/phenotype-specific test points to the need for the professional role in delivery of genetic tests.

Moreover, the field is undergoing rapid change in technologies from "traditional" targeted LDPs to genome-scale sequencing. Traditional LDPs are validated against disease/phenotype associations and the biological and pathological implications of the genetic change while newer technologies allow for the variation to be identified and subsequently evaluated to determining its likelihood of being

associated with the disease/phenotype. For example, next generation sequencing (NGS) is performed by complex machines but must be interpreted by a medical genetics expert. This is analogous to medical imaging, where the equipment is regulated, but a physician interprets the images.

These examples clearly specify the importance of recognizing that genetic tests have a technical and a clinical component; and, while these are intrinsically linked, ACMG believes that FDA regulation of genetic tests as LDTs is inappropriate.

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?*

There are two types of risks to consider. Medical risks associated with a test involve the interventions to be pursued based on the test result and are relatively straightforward. However, in genetics, risks can be to individuals or families; prenatal or postnatal; germline or somatic. There are also non-medical risks that arise from the information itself and other risks that arise from the unknowns of new technologies and tests.

Our view is that laboratories must continue to innovate to bring new tests forward and that our current models of comparing the performance of the new technologies against the predicate technologies in a way that is specific to their intended use remains appropriate. As with all predicate technologies in genetics and genomics, the more difficult problem arises when information not previously available comes into play. It is critical that practice standards continue to evolve to guide development.

As to risk classifications, ACMG has a well-developed position. “We recommend that all clinical molecular genetic tests fall into either the moderate-risk or high-risk category. Tests that (i) do not utilize proprietary methods or algorithms, (ii) are amenable to inter-laboratory comparisons, and (iii) are evaluated by external proficiency testing should be categorized as moderate risk. Due to the potentially serious implications of an incorrect result or interpretation for the patient and the patient’s blood relatives, we recommend that all clinical molecular

genetic test results be reviewed and interpreted by an individual certified in either Clinical Molecular Genetics (American Board of Medical Genetics and Genomics, ABMGG) or Molecular Genetic Pathology (American Board of Pathology/ABMGG). The professional interpretation of test results should be provided by an individual certified in clinical genetics (ABMGG), clinical cytogenetics (ABMG), clinical molecular genetics (ABMGG), or molecular genetic pathology (American Board of Pathology/ABMG). In addition, we recommend that an ABMGG-certified clinical geneticist and/or American Board of Genetic Counseling/ABMGG-certified genetic counselor provide pre- and post-test counseling to patients, as necessary.”¹

In sum, we recommend that the Committee, and the FDA, recognize the distinct risk-based aspects of genetic testing, and that a new paradigm specific to such testing (and distinct from general LDT testing) be developed that both preserves both incentives for innovation and an access to treatments while protecting against harms or risks.

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?*

All medical tests and procedures should be safe and effective whether they are through FDA cleared products, LDTs or LDPs, but how they are overseen must be different. Genetic and genomic tests have a distinct set of checks and balances in the existing oversight of the products used in testing that reduces the need for extensive oversight of the laboratory and clinical practices associated with testing. Particularly given that most genetic tests require professional clinical interpretation that ranges from associating the test result with the indications for testing to putting that result into the direct context of the medical and family history of the individual who is tested, a different paradigm from that applicable to LDTs is warranted. Aside from the medical risks, most other potential harms are best managed through professional responsibilities in the pretest and posttest environments. Decisions about which test to order and what the result means in an individual patient's context are clearly within the practice of medicine.

5. *Are there areas where the balance between pre-market review versus post-market controls should be reconsidered?* Premarket FDA review of genetic/genomic tests in the high-risk category remains appropriate, particularly when the results cannot be independently confirmed by a

physician or when the actions to be taken based on the test results impart high medical risks. However, the biggest gap in genetic testing has been the over emphasis on privacy issues—particularly in the rare disease arena—which can harm patient access to cures, instead of prioritizing quality improvement (which requires bringing data together about those tested in order to improve interactions with future patients). Programs such as NIH’s ClinGen Resource Project aim to fill this void.

FDA, in partnership with CMS, should focus its efforts on developing “special” genetic testing controls by setting high standards for 1) the training, experience, and certification of personnel, 2) quality management of laboratories, and 3) collection of data that allows continuous quality improvement. Some aspects of this are already occurring under the CLIA and the CAP Proficiency Testing programs. However, we emphasize that the standards are completely different from those applicable to standard LDTs. We urge Congress to recognize the distinction in whatever policy recommendations it proposes.

How can post market processes be used to reduce barriers to patient access to new diagnostic tests?

Unlike LDTs in general, in the genetic testing arena the rarity and diversity of abnormal test results can often confound test interpretation and the development of clear treatment methods. The only remedy for this problem is to develop an organized approach to robust collection and aggregation of data about patients with similar results to inform test result interpretation. Directly put, only through the creation of large data sets will the best information be available to guide and improve clinical practices. Unfortunately, the very strict privacy laws in effect today have impeded the needed data collection efforts, resulting in deficiencies in the data that have led to ill-informed decisions (including those related to coverage). A system that utilizes third party review should be sufficiently nimble to move quickly as needs arise. Recognition by FDA of tests evaluated through third party review should facilitate payer coverage decisions.

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Most of the traditional medical devices used in genetics and genomics are LDPs which are also used in diagnosis and screening. Ultimately, national level databases are needed to inform clinical practice. Such databases have been developed in other contexts by HHS agencies, such as NIH. Rather than replicating this shared investment, FDA should develop mechanisms to tap into this rich public resource, already designed to aggregate data and being continuously refined by the scientific community through their contributions and continuous, dedicated use.

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8. *The Section 1143 guidance documents raise important questions about the relationship between the FFDCAs 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 regulations 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?*

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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. Ebola)?*

We believe that rare disease applications of genetic testing should be considered procedures performed in clinical laboratories. The overwhelming majority of the 3,000+ genetic tests currently in use were developed in clinical laboratories, both private and academic. Clear exemptions to or latitude in regulatory requirements to protect innovation and rapid translation of new tests are necessary. For that reason, we urge the Committee to distinguish between general LDTs and genetic testing.

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?*

Tests are services, not devices; a device (such as testing equipment or a platform) may be part of the service. As with prior changes to FDA oversight, existing “traditional” LDTs (low- to moderate-risk) would be ‘grandfathered’ into continued use. New targeted tests would be subject to premarket review through a third party review body that is jointly administered by FDA and CLIA. New genomic/proteomic/metabolomic technologies can be subjected to platform oversight by FDA and clinical oversight through CLIA rules and under the practice of medicine, but a separate regulatory oversight regime is needed to distinguish genetic testing from general LTD use.

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

Today’s health care system has not been well aligned with the needs of a learning health system that requires as much data as possible to drive improvement and monitoring. Current rapid movement from genetic testing (for single genes and mutations) to clinical genome-based testing will mitigate this issue because of the universal applicability of the platforms used.

Incentives to drug manufacturers have included tax breaks for R&D activities, acceptance of the limited test clinical performance data that can be provided, time-limited marketplace advantages, and exemption

from LDT post-registration oversight rules. Incentives to support the clinical practice of genetic and genomic testing should be included in the Committee's proposal, such as support of projects that seek to aggregate data from genetic testing to inform safety and clinical interpretation of test results.

The ACMG appreciates this opportunity to provide input to the 21st Century Cures Initiative of the U.S. House of Representatives' Committee on Energy and Commerce, Health Subcommittee on these crucial issues. We would welcome the opportunity to discuss them in more detail with members of the Subcommittee and its staff. A copy of ACMG's published risk categorization for oversight of laboratory-developed tests for inherited conditions is also attached.

Sincerely,



Michael S. Watson, PhD, FACMG
Executive Director

¹Monaghan KG, Benkendorf J, Cherry AM, Gross SJ, Richards CS, Sutton VR, and Watson MS; a joint working group of the Laboratory Quality Assurance and the Professional Practice and Guidelines Committees of the American College of Medical Genetics and Genomics. Risk categorization for oversight of laboratory-developed tests for inherited conditions. *Genet Med* 15 (4):314-315 (April 2013)