

January 5, 2015

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

The Honorable Diana DeGette  
Member  
House Energy & Commerce Committee  
2368 Rayburn HOB  
Washington, DC 20515

Dear Chairman Upton and Congresswoman DeGette:

The Leukemia & Lymphoma Society (LLS) appreciates this opportunity to comment on the *21<sup>st</sup> Century Cures: Request for Feedback: A Modernized Framework for Innovative Diagnostic Tests* white paper. LLS appreciates the efforts by both the Committee and the Food and Drug Administration (FDA) to ensure that patients have access to accurate, safe, and effective diagnostic tools.

As the world's largest voluntary organization dedicated to the needs of blood cancer patients, LLS is a strong supporter of action that will facilitate the discovery, development and delivery of new, safe, effective therapies and diagnostics for blood cancer patients. Our mission is to cure leukemia, lymphoma, Hodgkin's disease and myeloma and improve the quality of life of patients and their families. We advocate on behalf of all blood cancer patients to ensure they have sustainable access to quality, effective, affordable, coordinated healthcare.

LLS has provided more than \$1 billion for research aimed at discovering, developing and delivering blood cancer cures since its founding. LLS-funded research has been part of nearly all of the FDA-approved therapies for blood cancer treatment. Recent scientific advances have changed the way that disease can be treated. Greater understanding of the genetic drivers of cancer have enabled the practice of precision medicine. The potential to identify and treat disease variants is becoming increasingly sophisticated. Increased diagnostic precision will allow the identification of patient sub-populations that will respond to treatment with greater benefit. In vitro diagnostics (IVDs), including laboratory developed tests (LDTs), are essential to this vital area of medical practice impacting patients across the country.

The Food & Drug Administration draft guidance on LDTs through a risk-based framework is an important step to ensuring the accuracy, effectiveness and safety of the diagnostic tools that patients need. As molecular and genetic tests are increasingly used to guide treatment decisions, patients should have confidence that the tests being used represent the best quality science. While the draft guidance represents a significant start, certain issues require additional clarity to ensure the development of these critical tools that are needed in the treatment and diagnosis of blood cancers.

### **Rare Diseases and Unmet Medical Need**

LLS is seeking clarity on how the FDA intends to address rare diseases and unmet medical need in regards to tests that may "act like companion diagnostics." Our focus on these issues stem from the fact that currently there are no prevention or screening methods for blood cancers. Therefore, blood cancer patients rely on diagnostic tests, many of them LDTs, to identify their diseases and determine their best course of treatment, tests that are frequently performed after they present with symptoms. For blood cancer patients, these LDTs represent the best, and often only, chance to receive the most effective treatment.

## Clarity Regarding Devices Acting like Companion Diagnostics

Throughout the guidance the FDA emphasizes that it will be focusing on specific high risk tests, including “LDTs with the same intended uses as a cleared or approved companion diagnostic” and “devices that act like companion diagnostics.” While there are currently no approved companion diagnostics in blood cancer, and thus no LDTs with the same intended use as cleared companion diagnostic, how clinical validity is demonstrated in IVD’s and LDTs is an important focus for LLS and thus any risk-based framework needs to provide additional clarity.

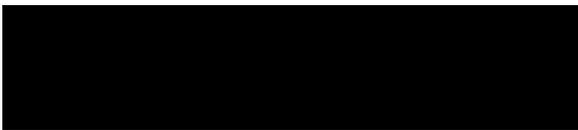
## Incentivizing Diagnostic Development

The Committee also asked the public to consider incentives to encourage the development of new, more accurate or more efficient diagnostic tests. LLS would like to revisit the concept of creating a voucher based incentive program, the specifics of which have been submitted previously to the committee and are attached here for the committee’s convenience

As stated above, although companion diagnostics are essential to advancing precision medicine, the list of FDA-approved companion diagnostics is surprisingly short. A clear and significant factor limiting investment in companion diagnostic development is the lack of sufficient economic incentives for developers. While the process for developing a companion diagnostic test and receiving FDA approval is costly, low reimbursement and longstanding intellectual property concerns (including questions regarding LDT regulation) lead to a low return on investment. This financial risk has dampened industry investment in these essential diagnostic tests and held back new advancements in personalized care, thus potentially impacting patient access to potentially life saving treatments. The establishment of a new Essential Companion Diagnostic priority review voucher pilot program would help to address these issues.

The Leukemia & Lymphoma Society thanks the committee for engaging all stakeholders, in particular patient groups, in this important discussion and we look forward to continuing this dialogue. Should you or your staff have any questions regarding our comment, please do not hesitate to contact me at [Brian.Rosen@lls.org](mailto:Brian.Rosen@lls.org)

Sincerely,



Brian Rosen  
Chief Policy, Advocacy & Patient Access Officer  
The Leukemia & Lymphoma Society

## Promoting Companion Diagnostics Innovation

### Summary

Problem: Insufficient market incentives have limited investment in the companion diagnostics necessary to choose targeted medicines that will have the greatest patient benefit.

Recommendation: Congress should establish a pilot program to provide a Priority Review Voucher for companion diagnostics developed to target certain therapeutic agents.

### Background

Recent advances in precision medicine are beginning to make it possible to provide patients with precision-based treatments that target their genetic mutations and disease state. Each of these breakthroughs speeds patient access to interventions that work and avoids wasting precious time and valuable system resources on interventions that would provide no clinical benefit to the patient. An integral component to this precision-based approach is a companion diagnostic test, which provides the patient information necessary for the safe and effective use of a corresponding therapeutic agent.

Although companion diagnostics are essential to advancing precision medicine, the [list](#) of Food & Drug Administration (FDA) approved companion diagnostics is surprisingly short. Despite FDA efforts to address and facilitate the concurrent review of therapeutic drugs and related companion diagnostics, significant hurdles still prevent companies from developing these essential tools.

A clear and significant factor limiting investment in companion diagnostic development is the lack of sufficient economic incentives for developers. While the process for developing a companion diagnostic test and receiving FDA approval is costly, low reimbursement and longstanding intellectual property loopholes lead to a low return on investment. This financial risk has dampened industry investment in these essential diagnostic tests and held back new advancements in personalized care, thus potentially impacting patient's access to potential life saving treatments.

### LLS Proposal

To address the above, LLS recommends that Congress establish a new Essential Companion Diagnostic priority review voucher (PRV) pilot program, building upon the experience of the Agency's existing voucher programs for Rare Pediatric Diseases, which was enacted in 2012. Under this pilot program, the sponsor of a companion diagnostic that is essential for the safe and effective use of a novel therapeutic agent would receive from the FDA a transferable voucher for the future priority review of a pharmaceutical agent. The diagnostic sponsor can sell the voucher to a drug manufacturer, who can use the voucher to file for priority review of a product in development. The diagnostic sponsor's ability to sell such a voucher would establish a significant new incentive for the production of companion diagnostic tests.

Priority review is an FDA designation that directs the overall attention and resources of the Agency to the evaluation of a drug application. Without sacrificing safety, this designation alters the FDA's internal processes such that the timeline for a decision on approval is shortened from ten months or longer to less than six months of the new drug or biologic application. In addition, the voucher does not create new federal spending, as the FDA continues to operate within its appropriated budget.

Access to this expedited review process has the potential to create a powerful incentive for the development of necessary companion diagnostics for vital new therapies—all at no additional cost to the federal government. In fact, in July 2014, the first Rare Pediatric Diseases program voucher was [sold](#) by BioMarin Pharmaceutical for \$67.5 million—establishing a powerful market for priority review vouchers.

In order to optimize the public health impact of this pilot program and prevent adverse impacts on the overall efficiency of product review at the FDA, the program would have the following characteristics:

1. The voucher would be awarded by FDA to the sponsor of the companion diagnostic on the date of (a) the approval of the associated pharmaceutical application or (b) the approval/clearance of the companion diagnostic application—whichever is later.
2. The voucher would be awarded for a companion diagnostic associated with a First-in-Class designated therapeutic agent that addresses a serious or life threatening disease.<sup>1</sup>
3. The companion diagnostic must be essential for the safe and effective use of a new novel therapeutic agent.
4. The voucher would be transferrable to another sponsor, without limitation on the number of transfers. This is a feature of the Rare Pediatric Diseases PRV.
5. The voucher could be used to establish priority review for any pharmaceutical product. This is a feature of the Rare Pediatric Diseases PRV.
6. The voucher user would be required to notify the FDA 90 days prior to the redemption of the voucher. This is a feature of the Rare Pediatric Diseases PRV.
7. The voucher user would be required to pay the FDA a priority review user fee in addition to any other fee required under the prescription drug user fee program. This is a feature of the Neglected Tropical Diseases PRV and the Rare Pediatric Diseases PRV.
8. The FDA would close this pilot program within one year after the date the Agency awards the third voucher from the program. This is a feature of the Rare Pediatric Diseases PRV.

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<sup>1</sup> The term “serious” has been defined by the FDA in the past for the purposes of accelerated approval (Food and Drug Administration, Final Rule, New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval (57 FR 58942, December 11, 1992)) and expanded access to investigational drugs for treatment use (21 CFR 312.300). A serious disease or condition is a disease or condition associated with morbidity that has a substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on factors such as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

**STATEMENT**

**of the**

**American Medical Association**

**for the Record**

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

**Re: 21<sup>st</sup> Century Cures—Request for Feedback:  
A Modernized Framework for Innovative Diagnostic Tests**

**January 5, 2015**

The American Medical Association (AMA) appreciates the U.S. House of Representatives Committee on Energy and Commerce Subcommittee on Health's (Subcommittee) efforts to build on and accelerate wide-spread clinical applications of innovative tests. We welcome the opportunity to respond to the questions posed by the Subcommittee. Our responses are below along with examples that demonstrate the differences between medical testing services offered by physicians in a single laboratory to address a specific patient medical need versus the packaged commercial products that are shipped by manufacturers to laboratories across the country. The AMA strongly supports both legislative reform of (1) the current oversight of laboratories where testing services are offered by physicians; and (2) the Food and Drug Administration's (FDA or Agency) regulation of mass-produced commercial test kits. Congressional action is needed in order to sustain and encourage widespread access to well-established tests while removing burdensome regulatory barriers to rapid adoption of innovative tests that are clinically indicated.

In the interest of safeguarding patient access to existing standard-of-care testing services and the innovation that has inspired development and provision of new cutting-edge tests, it is critical that the Subcommittee move quickly to advance legislation that:

- **Rescinds FDA Proposed Guidance:** Directs the FDA to rescind the Agency's proposed guidance to regulate laboratory developed testing services and clarifies that the Agency is prohibited from regulating physicians engaged in the practice of medicine including the procedures and analysis that physicians perform in clinical laboratories;
- **Modernizes CLIA:** Modernizes the Clinical Laboratory Improvement Amendments (CLIA) to, among other things, strengthen the role of third party accreditors;
- **Reforms FDA Oversight of Commercial Kits:** Reforms current FDA regulation of commercial diagnostic kits distributed by manufacturers in order to address the extensive and well-documented concerns of manufacturers that the current FDA regulation is costly, overreaching, and so slow that some commercial kits become obsolete before they reach the market;
- **Provides Limited FDA Oversight of Black Box Testing:** Confers limited authority on the FDA to regulate direct to consumer tests and testing services where incorrect results could cause harm to

patients and the test methodology is **not transparent nor well understood** (as in the case of tests that use black box complex algorithms to produce results).

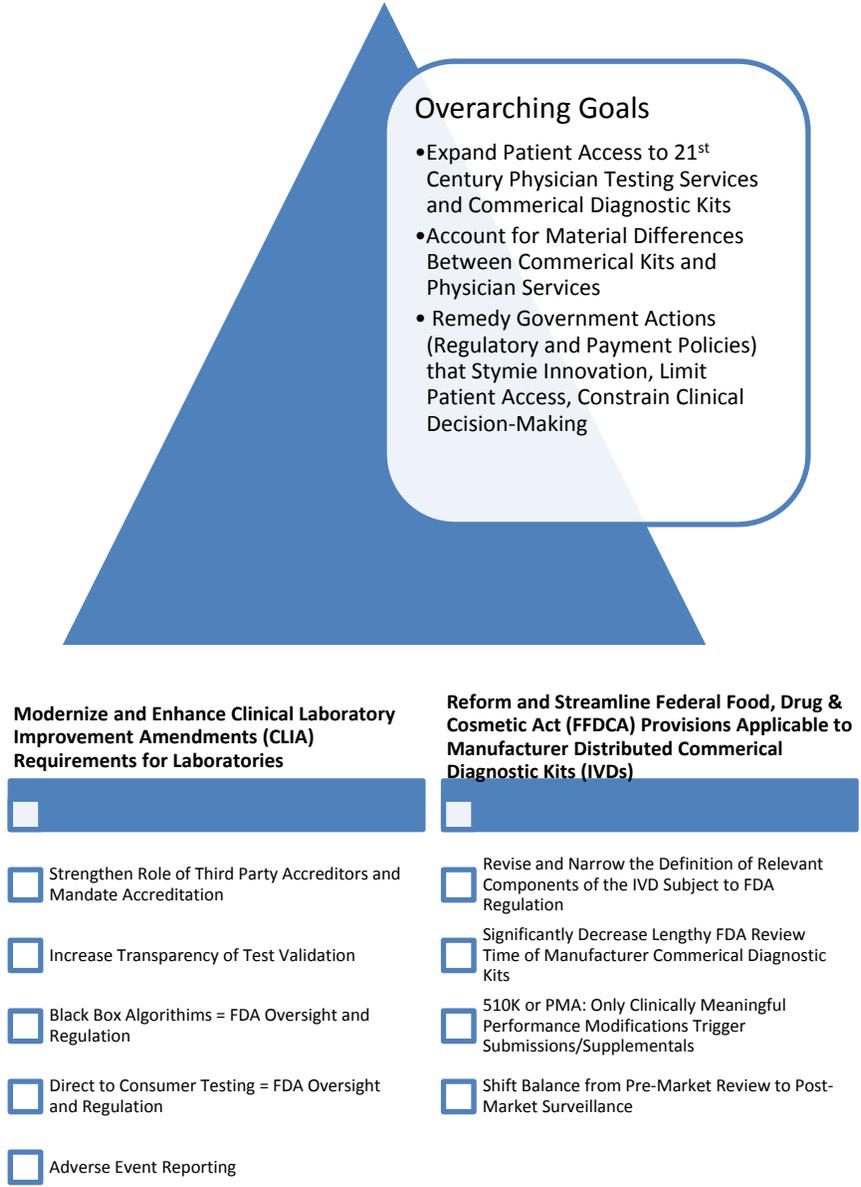


Figure 1. Changes to CLIA and the FFDCA are needed to promote patient access to effective tests, account for differences between commercial kits and physician services, and remedy government actions that harm innovation, limit patient access, and hamper clinical decision-making.

**Context: FDA’s Current and Proposed Regulation Jeopardizes Access to Established Testing Services that Will Negatively Impact Patient Clinical Care**

Physicians have been and continue to be at the forefront of the intersection of providing patients’ medical care and advancing medical knowledge to improve upon the current standard of care. Physicians are unique stakeholders who have both an ethical and legal obligation to each individual patient to whom they

render medical care. The first directive of physicians is to do no harm and to advance the interest of their patients to whom they provide medical services. While there are important interested stakeholders focused on commercializing innovations and regulators tasked broadly with safety, physicians have a direct relationship with patients and an obligation to provide medical services that meet patient specific clinical needs; these are services physicians have provided for decades in the context of laboratory developed testing services.

The AMA is very concerned that patient access to **well-established, standard-of-care** testing services provided by physicians to millions of patients each year will no longer be available once the FDA finalizes the Agency's proposed regulation of laboratory developed testing services. Though there are many unanswered questions raised by the FDA's proposal, it is already clear that the proposed guidance would impose new, costly, and burdensome requirements on even low- and moderate-complexity testing services. More troubling, the Agency has repeatedly acknowledged it does not know the number of times these testing services are offered or the universe of services being offered by physicians that would be subject to this regulation while at the same time claiming that adequate Agency capacity exists to regulate such physician services. Many of these testing services, along with those that potentially will be categorized as high-risk by the Agency, have represented the standard-of-care for years.

As a threshold matter, the FDA has offered little to no evidence that patients have suffered harm on a persistent or widespread basis justifying the imposition of broad new and costly regulatory requirements that will harm patients who are unable to obtain needed testing services. When queried as to what problem the FDA is addressing and any corresponding documented patient harm, the Agency has declined to identify the number of testing services and patients that the FDA has identified or tracked or scoured from literature or media accounts. We have urged the FDA to define and identify the problem(s) and the breadth thereof before proceeding with any plan to implement oversight. The FDA appears to have conflated one problem—lack of incentives to seek FDA approval/clearance—with a poorly articulated statement of patient harm vis-à-vis laboratory developed testing services.

To the extent that the Subcommittee and others are interested in developing new incentives to accelerate the commercialization of mass-produced testing kits—particularly genetic or next generation commercial kits, we strongly urge reform to the FDA's current regulation of mass-produced testing kits. We further support CLIA modernization to enhance the oversight of laboratories where physician services are offered through increased transparency as opposed to the expansion of the flawed FDA commercial kit regulation framework to physician services.

**The FDA's proposed regulation of laboratory developed testing services will have a sweeping and widespread negative impact on patient access to established testing services representing the standard-of-care. The proposed regulation will leave the country vulnerable to biothreats and outbreaks of infectious diseases. Why? Because the Agency's action will lead to a reduction in the number of testing services that physicians are able to offer and the laboratories where these services are performed.** The FDA's actions will create strong disincentives to maintenance of laboratory resources needed to offer new laboratory testing services because of the potentially short duration of time in which the tests could be offered and, over time, there will be fewer physicians with the training and expertise to offer these services. The Agency's proposed regulation will markedly dampen the ground-breaking innovations developed by physicians as part of their laboratory clinical practice of medicine—innovation that is the genesis of commercial tests kits and a key part of a physician's ability to properly diagnose and treat patients. At the same time that the FDA's regulation will erect additional impediments to medical advancement in the U.S., it will contribute to increased costs associated with (1) poor patient outcomes given decreased access, and (2) increases in per test costs because of limited competition.

Finally, if the FDA's concern is primarily related to highly complex genetic/genomic tests, the proposed ten year window for phasing-in FDA's regulation of all laboratory developed testing services (including a large number that are not genetic or genomic tests) will divert limited Agency and health care system resources away from developing a workable regulatory framework to address the manufacturing challenges associated with next generation and whole genome sequencing and associated testing. The technical and clinical expertise that will be required to develop such a framework, implement the framework, and monitor compliance will be significant. The FDA's approach—creating a highly complex regulatory and rigid framework when the field is undergoing seismic changes that will bring ground breaking testing and treatment advances—is at odds with this Subcommittee's goal of promoting 21<sup>st</sup> Century Cures.

## **Subcommittee Questions & AMA Answers**

### **Answer to Question #1: Practice of Medicine v. Commercial Kit**

*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 AMA would like to underscore the differences between the practice of medicine (which laboratory developed testing services are) and mass produced commercial kits that are shipped by manufacturers around the country. Laboratory developed testing services are procedures performed by physicians for specific patients equivalent to a surgeon who provides surgical services to a specific patient. A physician practicing laboratory medicine will utilize reagents (products that are subject to FDA regulation) and machines (which may or may not be FDA regulated) when conducting testing, but the laboratory testing services are the technical expertise and clinical judgment of a physician who develops and validates the test performed under testing conditions that are already subject to oversight under CLIA. The physician makes a clinical determination as to what products to utilize, what patient sample preparation is needed, and what machines are used in order to perform the testing services. A physician who develops, validates, and performs the testing procedures is knowledgeable about each component part and each step and procedures involved with the test. The physician's services cannot be packaged and shipped to multiple laboratories.

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Critical distinctions exist between laboratory developed testing services and commercial diagnostic kits

Commercial diagnostic kits are an actual product that can be packaged, labeled, and **shipped in interstate commerce to numerous laboratories**, in contrast to the services and procedures offered by a physician in a **single laboratory as part of his or her practice of medicine**.

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Once the manufacturer distributes the commercial diagnostic kits, the **manufacturer no longer retains control** over how the test is conducted, what patient is tested, and how the information is shared with the treating physician, whereas **physicians retain control and decision-making authority** throughout the continuum from design to delivery of test results.

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Physicians who utilize a **commercial diagnostic kit are not able to evaluate the underlying methods and components of the commercial kit, nor are the test results detailed**; instead, they are limited to yes/no results. In contrast, when offering laboratory developed testing services **physicians have a complete understanding** of the results as well as the underlying methods, sample preparation, inputs, procedures, and validation of the test.

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A commercial diagnostic kit is a packaged product that is **engineered** to be performed **anywhere** for a **“standard” patient**, not a specific patient in contrast to **laboratory developed testing services that physicians offer to a specific patient** based on their clinical condition and in consultation with the patient's treating physician.

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Simply stated, laboratory developed testing services are analogous to a unique home built by a master craftsman to meet the specifications of the homeowner, and manufactured commercial diagnostic kits are standard tract housing built with prescribed specifications and products with no consideration of the preferences of the homeowner or the conditions under which the house is to be built.

Oversight and responsibility for design, development, validation, monitoring, and reporting attendant to laboratory developed testing services constitute the practice of medicine. These are within the scope of a physician's practice and physicians have a legal responsibility for them. In contrast, with commercial diagnostic kits the design, development and manufacturing is physically and distinctly separate from the laboratory operations, including sign-out of tests (meaning the reporting, record review, and other components of communication with treating physician colleagues). With laboratory developed testing services, the physician practice components of design, development, monitoring, and application to clinical care are inseparable and inextricably linked.

In order to offer these medical services to patients, physicians practicing laboratory medicine have completed post-graduate medical training and, taken board-certification examinations administered by the American Board of Pathology or the American Board of Medical Genetics and Genomics under the umbrella of the Accreditation Council for Graduate Medical Education. Physicians continue to maintain certification under the American Board of Medical Specialties, are licensed by state medical boards, and pay for and are covered by medical malpractice insurance.

### *Real Life Implications for Patients*

Dr. X consulted me (a physician laboratory director) about a patient taking clopidogrel and testing for CYP2C19. I explained that while there is both the FDA-cleared assay and the laboratory-developed procedure and that they are analytically equivalent (report the same genotype), the difference between the two assays is the interpretation for CYP2C19 heterozygotes. The FDA-cleared assay reports all heterozygotes as extensive or normal metabolizers. This suggests that a normal dose of clopidogrel can be given to the patient. The laboratory developed procedure, in accordance with the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines, reports heterozygotes as intermediate metabolizers. CPIC recommends an alternative antiplatelet therapy (if no contraindication), e.g., prasugrel or ticagrelor, be given to heterozygotes. I also explained that we could not change the interpretation of the FDA-cleared assay.

After obtaining my medical degree and completing a residency in medical genetics, I trained for an additional two years and obtained board certification in clinical molecular genetics from the American Board of Medical Genetics and Genomics. I have almost 20 years' experience as a practicing geneticist developing and offering clinical laboratory testing services. On average in my previous laboratory, my team conducted and reviewed approximately 2,000 tests a day. I actively maintain my certification by reviewing literature, writing papers, attending seminars and conferences as a part of my professional development. I understand that some are pushing the FDA to regulate individuals like myself as manufacturers when rendering clinical decisions. This is nonsensical. Laboratory service is part of the practice of medicine. Where professional judgment is used to diagnose and determine a treatment course for a patient, I work in concert with healthcare professionals to determine the appropriate method and test. I am not a "robot" that automatically sends a result regardless of whether the testing is appropriate or not. I continually try to improve my tests and their performance through analytical validation and clinical evidence. Patients are at the center of everything that I do.

### **Combined Answer to Question #2 and #7: FFDCa Does Not Apply to 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 by the FDA?*

*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?*

Physician services are not devices and cannot be shoehorned into the FFDCA for purposes of regulating the practice of medicine. This is clearly demonstrated by the device labeling requirements of the statute.

For commercial diagnostic kits, the components of the kit are unambiguously medical devices subject to regulation and the engineered copies of the test kit *in toto* also are a product.

Demonstrating the incongruity of the FDA's proposal, the Agency did not specify in the draft guidance what should be labeled in the context of laboratory developed testing services even though this is an essential element of compliance under the FFDCA. The following is but one example of the Agency's statutory overreach in proposing to regulate physician procedures and clinical decision-making. The FFDCA section 201(k) provides:

(k) The term "label" means a display of written, printed, or graphic matter upon the immediate container of any article; and a requirement made by or under authority of this Act that any word, statement, or other information appear on the label shall not be considered to be complied with unless such word, statement, or other information also appears on the outside container or wrapper, if any there be, of the retail package of such article, or is easily legible through the outside container or wrapper.

(l) The term "immediate container" does not include package liners.

(m) The term "labeling" means all labels and other written, printed, or graphic matters (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.

It is unclear why the FDA did not specify in its proposal what should be labeled in the context of laboratory developed testing services unless it is the intent of the Agency to be the federal regulator of physician medical practice. There are no packaged containers of laboratory developed testing services and the Agency's effort to create a "package" to be labeled would be an obvious legal fiction.

Furthermore, even to the extent that the FDA proposes to define laboratory developed testing services as something other than what they are—physician expertise and procedures—the Agency's application of these provisions to physicians would create liability for off-label use and "promotion" for physicians. Currently, when physicians determine that a product labeled for a specific intended purpose has an alternative beneficial clinical use physicians are permitted to use the product for an "off-label" purpose and are permitted to discuss such use with other physicians. Although there remains an ongoing legal dispute between the FDA and drug, biological, and device manufacturers, manufacturers are generally prohibited from promoting off-label uses and face significant sanctions if and when the Agency can establish that the manufacturer has "misbranded" the product.

Physicians in contrast are able to inform patients and other physicians when a commercial diagnostic kit, labeled for one purpose, has a clinical benefit for another purpose. This is the very definition of medicine, i.e., a physician using his or her clinical expertise to appropriately diagnose and treat a patient who may require care that is not "one-size fits all." Competent and quality medical care rests on physicians' discretion and responsibility to treat patients in a manner that meets each patient's individual needs. Removing a physician's ability to practice medicine off-label will jeopardize patient access to medically necessary, and potentially lifesaving, treatment.

### *Real Life Implications for Patients*

An oncologist at my medical center requested that our laboratory, directed by myself, a board-certified molecular pathologist, assess a formalin-fixed paraffin embedded tissue sample from recently-diagnosed papillary thyroid carcinoma. The oncologist was aware that 30-50% of papillary thyroid carcinomas contain the BRAF V600E mutation. Since carcinomas carrying the V600E variant are

responsive to several drugs (vemurafenib, dabrafenib, trametinib), the oncologist wanted to find out whether his patient may be a candidate for one of the drugs. The FDA-approved BRAF V600E test kit is intended only for testing melanoma, not thyroid carcinomas. However, using my expertise as a molecular pathologist, I was able to make a slight modification to the FDA-approved kit so that I could detect the BRAF variant in thyroid carcinoma cells. The patient's thyroid carcinoma tested positive for the presence of the V600E variant, an indication that she was a candidate for drugs targeting BRAF V600E. Her oncologist prescribed dabrafenib, and the growth of her tumor has slowed dramatically.

Use of the FDA-approved BRAF V600E kit on any tissue other than melanoma is considered a modification to the intended use, i.e., an off-label use, making it a laboratory developed testing service. As a physician, I need to use every tool available and appropriate to treat my patients. I would have failed my patient if I had not practiced the best medicine possible by testing her thyroid carcinoma for the presence of the V600E variant. Importantly, if the FDA had required that I obtain its approval to use the FDA-approved BRAF V600E test on a tissue for which it was not approved, my patient would have experienced an unacceptable delay in her care that could have severely affected her chances of survival.

When physicians determine that a test “labeled” for a specified use is appropriate for another use, a physician is permitted to employ off-label uses and permitted to discuss off-label uses with other physicians and patients. In contrast, manufacturers are prohibited from off-label promotion. The Agency would have to create a carve-out for off-label promotion in the context of laboratory developed testing services for physicians since such a prohibition on discussing testing options with patients and treating physicians including off-label uses would prevent physicians from meeting both ethical and legal obligations. Furthermore, not only are physicians permitted to discuss off-label uses of devices, drugs, and biologicals, but this is at the heart of innovation. In the course of providing care to patients, physicians are able to identify emerging previously unknown patterns, symptoms, and outcomes that were not otherwise contemplated when a method, approach to medical care, procedure, device, drug, or biological was initially devised for patient care.

Even assuming the FDA had the capacity to timely process a far larger volume of submissions from both manufacturers as well as physicians and laboratories, the latter do not have the resources needed to prepare a submission for FDA clearance or approval. FDA approval is costly and time-consuming even for large corporations often singularly focused on a very small sliver of the universe of tests patients need daily. If off-label uses (also called clinical practice enhancements) required FDA clearance or approval once one manufacturer commercialized a product, all versions of the test including superior versions would most likely cease given the cost and resource barriers. Even if an application could be submitted, timely processing is already a concern as discussed below.

### **Answer to Question #3: Risk-based Approach**

*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 AMA generally agrees with other major stakeholders that risks posed by clinical tests are different from therapeutic medical devices. **The current FDA medical device classification, therefore, is not**

**appropriate for clinical tests. A new risk-classification for clinical testing, developed with significant stakeholder input, that balances the relative risks posed by clinical tests with the potential benefit of the information that they provide would be most appropriate.** As discussed above, there are differences between physician services and mass produced commercial diagnostic kits shipped all over the country. In short, manufacturers lose control over the commercial kit once the kit is shipped. In sharp contrast, a physician remains responsible for providing testing services from design to finalizing the report and discussing with the treating physician. Given the risk associated with rapid multiplication of potential erroneous testing that accompanies commercial diagnostic kits, the FDA establishes rigid rules for test performance to substitute for professional judgment that is not appropriate or desirable for physician testing services. In addition, the test results for commercial kits are extremely limited with few details on how the results were produced, which increases risk associated with evaluating implications for a specific patient.

The AMA supports risk-based regulation of tests. Risk categorization should be determined by (1) the potential of a misinterpreted result to cause harm to a patient, and (2) by test characteristics, e.g., test methodology that is not transparent or well-understood (as in the case of tests that use complex algorithms to produce results). The AMA is seriously concerned, however, by the *a priori* classification of some test types as “high risk” in the absence of any formal risk classification criteria by the FDA. The Agency has stated that high-risk tests will be subject to pre-market approval requirements within 12 months of the guidance being finalized, and that it will release additional guidance on risk classification criteria once its proposed framework is finalized. But it has failed to clearly define the criteria it will use to determine risk. This leaves physicians uncertain of how to determine whether the tests they offer are high-risk and subject to pre-market review within 12 months, and unable to effectively plan for the additional effort and manpower that would be required for pre-market submission. We believe it is essential that the Agency clearly define risk classification criteria before subjecting physicians and the laboratories where they offer their services to burdensome requirements. Further, we find it puzzling that the FDA has already named certain test classes that will be considered high-risk without stating how risk classification criteria were applied to these tests to place them in the high-risk category.

When taking into account the potential of a misinterpreted result to cause harm to a patient, one must keep in mind number of “checks and balances” that accompany laboratory developed testing services. Every laboratory performing clinical testing is CLIA-certified, assuring laboratory performance standards and test accuracy and reliability. Additionally, those performing high-complexity tests must undergo regular proficiency testing. Even further, almost every clinical laboratory chooses to obtain accreditation by a third-party, such as the College of American Pathologists, which holds laboratories to rigorous quality standards and regular inspections.

Once the laboratory test has been run, it is reviewed and signed by the laboratory director—a physician or laboratory medicine expert who is legally responsible for the result. The ordering physician then receives that result and, often in consultation with the laboratory director, uses his or her expertise to subsequently manage patients. This application of professional expertise – by highly trained experts in laboratory medicine and patient care – is essential in mitigating the risk of harm that could come to a patient through a misinterpreted result. **This professional responsibility is present now, without FDA oversight of laboratory developed testing services, and will continue irrespective of additional oversight.**

**The professional responsibility of a laboratory director is to ensure that a test run in his or her laboratory produces accurate and reliable results.** This often means evaluating the methodology and components of tests and optimizing performance in the laboratory. However, it is impossible to apply these activities to many commercial kits that use “black-box” methodology, i.e., those that use complex, non-transparent, or proprietary algorithms to determine a result. Test results that could potentially cause

harm to patients if incorrect and do not lend themselves to evaluation by the laboratory physicians and the patient's treating physician are most concerning to the AMA and are the type of test that belongs in the high-risk category. To the extent that many companion diagnostic tests are run using simple sequencing or variant identification methodology that is transparent and easily evaluated, the AMA believes it is inappropriate for the FDA to assign all companion diagnostic tests to the high-risk category. Aside from the absence of established risk criteria applied to each individual test's methodology as a basis for their placement in the high-risk category, the FDA appears to be casting aside the risk mitigation that occurs with a physician's (both ordering and laboratory) oversight and expertise in running the test and subsequently managing the patient.

#### **Answer to Question #4: Safety and Effectiveness**

*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 AMA does not support application of current medical device safety and effectiveness concepts to laboratory testing services because procedures and physician expertise are not devices. Furthermore, the FDA's application of statutory provisions intended for actual medical devices, drugs, and biologicals to manufactured commercial diagnostic kits is statutorily compulsory, but ill-suited to the consideration of validity (analytical and clinical) and risk/benefit relevant to diagnostics. Instead the Subcommittee should invite additional discussion on clinical and analytical validity as well as relevant risk/benefit models under both CLIA for laboratories where physician services are performed and FFDCa for commercial diagnostic kits, because laboratory developed testing services and commercial kits have relevant distinctions as outlined above.

#### *Real Life Implications for Patients*

One difficulty in applying the safe and effective standard devised for devices is that laboratory developed testing services are not devices. A suboptimal assay may function well and hence be "safe and effective" for what it does, but use of the information for a particular patient may result in suboptimal treatment. The current assay for KRAS testing of colon cancer is FDA approved (safe and effective), but it only detects mutations in codons 12 and 13. We now know that complete testing of colon cancers requires evaluation of multiple other codons in the KRAS gene (12, 13, 59, 61, 117, 146) and in the NRAS gene. Hence, in the recognized application of that assay, the limited test for KRAS would be of limited effectiveness and safety. The package insert for the drug panitumumab (Vectibix) states:

Vectibix® is not indicated for the treatment of patients with KRAS-mutant mCRC or for whom KRAS mutation status is unknown.

Vectibix® in combination with oxaliplatin-based chemotherapy is not indicated for the treatment of patients with RAS-mutant mCRC or for whom RAS mutation status is unknown.

RAS is defined as exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of either KRAS or NRAS and hereon is referred to as "RAS."

So whether the limited KRAS assay is safe and effective depends on the intended treatment. There is no way for FDA to collect “adverse effects” of the clinical misapplication of this assay.

### **Answers to Question #5 and #6: Reforms to FDA Regulation of Commercial Testing Kits**

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?*

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?*

These two sets of questions underscore why comprehensive reform is required of current FDA regulation of commercial test kits and why expansion of FDA oversight to laboratory developed testing services would harm patients and undermine the practice of medicine across the country. Manufacturers have laid out a compelling case that the FDA’s current approach lacks an appropriate balance between pre-market review versus post-market controls. If this has not been a large enough albatross hampering commercialization efforts by manufacturers, the Agency’s moving target exercise of discretion around when a supplemental premarket submission is required for a modification has hamstrung efforts to improve upon commercial kits that would accelerate the availability of enhanced test kits that improve upon the earlier version. Reforming FDA authority over commercial kits on both counts would level the respective positions of commercial kits and physician testing services while increasing options and protecting physician clinical decision-making. In short, only clinically meaningful performance modification should trigger a supplemental for commercial kits. **The CLIA model of oversight has served as the engine of innovation in this space and rapid application of validated clinical discovery to patient care; therefore, any modifications should involve enhancements to CLIA and clear prohibitions against the FDA regulation of physician services because a commercial version of the test has been modified.**

### **Answer to Question #8: Reduce Duplicative and Costly Government Regulation**

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?*

We agree that the Subcommittee is asking the right questions, but the FDA’s draft guidance does not provide sufficient detail to ascertain where CLIA requirements end and where the FDA requirements begin. Years ago, the FDA committed to issuing a clear statement of CLIA and FDA requirements when it issued proposed draft guidance on regulation of physician developed laboratory testing services. The AMA has asked the Agency for this information and months have passed without a response. **The AMA strongly urges this Subcommittee to consider the compelling need to avoid duplicative and confusing regulation and oversight by two federal agencies, a number of states, and accreditation bodies with deeming authority.** The FDA has proposed a framework for regulation of LDTs, but has

not clarified nor produced any documentation of coordination with CMS based on this new proposal. Furthermore, the FDA has been silent as to the role of the Center for Disease Control and Prevention vis-à-vis CLIA and the new FDA requirements. (CDC, in partnership with CMS and FDA, supports the CLIA program and clinical laboratory quality.) Just as Congress charged the FDA, the Federal Communications Commission, and the U.S. Department of Health & Human Services Office of the National Coordinator for Health Information Technology to jointly develop a proposed regulatory framework for digital health to avoid duplicative and burdensome regulation, **there is similarly an urgent need to, at a minimum, require CMS, the CDC and the FDA to engage major stakeholders in a transparent process and propose a framework that clearly and specifically identifies areas where the agencies will avoid contradictory, overlapping, and or/and ambiguous oversight parameters.**

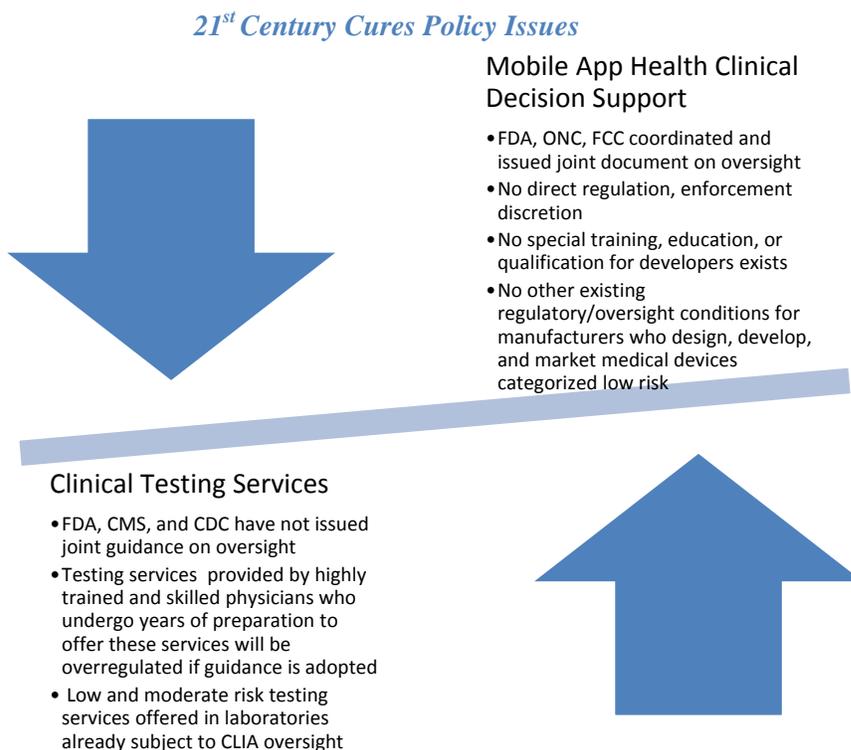


Figure 2. The FDA has taken markedly different regulatory approaches to certain clinical decision support mobile apps that are medical devices which will not be subject to direct regulation and may lack learned intermediaries for use as compared to physician laboratory developed testing services which are offered under regulated conditions by experienced and highly trained medical professionals.

Reportedly, there could be substantial overlap in the regulatory requirements under FDA medical device regulation and the applicable regulations under CLIA concerning quality system requirements, design controls, document controls, purchasing controls, production and process controls, acceptance activities, nonconforming products, corrective and preventative actions, and records. **We urge the Subcommittee to, at a minimum, direct the FDA to identify with CMS and the CDC the respective requirements and direct the FDA to defer to CLIA requirements where there is overlap.** Stakeholders must have an opportunity to comment on the proposal before it is finalized through notice and comment processes.

We are concerned that the Agency has already demonstrated that it lacks the bandwidth to expand oversight to laboratory developed testing services when it is unable to produce a guidance document promised years prior and which multiple stakeholders have requested in order to provide meaningful and informed comment on the FDA's proposed new and far reaching regulation.

### **Answer to Question #9: CLIA—The Proven Innovator**

*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 strongly urge the Subcommittee to build on and modernize the existing CLIA regulatory framework consistent with our recommendations because the current CLIA framework has a demonstrated track record of:

- Providing the necessary flexibilities to ensure patient access to testing services for rare diseases and conditions;
- Supporting customized testing services based on particularized patient need; and,
- Enhancing the capabilities of the country's safety net of highly skilled professionals and laboratories that can provide essential surge capacity and frontline access when there are outbreaks of infectious diseases and biothreats.

In sharp contrast, we are concerned that the FDA's regulation of commercial diagnostic kits—which for the most part has not been able to meet most of the foregoing needs—demonstrates unambiguously that the FDA framework of regulation is overly bureaucratic, expensive, and slow. The ability and capacity of the FDA to approve or clear commercial diagnostic kits has been paltry when compared with the breadth and range of testing services offered to patients under CLIA—with high rates of accuracy and rapid application of new and validated clinical knowledge. The Subcommittee should carefully consider that comprehensive reform of testing services should not expand the reach of a flawed FDA regulatory model that has created barriers to innovation, limited patient access to testing improvements, failed to provide any viable pathway for rare diseases and conditions, and utilizes a top-down, bureaucratic approach to outbreaks and potential biothreats. In addition to CLIA modernization, there is an urgent need to address and streamline the FDA's regulation of mass-produced commercial kits consistent with the AMA's recommendations.

The proposed application of the FDA regulatory framework to testing services for rare diseases, unmet needs, or emergency use—even with exemptions and carve-outs is unworkable and dangerous to individual patients and undermines overall public health by limiting and constraining the number of physicians and laboratories able to handle biothreats and infectious disease outbreaks.

Laboratory developed testing services are often the only option for those with suspected rare diseases. The commercial market for such tests is nearly non-existent, so laboratory-developed tests are a vital tool for patients and their physicians. As currently written, the FDA's proposed exemptions for rare diseases are inadequate in ensuring the continued availability of laboratory developed testing services; the definition pertains to rarely-performed tests, not rare diseases. For example, in one of the most stunning public health successes in history, every newborn in this country undergoes testing for dozens of conditions, which, if not identified within days of birth, can result in serious morbidity and mortality. Many of the conditions being tested are rare diseases, but that does not diminish the public health imperative for them to be identified and diagnosed in patients. However, since the number of newborn screening tests that are performed far exceeds the FDA's definition of rare disease (fewer than 4,000 persons tested each year), each one of the dozens of newborn screening tests may be subject to

burdensome requirements that could endanger their availability. The very definition of “rare” implies that many people will need to be tested in order to identify one, the equivalent of finding a needle in a haystack. For that reason, the cut-off of 4,000 persons per year being tested is utterly unreasonable. Because these tests often constitute a small volume of testing for most laboratories, FDA oversight would likely result in laboratories dropping the tests completely, leaving patients and physicians without an option for screening and diagnosis.

Similar to the lack of commercial availability for tests for rare diseases, many thousands of laboratory developed tests exist simply because commercially-developed kits do not exist, i.e., they fulfill “unmet needs.” These laboratory developed testing services are for a broad range of conditions, and constitute the standard of care. For example, clinical guidelines recommend testing all newly-diagnosed colon cancers for Lynch syndrome, a hereditary colorectal cancer syndrome. Lynch syndrome testing includes assays for mismatch repair variants and microsatellite instability. This type of testing has been available as a laboratory developed testing service for more than 10 years and has been continually improved-upon as new research data emerges (e.g., including BRAF as part of the Lynch syndrome testing protocol). There are no FDA-approved tests for Lynch syndrome nor for microsatellite instability. Yet, the FDA’s proposed exemption for this “unmet needs” test category ends as soon as a commercially-developed kit becomes available. When this happens, every laboratory that has developed a Lynch syndrome testing protocol would need to submit it to the FDA, likely as a pre-market approval application. The expense and burden required for such an activity would not be feasible for many laboratories, which would then decide not to continue Lynch syndrome testing. This would drive up costs, and would freeze further innovation and improvements to Lynch syndrome testing, leaving patients without access to cutting-edge care.

The nature of public health outbreaks demands that health systems respond rapidly. Laboratory medicine experts are able to fulfill this need by developing tests that accurately identify pathogens far more quickly than would be possible if FDA approval or clearance were required. For example, in April 2009 an unknown respiratory outbreak emerged in the U.S. and Mexico. During the first week of the outbreak, several dozen laboratories had already developed molecular assays that could identify the outbreak as being caused by influenza, and could distinguish the A and B strains. Several of the laboratories were further able to identify the H1N1 virus from other H1 viruses. Most results from these tests were available within 24 hours, speeding treatment of patients and decision-making by public health officials. FDA approval requirements would have severely crippled this response. FDA has the capability to issue Emergency Use Authorization, but these are temporary and therefore do not adequately or permanently address the problem.

### **Answer to Questions #10: Transition**

*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 AMA proposal of modernizing CLIA oversight of laboratories where physicians provide testing services and reforming FDA regulation of commercial diagnostic kits would not create the disruption to patient clinical care and innovation that the FDA’s current and proposed regulation have and will. Any congressional action to modify the existing oversight and regulation should grandfather in the vast majority of laboratory developed testing services as there is not adequate capacity outside of the AMA’s proposal to account for the time and resources that will be required. In addition, Congress must consider that Medicare’s reduction in coverage and reimbursement in the context of testing services will coincide with increased oversight and regulatory obligations. We strongly urge the Subcommittee to consider the

interplay between these dynamics for patient access to existing testing services as well as future innovation.

### **Answer to Question #11: Incentives**

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

There are two major barriers to the development of new, more accurate, and efficient clinical testing: (1) current FDA regulation of commercial diagnostic kits and proposed regulation of laboratory developed testing services; and (2) draconian federal health care coverage policies. Simply stated, incentives are not created by limiting patient access through overregulation and coverage policies that deny access to demonstrably beneficial testing services. These government actions are adversely impacting the ability of patients to obtain medical care and exerting pressure on physicians who have led the innovation to accelerate 21<sup>st</sup> Century Cures and related testing.

**FDA Regulation Stymies 20<sup>th</sup> and 21<sup>st</sup> Century Cures and Testing.** Manufacturers face commercialization challenges largely because of the burdensome, opaque, and lengthy FDA clearance and approval process. A recently issued independent analysis of the FDA's 510(k) review times belies the FDA's published statistics on the topic. In a study by the Medical Device and Diagnostic Industry (MDDI), and soon to be published in a 2015 MDDI periodical, the authors analyzed 510(k) review time data from FDA's publicly available database. The highlighted conclusions include the following:

- Use of the third-party review program has significantly declined, while the review times for 510(k)s have increased.
- There is no review-time advantage to submitting an Abbreviated 510(k) compared to a Traditional 510(k).
- Even those devices most frequently reviewed by FDA still saw an increase in their overall review times between 2008 and 2012.

The foregoing data analysis is only half the story. The agency's poor performance on review times for commercial diagnostic kits includes:

- Commercial diagnostic kit 510(k)s take significantly longer to review than 510(k)s for other types of devices.
- Between 2008 and 2012, the average review time for an IVD 510(k) was 183 days compared to a non-IVD 510(k) which was 127 days.

As noted by the authors of the article, the above findings are of particular importance given the FDA's proposed plan to regulate laboratory developed testing services. Reportedly, the same FDA staff reviewing commercial diagnostic kits will review laboratory developed testing services. It is highly improbable given budget forecasts that the FDA will have significantly more capacity to rapidly review and approve new tests. Understandably, the authors report that manufacturers have expressed concerns that FDA review of commercial kits will be further slowed once it begins regulation of physician laboratory developed services.

### ***Real Life Implications for Patients***

I am a laboratory physician in a community teaching hospital. A few months ago a patient in his 20s presented symptoms of ureteral obstruction. A ureteral mass was surgically removed and diagnosed as an adenocarcinoma most consistent

with lung origin. Subsequent evaluation identified multiple lung nodules, with metastases to the mediastinum and abdomen, and pleural and pericardial malignant effusions (Stage IV). His course was complicated by cardiac tamponade due to the malignant pericardial effusion which was relieved by pericardiocentesis.

Biomarker evaluation of his tumor showed it to be negative for KRAS codon 12 and 13 mutations and negative for EGFR exon 19 and exon 21 mutations. Evaluation for the EML4-ALK translocation by fluorescence in situ hybridization (FISH) was negative, but a laboratory developed FISH assay was positive for the ROS-1 translocation, indicating that the tumor would likely respond to treatment with the targeted tyrosine kinase inhibitor crizotinib.

An initial request for coverage from his private insurer for crizotinib therapy was denied because neither the ALK nor ROS translocations had been documented at the time of the request. Once reported, the patient was started on crizotinib therapy. His oncologist reports that "after about three weeks on crizotinib, he began to feel better overall with less pain and improved ability to function. Based on the New England Journal of Medicine paper, I am hopeful that he will continue to improve clinically and his follow up imaging will confirm response." He is scheduled for follow-up evaluation shortly.

**There is no FDA approved assay for detecting the ROS-1 translocation although it is rapidly becoming standard practice to test for it and to treat with crizotinib if the translocation is present, as evidenced by the insurer's coverage policy.** My laboratory has been testing non-small cell lung cancer for the ROS-1 translocation for over a year and, more recently at the request of our oncologists, the laboratory now tests all non-small cell lung cancers for ALK and ROS-1 translocations.

The rate of clinical discovery has increased over time, largely as a result of the flexibility of the CLIA oversight model and increased computing capacity, CLIA allows for the rapid adoption of validated clinical discovery into medical practice. The FDA has consistently demonstrated it is not capable of keeping pace. There would be real consequences for the above twenty year old patient with adenocarcinoma if he had to wait for FDA clearance or approval.

The Agency has proposed a carve-out for "unmet needs" testing services, presumably like those testing services discussed above, until the FDA approves a commercial kit under the FDA proposed regulation. The testing service then becomes a "high risk" test for which pre-market approval must be pursued. This demonstrates that the Agency's characterization of "risk" is a fiction and not rooted in actual risk. These are testing services used for the same purpose, performed with the same care and diligence and conditions in a CLIA certified laboratory. Why do the consequences amplify once a FDA approved or cleared commercial diagnostic kit exists? The physicians who are uniformly concerned about patient care and safety are the skilled medical professionals who make the effort to develop and validate laboratory developed testing services for patient care, and who have the patients' best interest in mind from day one. Secondly, the mere prospect of having to pursue FDA pre-market approval would deter most laboratories from developing this as an interim "unmet need" laboratory developed testing services. This test would not be as readily available, if at all, for this patient in the kind of world envisaged by FDA.

**Medicare Coverage Policies: Hostile to 20<sup>th</sup> and 21<sup>st</sup> Century Cures and Testing Services.** At the same time that Congress has actively discussed incentives to increase access to innovative testing options through changes to the regulatory pathway, the Medicare program, a pace setter for coverage among both

private and public payers, has implemented coverage decisions contrary to the weight of clinical evidence and clinical expertise of nationally recognized subject matter experts. The experts who have expressed opposition to these coverage policies hail from flagship academic medical centers, community laboratories, and leading reference laboratories. **These coverage decisions have constrained patient access to current testing and 21<sup>st</sup> Century cures.**

The College of American Pathologists, the American College of Medical Genetics and Genomics, and Association for Molecular Pathology have submitted detailed comments, peer-reviewed evidence and clinical practice guidelines to a key Medicare contractor that has issued coverage denials for a range of genetic clinical tests. To be clear, the coverage denials cover a broad number of previously covered genetic tests that represent the standard of care. These tests end the often lengthy and expensive diagnostic journey and result in patients obtaining life-saving treatments. These denials by the Medicare program create significant barriers to existing testing services, but also hamper the next generation of testing services (which are typically the necessary prerequisite to identification of viable commercial diagnostic kits). The Subcommittee should consider carefully scrutinizing the current Medicare coverage activities that are a real threat to appropriate patient medical care and the future of innovation.

### *Real Life Implications for Patients*

We [the Wilson's Disease Association (WDA) . . . ] received a communication from one of our members that a Medicare contractor, Palmetto GBA, has determined that gene testing for the diagnosis of Wilson Disease is not a covered Medicare benefit, stating:

ATP7B gene mutations have been primarily associated with Wilson Disease, a disorder of copper metabolism. However, serology remains the gold standard for testing and treating the signs and symptoms of this condition. At present the literature does not support that ATP7B gene testing changes physician treatment or improves patient outcomes. Therefore, Palmetto GBA has determined ATP7B gene testing is a statutorily excluded service and panels of tests that include the ATP7B gene.<sup>1</sup>

Palmetto is mistaken in its assertion that the literature does not support gene testing and that such gene testing will not change physician treatment or improve patient outcomes [for Wilson disease]. In fact, the peer reviewed clinical literature is clear, and well-established practice guidelines include gene testing: “[d]iagnosis of Wilson disease cannot be made by a single test alone and a combination of tests is always needed.” Weiss KH. (2013) Wilson Disease, GeneReviews. Furthermore, [...] the American Association for the Study of Liver Diseases (AASLD) Practice Guidelines states: “[m]utation analysis by whole-gene sequencing is possible and should be performed on individuals in whom the diagnosis is difficult to establish by clinical and biochemical testing.” In order to correctly treat individuals suspected of having Wilson disease, a diagnosis must be made. The notion that accurate diagnosis will not promote improved patient outcomes flies in the face of basic common sense as well as documented clinical evidence. The member who flagged this issue for WDA had

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<sup>1</sup> Per Palmetto's website: Statutory Exclusion [Medicare] covers diagnostic testing “except for items and services that are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member,....”.

a parent who was/is a Medicare beneficiary who had a host of symptoms that suggested Wilson Disease, but for whom all other tests were not conclusive. (Contrary to Palmetto's assertions, the foregoing is not an uncommon occurrence.) This Medicare beneficiary underwent a significant diagnostic journey with multiple hospitalizations and visits to a large number of specialists. It was not until she underwent genetic testing that it was established she had Wilson Disease. This Medicare beneficiary's costly and deleterious diagnostic journey ended and she began to receive treatment.

The foregoing excerpt from a patient group to Medicare is an accurate characterization of the overwhelming medical literature and clinical expertise supporting continued access and coverage of genetic testing for suspected Wilson Disease (WD) when conventional testing is inconclusive. About 10 U.S. laboratories have medical professionals able to offer DNA sequencing analysis of the ATP7B gene, which causes WD. At least one laboratory has offered this service for nearly a decade. This test is an important tool in the WD diagnostic armamentarium as the more traditional testing procedures are all prone to inconclusive results. Furthermore, another option, a liver biopsy is expensive and often an unnecessarily invasive procedure for medically compromised patients as compared to genetic testing. The proper diagnosis of WD has very effective treatment options for most patients. When diagnosed early, patients have treatment options that will allow them to live long and productive lives. **If left undiagnosed/misdiagnosed these patients will suffer extreme morbidity, physically and mentally, ultimately leading to death.** Unfortunately, if the diagnosis is made late, treatment often at this stage cannot reverse all symptoms, especially psychological damage.

Despite all of the foregoing, Medicare, as with a large number of other genetic tests with equally compelling clinical evidence to support coverage, has left unchecked the coverage decisions of key contractors that are not supported by the weight of clinical evidence and the recommendations of the leading medical authorities. The negative impact of these coverage decisions undermines any efforts to innovate as the evidence bar moves in a capricious manner and contrary to patient interests. CMS coverage policies coupled with the FDA's overregulation of commercial kits and proposal to expand to laboratory developed testing services have begun to turn back the clock of medical innovation, patient access to life saving testing services, and the promise of widespread access touted when the Human Genome Project mapped the first reference genome. **A critical juncture has been reached and there is an urgent and immediate need that the Health Subcommittee clears the barriers that two overreaching federal agencies have erected to personalized medicine and 21<sup>st</sup> Century Cures.**

### **Concluding Comments**

The Subcommittee is considering issues that have real consequences for whether patients are able to obtain often life-saving clinical testing services. The rate of discovery and innovation has been fueled by physician laboratory medical practice. The real question is whether heavy-handed government actions will obstruct continued progress in 21<sup>st</sup> Century medicine. We strongly urge the Subcommittee to move forward legislation that will rescind FDA's proposed regulation of laboratory developed testing services while modernizing CLIA and reforming FDA oversight of commercial kits. We further urge the Subcommittee to consider the negative impact of coverage decisions by federal health care programs on current patient access and future innovation.



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January 5<sup>th</sup>, 2015

To  
The House Energy and Commerce Committee  
United States Congress and Senate  
Washington, D.C

Honorable Committee members,

**REF: 21<sup>st</sup> Century Cures – Request for Feedback: A Modernized Framework for Innovative Diagnostic Tests**

Kindly accept our feedback for the above request. We have listed each of the questions posed by the committee and provided feedback below to each question.

1. 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?

**Our feedback.** Risks are minimal with LDTs compared to medical devices and distributed test kits. Because LDTs are under the supervision of CLIA, regulation already exists and are performed by highly trained personnel and are also supervised by M.D or Ph.D level professionals. Whereas the distributed kits are not CLIA regulated, are not performed by technical personnel and are not supervised by higher level professional personnel. Therefore, some level of risk exists with distributed kits. Traditional medical device classification is not appropriate for LDTs as described in feedback to question #2 below.

2. 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?

**Our Feedback.** Medical devices and 21<sup>st</sup> century LDTs are two different worlds. The 21<sup>st</sup> century LDTs are developed based on solid basic biochemical or molecular research conducted *In Vitro* in the laboratory. Majority of LDTs are also developed based on solid publications in peer reviewed journals. Whereas devices are instruments developed to measure gross changes that may indicate an abnormality but instruments do not conclusively establish an abnormality unless confirmed by laboratory testing. Therefore, the authentication of the instruments have to be thoroughly established and regulated rigorously for clinical usage. The high accuracy of LDTs and low percentage of false positives and negatives do not require same level of regulation as devices. LDTs are also of low risk because highly accurate biochemical testing is performed directly on the tissue of the disease, whereas a device measures a gross change based on non-chemical readings which are not performed on the isolated disease tissue. We believe the direct biochemical testing involved in LDTs pose little risk compared to devices which measure gross changes and are not accurate. The radical difference between the two warrants regulation of devices but not LDTs.

3. 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?

**Our Feedback.** Pre-market regulatory review process will be a major barrier to patient access to new diagnostic tests. Currently due to low interest in funding LDT development by NIH, lukewarm interest by investors in LDTs because of unpredictable reimbursement, weak patent protection, LDT industry is already limping. LDT development and access to patients especially difficult to cure diseases such as cancer will come to a standstill if a burden of pre- market process will be instated.

4. 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?

**Feedback.** We believe the process described below will be most appropriate.

The Secretary shall approve an application for a provisional premarket approval application if the information contained in the application demonstrates that, the probable benefit to health from the use of the LDT outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available LDT or alternative forms of diagnosis if any, as well as the risk of having now such diagnostic test; and the applicant must demonstrate that no comparable LDT are available to treat or diagnose the disease or condition.

The requirements and evidentiary burdens required by the Secretary in evaluating and approving applications for a provisional pre-market approval shall be no greater than those for a Humanitarian Device Exemption unless stipulated otherwise under this section using an application and maintenance process to be promulgated by the Secretary.

- A. The Secretary shall approve a provisional premarket approval application that meets the requirements of this section within 90 days of receipt of the application.
- B. An application that meets the requirements of this section is not subject to the fees set forth in this chapter for premarket approval applications if the applicant is a small business. As used in this section a small business is a business with fewer than 100 full-time employees.
- C. An approved provisional premarket approval application is subject to the following requirements:

A report to be submitted to the Secretary annually which shall contain the information prescribed by the Secretary describing the marketing experience and real-world clinical performance, of the LDT, including any adverse events. ii. The labeling must state that although the device is authorized by Federal Law, the effectiveness of the device for the specific indication has not been conclusively demonstrated.

The provisional approval expires five years from the date that it was approved, provided, however, that the applicant may request that the Secretary grant one or more two year extensions upon demonstration that the cost of developing and making available in the United States the test for the unmet medical need have not been recovered from revenues received in the United States from said test.

Nothing in this provision precludes the holder of a provisional premarket approval application or any other entity from submitting a non-provisional premarket approval application for the same or a substantially similar intended use.

- 5. 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?

**Feedback:** Addresses above

6. 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?

**Feedback:** CLIA regulation is thorough in that they review periodically how the LDT is administered to ensure no risks are posed to health of public. CLIA has all regulatory procedures in place to ensure that the LDT is provided to clinician clients. FDA regulation will be repetitive of CLIA. It adds to the burden of already anemic LDT industry because of low reimbursement rates. **The double regulation by CLIA and FDA will be lethal to the already limping LDT industry.**

7. 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)?

**Feedback:** Addressed above.

8. 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?

**Feedback:** Obviously already existing LDTs should be continued otherwise the healthcare industry will collapse. If any regulation will be introduced, a timeline as for a new test can be drawn as stated above for the existing tests except that the limitation on the volume (number of tests/year) should be changed to the number that is currently in existence. In addition, they will be required to submit the regulatory application in 1-2 years rather than 5-7 years given for new LDTs

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

**Feedback on incentives:**

- a. **Incentive 1. Changes at the NIH/NSF in funding LDT development.** Sequencing of human genome and sophisticated technological developments in molecular analysis of diseased tissues have opened unlimited opportunities to device LDTs for molecular classification of diseases for prognostication and personalized treatments. However, **the biggest impediment in developing the molecular LDTs for 21<sup>st</sup> century has been the outdated funding practices followed by NIH/NSF.** Although SBIR funding is available for developing innovative technologies, LDT development has received very low priority because it is considered not innovative.

Although we currently have enormous knowledge on diseases, that knowledge has not benefitted tax payers because of lack of interest by NIH in funding LDT development. We also like to point out here that none of the LDTs in the market currently are funded by NIH. We strongly urge the committee to bring changes at the NIH to promote funding for LDT development for 21<sup>st</sup> century cures. One way of bringing changes could be prioritizing SBIR funding for LDT development, establishing study sections on LDT development, changes at the review level to bring experienced experts in LDT development for selection process for unmet needs

- b. **Incentive 2. Changes at the Regulatory level.** Funding for LDT development from private investors has been lukewarm due to regulatory burden, low and unpredictable reimbursement, and weak patent protection. The recent FDA draft guidance on regulating LDTs has brought to a near standstill what little investment interest there was. To jump start the LDT development for 21<sup>st</sup> century cures, we urge the committee the following changes at the regulatory level.

- 1). Pre-market approval of LDTs by FDA. Approving the LDTs for unmet needs by diagnostic industry including small businesses within 90 days of receipt of the application.
- 2) Approve testing for a limited number of tests each year in the USA not to exceed 20,000-40,000 tests.
- 3) The provisional premarket approval could expire between 5-7 yrs which will give enough time for the companies to establish the reimbursement and gather enough prospective data to submit full application to FDA for final approval.

We want to thank the committee for giving us an opportunity to submit our feedback on LDT development and regulation. If any additional information is required or attendance in person, we will be happy to do so.

Thank you and best regards,

Sincerely,

  
Indira Poola, Ph.D  
President, Silbiotech, Inc

January 5, 2015

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

Dear Chairman Upton:

The American Association for Clinical Chemistry (AACC) welcomes the opportunity to provide input regarding the Energy and Commerce Committee's 21<sup>st</sup> Century Cures initiative, particularly in response to your questions regarding laboratory developed tests (LDTs). In general, we have serious concerns about the Food and Drug Administration's (FDA's) plans to expand its oversight to all LDTs.

Traditionally, the Center for Medicare and Medicaid Services (CMS) and various states and private sector accrediting organizations have provided effective oversight of LDTs. Without documented evidence of a problem we are concerned that the proposed level of FDA involvement, if implemented, may stifle laboratory test innovation and hinder improvements in patient care.

It's important to note that LDTs of the 21<sup>st</sup> century benefit patients of all ages, from babies still in their mother's womb who undergo fetal lung maturity testing to newborns who are screened for myriad genetic diseases or conditions. LDTs also aid children who must undergo follow-up testing if indicated by the results of newborn screening tests, as well as subsequent monitoring if a genetic disorder is detected. Bacterial speciation to determine appropriate antimicrobial drug therapy, as well as therapeutic drug monitoring, may help both children and adults who have bacterial infections. These are but a few of the many LDTs that have become critical components of modern patient care. Our specific comments follow.

***Stakeholder Access***

Testing of patient samples falls within the practice of laboratory medicine. Health care providers within this discipline include pathologists, doctoral level clinical scientists, clinical laboratory technologists and technicians. The positions, roles and responsibilities for these individuals are clearly defined in the regulations implementing the Clinical Laboratory Improvement Amendments of 1988 (CLIA'88). Their responsibilities include conducting the analytical aspects of a test as well as providing guidance on appropriate test utilization and interpretation of laboratory test results.

Laboratories typically develop LDTs to address special needs associated with unique patient populations and in cooperation with physicians to assist in the diagnosis and treatment of their patients. More recently LDTs have evolved as part of many multidisciplinary translational research efforts. Once a new method or test is developed, the laboratory frequently shares its data with other laboratories by publishing its findings in a peer-reviewed scientific journal and/or by presenting a paper and seminar at a scientific meeting. This process allows other testing facilities to critically evaluate and verify the performance and claims of such test methods or to identify issues and make improvements. To limit physician and patient access to these ‘personalized’ tests could result in misdiagnosis, worse patient outcomes and higher health care costs. We suggest that any regulatory changes in this arena be carefully researched and evaluated before adoption.

#### ***Current FDA Model and Adoption of Risk-based Model***

The FDA regulatory structure for IVD medical devices is not appropriate for the vast majority of LDTs performed by clinical laboratories. The FDA clears and approves IVD medical devices that are marketed to be used in a variety of medical settings by a diverse group of health care personnel. LDTs, on the other hand, can only be performed by high complexity CLIA laboratories under the direction of highly trained and experienced personnel. Although each is invaluable to patient care, LDTs and IVD medical devices are distinctly different tools in the health care process and as such they need to be regulated separately and differently.

AACC supports the use of a risk-based classification approach to differentiate those medical laboratory tests that should be subject to FDA oversight. This classification scheme should identify three risk categories: high, moderate, and low. Only high risk laboratory tests (we expect this to be a small subset of LDTs) should be subject to joint FDA and CMS oversight. We recommend that professional laboratory associations, such as AACC, medical societies, medical device manufacturers and other stakeholders work collaboratively with the FDA to identify criteria and categorize LDTs prior to finalizing the guidance. Two candidates for inclusion in the high risk category are: In Vitro Diagnostic Multivariate Assays (IVDMIA) (IVDMIA are LDTs developed and performed by a single laboratory that cannot be independently validated) and direct-to-consumer genetic tests (predictive tests that may have unsubstantiated test claims and no mechanism for professional interpretation/involvement).

#### ***Post Market Controls and Supplemental premarket submission***

Post-market controls require the evaluation of patient events (and near-events) as a consequence of LDT failures, malfunctions and use-errors. Which types of events should be reported is subject to debate, as most LDTs have internal laboratory controls associated with the analysis that will detect many analytical and pre-analytical errors and prevent wrong results from being reported. Those high risk LDTs that experience failures and ultimately impact a patient should be investigated by the laboratory – to change processes and help to prevent recurrences. We also

agree that such occurrences should be publicly reported as part of post-market monitoring to enable the identification of trends and weaknesses associated with particular tests or methodologies.

Regarding the issue of supplemental pre-market submissions for high risk LDTs that may be subject to regulation by FDA, only those modifications that change the intended use should be subject to supplemental premarket submissions. If a modification to a test improves analytical performance, but does not change the intended use or interpretation of the test, then no supplemental review should be required.

### ***Product Labeling***

Most LDTs are created to meet a specific and highly specialized clinical need for particular patients under the care of medical institutions served by a given laboratory. The LDT results are applied in light of the specific clinical management pathway designated for the target population of patients and are often incorporated into an algorithm that includes clinical and other diagnostic information to make the best treatment decisions. These tests are being utilized in conjunction with best practice algorithms of care and through direct interactions with clinicians and other clinical information.

Although LDTs performed within a clinical laboratory are not currently subject to FDA labeling requirements, the laboratory must comply with disclosure obligations prescribed by CMS and its deemed accrediting bodies. These criteria stipulate that results from an LDT must be accompanied with a statement that the data were produced using a method that has not been reviewed by the FDA and was developed by the reporting laboratory. Similarly, the College of American Pathologists requires the use of a disclaimer when the laboratory is asked to perform a test/analysis that has not been validated by the FDA process. The statement often includes the caveat that the provider must interpret the results in the context of the total patient findings.

### ***Relationship between FDA and CMS***

The FDA is responsible for regulating commercial IVD medical device test kits that have been cleared or approved for use in clinical laboratories. Commercial IVD medical device manufacturers must research and develop the test, acquire evidence to support its intended use and indications, meet various quality system controls and comply with marketing, labeling and post-market surveillance requirements. These companies are also subject to periodic inspections and pay user fees to the FDA.

Clinical laboratories utilizing LDTs under the existing CLIA '88 regulations must go through a similar process of research, development, performance evaluation, quality assurance and inspection, but are subject to different regulatory requirements. An IVD medical device is a product sold typically to a large number of unaffiliated and diverse clinical laboratory providers by a broad range of foreign and domestic commercial entities, whereas LDTs developed in clinical laboratories provide a service offered to well-known and affiliated physician partners.

Chairman Upton  
January 5, 2015  
Page Four

AACC believes the current CMS oversight process should remain in place for the vast majority of LDTs. CMS and FDA should work together, however, to streamline any overlap between the two agencies regarding oversight of high risk laboratory tests, particularly in regards to test validation (many laboratories performing high risk tests may already be participating in a private sector accreditation program that requires clinical validation prior to introducing a test), quality control and post-introduction test evaluation. This collaborative effort should also consider the important role that private sector accreditation bodies play in LDT oversight.

### **Public Health Testing**

The current regulatory structure has permitted clinical laboratories to respond quickly to public health emergencies, such as HIV, SARS & Ebola, develop LDTs for individuals with rare conditions for which it may never be cost-effective for an IVD medical device manufacturer to develop a test, and modify existing commercial IVD kits to meet specific clinician/patient needs. AACC is concerned that additional, duplicative regulatory requirements could obstruct efforts to meet public health emergencies and hinder the innovative abilities of clinical laboratories.

### **Grandfathering of LDTs and Maintaining Innovative LDTs**

Grandfathering existing LDTs is a disincentive for labs to introduce new LDTs. There needs to be a fair and comprehensive system that focuses on high risk laboratory tests, while continuing to allow moderate and low risk tests to be performed under current CMS regulatory oversight.

The development of LDTs plays a critical role in providing new innovative technologies that offer hope and assistance to many patients. The clinical laboratory community has historically been quick to respond to changing clinical and service needs, such as meeting the need for more sensitive and specific therapeutic drug monitoring tests, and filling the gaps when FDA-cleared or approved commercial tests are unavailable. The best means of maintaining this innovative process is to keep the current regulatory structure in place with only minor modifications.

By way of background, AACC is the principal scientific association of professional laboratorians—including MDs, PhDs and medical technologists. AACC's members develop and use chemical concepts, procedures, techniques and instrumentation in health-related investigations and practice in hospitals, independent laboratories and the diagnostics industry worldwide. The AACC provides international leadership in advancing the practice and profession of clinical laboratory science and medicine and its applications to health care. If you have any questions, please call me at (404) 616-5489, or Vince Stine, PhD, AACC Director of Government Affairs, at (202) 835-8721.

Sincerely,



David D. Koch, PhD, DABCC  
President, AACC



## COLLEGE of AMERICAN PATHOLOGISTS

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January 5, 2015

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

[cures@mail.house.gov](mailto:cures@mail.house.gov)

Dear Chairman Upton:

The College of American Pathologists (CAP) appreciates the opportunity to comment on the Energy and Commerce Committee's 21st Century Cures Initiative regarding Laboratory Developed Tests (LDTs). Pathologists are at the forefront of utilizing new methods of molecular and genomic testing to predict and diagnose disease, and to guide specific patient treatment. Therefore, CAP welcomes the opportunity to offer our expertise as it relates to laboratory medicine. Specifically, we are responding to the committee's request for feedback on a list of questions regarding the Food and Drug Administration's (FDA) issuance of guidance for LDTs.

CAP represents 18,000 pathologists who practice clinical and/or anatomic pathology in community hospitals, independent laboratories, academic medical centers and federal and state health facilities. With extensive experience as a quality standards-setting organization, the CAP accredits more than 7,000 laboratories and enrolls as many as 23,000 laboratories in its Proficiency Testing (PT) programs.

As you know, the FDA released its draft guidance notification to Congress in July. The CAP is working with both private and public stakeholders on the guidance and plans to participate in FDA's public hearing and to submit official comments. The CAP will share our comments with the committee as we continue our discussion with the FDA. CAP is not opposed to the guidance review process, as opposed to official rule making, since we believe it provides stakeholders and the FDA with greater flexibility to change the proposed oversight document. In addition, it facilitates FDA's ability to make changes after the final guidance that can adapt to new innovations in science and technology.

However, for support, the CAP maintains that the final guidance document must be consistent with the College's longstanding LDT policy. The CAP's principles are to 1) assure quality laboratory testing for patients 2) allow for continued innovation in diagnostic medicine and 3) to establish the least burdensome regulatory requirements for laboratories.

CAP believes that a balanced risk-based approach to the federal oversight of LDTs is necessary to promote and foster innovation and to meet patient needs. In addition, LDTs should meet certain analytical and clinical validity standards. Test classification should be based on overall test complexity and potential risk to patients. Our proposal (attached) achieves this balance by providing a role for oversight of low to moderate risk tests under the Clinical Laboratory Improvement Amendments (CLIA), with validation through third party accreditation organizations to prevent unnecessary delays in test offerings, as well as a role for the FDA for review of only high risk tests.

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## COLLEGE of AMERICAN PATHOLOGISTS

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CAP supports the grandfathering of diagnostic tests developed prior to 2003. Our goal is to ensure a reasonable framework that provides accurate testing for patients without overburdening laboratories with regulations or stifling innovation.

LDTs represent some of the most innovative and highest quality tests offered in health care. They are developed by laboratories as a service to patients and not as products to be sold or distributed commercially. Typically, LDTs are well-established pathology tests intended to be used by pathologists and physicians within a healthcare system in which both are actively part of the patient's care. The definition of an LDT should include tests developed by a CLIA certified laboratory and performed by a clinical laboratory in the healthcare system in which the test was developed. CAP does not support a narrow definition of an LDT that places established LDTs into a medical device category. CAP also does not support a broad category of high-risk tests that includes companion diagnostics. CAP believes LDTs may incorporate a myriad of components from research use only to FDA approved/cleared tests, including modified kits.

The regulation of LDTs presents challenges in both the scope as well as in the intrinsic complexity associated with the way they are performed in the clinical laboratory. CAP strongly believes that the majority of LDTs represent a relatively low risk to patients. Therefore, it is vital that any regulatory structure strike the right balance in asserting authority over the regulation of LDTs.

Sincerely,

John Scott  
Vice President, Advocacy  
CAP

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January 5, 2015

**VIA email to: [cures@mail.house.gov](mailto:cures@mail.house.gov)**

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

**RE: 21<sup>st</sup> Century Cures – Request for Feedback: A Modernized Framework for Innovative Diagnostic Tests**

Dear Chairman Upton:

On behalf of Genetic Alliance, I respond to your request for responses to the questions you posed to stakeholders regarding the regulation of innovative diagnostic tests.

Genetic Alliance is a network of patient organizations and other health organizations that work toward individuals, families and communities transforming health. We create products and processes to enable action and advocacy. Examples of our work include: Genetic Alliance was the lead organization in the passage of the Genetic Information Nondiscrimination Act in 2008, and Genetic Alliance has a leadership role in the Patient Centered Outcomes Research Network (PCORnet) Patient Powered Research Network (PPRN).

I am just a mom, a mom of two kids who have a genetic condition - pseudoxanthoma elasticum (PXE). In 2000, as a lay person (I have a master's degree in theology) with my husband (who was a construction engineer having only attended high school), we discovered the gene associated with PXE. We then attempted, with the help of a diagnostic company (Transgenomic), to create a FDA cleared diagnostic test – we always take the high road. That process took three years, and cost Transgenomic enormous amounts of money. In the end, we did not have a cleared test, despite having data on hundreds of individuals. This is because FDA did not have a way to oversee this development, the goal posts kept moving, and in the end it was clear that the test belonged in a service environment. Having patented the gene to be good stewards of it, we licensed the test to a lab, GeneDx, for \$1. We learned a great deal in the process. What I comment here is hard earned knowledge from an experience few people or companies have had.

Our responses follow the Committee’s language in bold.

- 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?**

We agree there should be clear lines separating the development and manufacturing of a diagnostic test, the actual conduct of a diagnostic test, and the practice of medicine. A test is developed by laboratory and is then ‘manufactured’ in the sense of having the various physical materials assembled. A test is then ‘conducted’; steps like baking a cake by following a recipe are taken. Then the practice of medicine occurs – the test is interpreted by a licensed healthcare practitioner. At this point the test might be used to guide treatment, or make a diagnosis.

- 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’ is the collection of physical materials required to run the test (e.g., reagents, supplies, equipment) together with the directions for use. The ‘development’ and ‘manufacturing’ of these materials may be appropriate for regulation by the FDA.

Conducting the test and interpreting it is subject to regulation under CLIA, state laboratory licensure, and practice of medicine laws and should not fall under regulation by the FDA.

- 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?**

Risk should be assessed in a number of ways. Families risk a great deal every day in their management of disease. That baseline and the standard for caring for that disease must be taken into account. The use of the test is critical in assessing risk. But the development and manufacture of the test is not where the risk lies except for the rather cut and dry assessment of analytic and clinical validity. Much of the ‘risk’ in the use of the test is a result of the interpretation that is conducted in the practice of medicine. This is not like a therapeutic in which the actual administration of the therapy can pose a risk. The ‘administration’ of the test is relatively benign. The healthcare professional’s actions pose a greater ‘risk’ and are covered by healing arts laws.

It is hard to see how tests can be regulated as ‘devices’ since they are not an intervention and are not inserted into the body as such. A test is an activity used to make a decision. The FDA is relying on antiquated categories when it attempts to make a test a device.

- 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 concepts of “safety” and “effectiveness” are not relevant to the critical elements of diagnostic test performance. As above, analytical validity (i.e., accurate, reliable, and reproducible) and clinical validity (i.e., that the result reported by the test accurately diagnoses diseases, determines prognosis, or predicts clinical outcomes) are key.

- 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?**

In all cases, our healthcare system should be learning. Learning requires post market data capture and analysis. This is done far too little in the administration of medicine in general. Precision medicine inherently means that every person has the potential to be different from the next person. Therefore, it would be very productive to emphasize post market processes to improve patient access.

However, our current healthcare structure is not configured to make this easy or inexpensive. Laboratories are often outside the loop of outcomes and only provide a service. This is an area that calls for a large (majority of the nation) national cohort, ready and willing to participate in an end-to-end learning system. Every day that we wait, we lose data that is critical to our health and our loved ones.

- 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?**

The beauty of laboratory medicine is that it does learn in its contained *in vitro* system. Thus tests should be regularly improved. No extra burden should be put on test developers unless the change in a test actually has a clinically meaningful impact on test performance. One WANTS a gene panel to add a new relevant gene, or test for more mutations, as the lab’s body of knowledge grows and the overarching feedback loop into the test development creates a more precise test. A good example of this is the BRCA1/2 tests. A lab should certainly report on variants in a gene that were previously classified as ‘variants of uncertain significance’ and are now known to be benign or pathogenic without requiring submission of a supplemental clearance or approval.

- 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?**

The ‘labeling’ for a diagnostic test may include the packaging and any other written, printed, or graphic material that is included with the packaging for or that otherwise accompanies the physical materials that are used in performing the diagnostic test. However, standards for dissemination of scientific information regarding diagnostic tests should differ from the standards applicable to ‘traditional’ medical devices.

A laboratory test is a clinical service. CLIA regulations require a number of elements for that service: clinical consultation to clients, assist clients in ensuring that appropriate tests are ordered, ensure that test result reports include patient information so that patient’s can interpret the result, and ensure that consultation is available and communicated to patients on matters related to the quality of the test results reported and their interpretation concerning specific patient conditions. Labeling requirements for diagnostic tests should not stand in the way of fulfilling these requirements. This disseminated information should be truthful.

- 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 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?**

There is duplication between the requirements outlined in the draft LDT guidance documents and those assessed under CLIA. A careful description of these should be made and duplication removed. The overall system suffers from a lack of resources and any extra expense that doesn’t add value should be avoided. Further, clarity through a single set of requirements would great benefit the testing industry and the patients they serve.

- 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)?**

Rare diseases, neglected diseases and public health threats through infectious diseases suffer an enormous burden. They are rarely interesting to developers, and certainly are not of much interest to the investment community because the return on investment is

limited. These tests deserve an expedited regulatory pathway, and manufacturers and laboratories that develop diagnostic tests used for rare diseases and unmet medical needs should be incentivized, not penalized.

'Rare disease' is defined in the Orphan Drug Act as a disease or condition affects fewer than 200,000 people in the United States. The FDA also has a device-specific exemption for rare conditions (the humanitarian device exemption (HDE)), and this exemption is available only for devices intended to treat or diagnose a disease that affects fewer than 4,000 people in the United States per year. Because *in vitro* diagnostics are often used for purposes of treatment selection – i.e., to identify a subset of patients with a condition in whom a treatment may be appropriate – it would be appropriate to make “rare” status consistent with those used to designate orphan drugs, not devices under HDE. The same consideration should be given to neglected diseases.

**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?**

Here, Genetic Alliance supports the recommendations of the Coalition for 21<sup>st</sup> Century Medicine:

- Existing distributed test kits – i.e., tests that are currently regulated as medical devices by the FDA – should be allowed, for a period of time after the implementation of the new framework, to comply with the requirements for medical devices under the FFDCAs or the requirements of a new diagnostics-specific framework. After a period of time, a previous approval or clearance under the FFDCAs should be deemed an approval under the new framework, and distributed test kits should be required to comply with the regulatory requirements established under the new scheme.
- Existing LDTs should continue to be under enforcement discretion for a period of time after the implementation of the new framework. Eventually, however, an LDT should be required to obtain an approval from the FDA to the extent such approval is required under the new framework. In deciding which LDTs should be subject to the regulatory scheme first, the FDA should prioritize the LDTs that pose the greatest risk to patient health based on a risk scheme that has been proposed, vetted by the public, and adopted through regulation prior to implementation so that providers have sufficient notice and time to adapt to the new regulatory process.
- New distributed test kits should, for a period of time after the implementation of the new framework, be permitted to submit a marketing application as either a medical device under FFDCAs or under the new framework applicable to diagnostics. Insofar as a new distributed kit is approved or cleared under the FFDCAs, such approval or clearance should be deemed an approval under the new framework at the same time such deeming occurs for existing distributed tests.

- New LDTs should be required to comply with the new regulatory framework from the date of implementation of the statute. This may involve notification and adverse event reporting when requirements for such notification and adverse event reporting under the new framework are implemented. With respect to pre-market submission, this should follow the same prioritization as for existing LDTs, above, considering which LDTs pose the greatest risk to patient health.

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

I co-chair the Institute of Medicine's Roundtable on Translating Genomic-based Research for Health. This is a subject we have debated over the seven years the Roundtable has been deliberating. I think we understand that a solid and predictable regulatory system is critical. Test developers must not face high burdens for evidence that exceed the practical value of the tests. The overall system must 'learn' – without a learning healthcare system, more accurate and efficient tests will continue to elude the healthcare system. Finally, partnerships between advocacy organizations, clinicians and test developers must be formed in order to take advantage of continual system improvement.

Sincerely,



President & CEO

January 9, 2015

## **A Modernized Framework for Innovative Diagnostic Tests**

### *Incentivizing the Development of New, More Accurate, or More Efficient Diagnostic Tests*

GlaxoSmithKline (GSK) appreciates the opportunity to provide our perspective on the need to modernize public policies affecting the development and delivery of diagnostic tests, particularly those tests guiding the use of precision medicines. GSK is a science-led global biopharmaceutical company dedicated to improving the quality of human life by enabling people to do more, feel better, and live longer. An industry leader, GSK discovers and develops a broad range of innovative products in Pharmaceuticals, Vaccines, and Consumer Healthcare.

Precision medicines or targeted therapeutics make use of genetic or other biomarker information to inform treatment decisions for patients. Over the past twenty years, the number of targeted therapies approved by the Food and Drug Administration (FDA) has increased, with targeted therapies representing approximately forty-five (45) percent of FDA new drug approvals in 2013.<sup>1</sup> The use of a diagnostic test is often required to identify the appropriate patient population for a targeted therapy. A “companion” diagnostic is a diagnostic test that is *essential* for the safe and effective use of a therapeutic product in a selected patient population.

As a manufacturer of precision medicines the use of which is guided by diagnostic tests, including companion diagnostics, GSK has a strong interest in ensuring a vibrant market for the development and use of high quality, reliable, and accurate diagnostic tests, both traditional *in vitro* diagnostic (IVD) test kits and laboratory developed tests (LDTs).

Where an IVD device is essential for the safe and effective use of a therapeutic product, FDA generally requires an approved or cleared IVD companion diagnostic device.<sup>2</sup> GSK markets several products with approved companion diagnostics developed by diagnostic partners, and we anticipate that certain investigational assets, if approved, will enter the market with companion diagnostics.

LDTs also are relevant to patient access to our medicines. Health care providers may and often do choose to use an LDT or a group of LDTs to guide their treatment decisions even when an FDA-approved/cleared alternative diagnostic test is available. Additionally, through our specialist HIV joint venture, ViiV Healthcare, we also market medicines for which clinicians use LDTs to inform treatment decisions.

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<sup>1</sup> Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, FDA, Statement Before the Subcommittee on Health, U.S. House Committee on Energy and Commerce, July 11, 2014.

<sup>2</sup> FDA, *In Vitro Companion Diagnostic Devices: Guidance for Industry and Food and Drug Administration Staff*, August 6, 2014, at 7-8.

Therefore, any change in regulatory or payment policy that impacts diagnostic tests, whether traditional IVD tests or LDTs, could have near- and long-term impacts on patients' ability to access our medicines and on the development of new targeted therapies.

GSK applauds the Committee's interest in modernizing governmental oversight of diagnostics tests. Each of the questions posed in the Committee's White Paper implicates complex issues that deserve thorough analysis, especially as they pertain to FDA's proposal to regulate LDTs. However, given the short timeline, we have chosen at this time to highlight a few themes in the context of question 11: *What incentives can be put in place to encourage the development of new, more accurate or more efficient diagnostic tests?*

## **Policy Challenges to Diagnostic Test Innovation**

Current and proposed regulatory and payment policy poses barriers to innovation in the development of diagnostic tests and associated precision medicines.

### *Regulatory Barriers*

The regulatory challenges to diagnostic test innovation are two-fold.

First, the regulatory path for companion diagnostic tests, especially in early stage development, is vague, constantly evolving, costly, and not fully aligned with the drug approval process. Regulatory uncertainties unnecessarily complicate and prolong efforts to make companion diagnostics – and thus their associated precision medicines – available to clinicians and patients.

For example, the regulatory requirement for contemporaneous pre-market approval (PMA) of a companion diagnostic test related to a drug with a Breakthrough Therapy designation poses a major challenge to approval of the drug. Investigational companion diagnostic tests used to make patient management decisions during an early phase therapeutic clinical trial are subject to FDA Investigational Device Exemption (IDE) regulations. However, the appropriate level of documentation needed to comply with the FDA IDE requirements in this context is not well understood. Presently, it appears that FDA applies the IDE regulatory requirements in a non-standardized, case-by-case manner. Consequently, GSK supports a recommendation by the Pharmaceutical Research and Manufacturers of America (PhRMA) that FDA provide clarity on the use of investigational companion diagnostics in early phase therapeutic clinical trials and in the area of IDE requirements for development of drugs for orphan indications requiring companion diagnostic tests.

Another area of regulatory uncertainty concerns clinical "bridging study" testing requirements for companion diagnostics. Often in clinical studies, precursors of the final commercial diagnostic assay are used. Innovators require additional clarity from FDA as to the requirements for demonstrating comparability between the earlier "clinical trial assay" format of the companion diagnostic and its final FDA approved version.

The regulatory challenges we and our diagnostic partners face are compounded by the fact that FDA has tended to regulate in this area through non-binding guidances. Although this approach gives the agency flexibility in an area of rapidly changing science, it creates uncertainty among regulated entities because the agency is not bound by its own recommendations and may change or retract the guidances without notice and public comment opportunity.

The second, potential regulatory barrier concerns the proposed regulation of LDTs. FDA's current draft proposals<sup>3</sup> to regulate LDTs as medical devices could, if not better defined and simplified, unintentionally lead some clinical laboratories – especially specialized labs focused on unmet medical needs – to cut back on the development or clinical availability of LDTs. A similar impact could be felt among small start-up diagnostic companies that presently offer their innovative tests as LDTs, either because they view the current IVD test kit approval process as cost prohibitive or while they work through that process. The unintentional result could be a contraction of the diagnostic test market and fewer testing options for clinicians and patients.

GSK shares FDA's commitment to advance the public health through the use of high quality diagnostic tests and appreciates the agency's intentions behind the draft LDT guidances. Prescribers' decisions about the use of our precision therapies depend on the availability and correct use of highly accurate and reliable tests. Indeed, the foundation and promise of precision medicine – to deliver the right medicine to the right patient at the right time – is predicated on accurate test results. All stakeholders can agree that patient safety and test quality and reliability are of paramount importance.

At the same time, as outlined in the Personalized Medicine Coalition's January 5, 2015, letter to the Committee,<sup>4</sup> we must recognize the risk of unintended consequences that could result from regulatory requirements for LDTs that are unreasonably burdensome, inappropriately tailored, vague, or duplicative.

LDTs differ from traditionally regulated IVD test kits in terms of FDA submission requirements regarding quality/manufacturing documentation, delivery of product labeling to the clinician, and the necessity of prospective clinical data for test validation. Unlike traditionally regulated devices, LDTs are not self-contained products but collections of different processes organized to produce a clinical result. The FDA's proposed LDT regulatory framework must reflect these realities or it will be unworkable for LDT developers and will not achieve FDA's stated aim of ensuring high quality LDTs.

### *Reimbursement Barriers*

Diagnostic test developers also face a challenging reimbursement environment. GSK recognizes that the Committee's focus on diagnostic tests is primarily from the regulatory perspective. However, we believe that an assessment of the regulatory concerns in this space must also take into account the challenging economics for diagnostics.

Historically, reimbursement levels for diagnostic tests have been much lower than for therapeutic medicines. This situation is likely to worsen in coming years. Reimbursement rates on a per-test basis are declining because of commercial payer demands and Medicare diagnostic test bundling and are expected to decline further when changes in Medicare payment policy for clinical laboratory tests begin to take effect in 2017 as mandated by Section 216 of the Protecting Access to Medicare Act of 2014 (PAMA).<sup>5</sup>

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<sup>3</sup> FDA, *Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)*, October 3, 2014; FDA, *Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)*, October 3, 2014.

<sup>4</sup> GSK is a member of the Personalized Medicine Coalition (PMC), and we endorse the central theme – the need to strike the appropriate balance among regulation, innovation, and access to safe and effective diagnostic tests and precision medicines – of its submission to the Committee.

<sup>5</sup> H.R. 4302, Pub. Law 113-93.

The combined effect of low (and declining) reimbursements, relatively weak intellectual property protections, and unclear and – potentially in the case of LDTs – new regulatory compliance obligations creates substantial disincentives for the development of new, innovative diagnostic tests and continued provision of existing tests. GSK is particularly concerned that some specialized clinical labs and small, innovative diagnostic test companies could decide that the economics do not justify the regulatory burdens and choose to exit or reduce their presence in the market. With a contraction of the market, clinicians and patients would have fewer testing options, test turnaround times could lengthen, and innovation in the development of new diagnostics could suffer. These effects could, in turn, have near- and long-term adverse impacts on patients’ timely access to precision therapies and further advances in personalized medicine.

## **Incentives for Diagnostic Test Innovation**

Changes in current and proposed public policies are needed to ensure continued innovation in diagnostic test development and advances in personalized medicine. We identify below themes and ideas for modernizing the regulatory and reimbursement environment for these tests.

### *Modernizing Regulatory Policy*

- Connections between the drug and test approval pathways should be streamlined.
- GSK appreciates FDA’s issuance in August 2014 of final guidance for the development of IVD companion diagnostic tests.<sup>6</sup> However, as illustrated by the above discussion of clinical “bridging study” testing requirements, multiple points of regulatory uncertainty remain. IVD test developers and manufacturers of precision medicines remain in need of a clearer regulatory pathway – in the form of rules where appropriate in light of scientific advances – for the development of companion diagnostics.
- Collection and analysis of biological samples during clinical research, and subsequent retrospective analysis of these samples, is fundamental to the development of diagnostic tests and precision medicines. However, FDA-established criteria for retrospective investigations on pre-existing biological samples create an unrealistically high bar that risks limiting progress. Greater regulatory flexibility in the retrospective use of samples is needed.
- A post-approval market exclusivity period for test manufacturers could create an incentive for investment while maintaining longer-term competition.
- With regard to possible regulation of LDTs, we suggest that FDA seek to partner with third-party laboratory accreditation bodies (e.g., New York state) to leverage their experience (and extensive data sets) in examining specific LDTs with regular updates. This would promote regulatory efficiency by avoiding duplication of effort. It also would enable the FDA to monitor test quality over time rather than at a single point prior to regulatory submission – an important consideration given that, as operational processes, LDTs can be open to greater interpretation and subject to a higher risk of operator error than IVD test kits.

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<sup>6</sup> FDA, *In Vitro Companion Diagnostic Devices: Guidance for Industry and Food and Drug Administration Staff*, August 6, 2014.

### *Modernizing the Reimbursement Environment*

- Although PAMA introduced positive changes for the assignment of reimbursement codes for laboratory tests, further advances in diagnostic coding are critical for innovation in this area. More specific and descriptive codes are needed so that payers (and health services researchers) can better understand what tests are actually being run – i.e., have visibility not only to what is being measured but how it is measured, including whether the test is an FDA-approved IVD test kit or an LDT.
- Differential reimbursement for FDA-approved IVD test kits versus LDTs would encourage diagnostic companies to collaborate with manufacturers of precision medicines to develop companion diagnostic tests for these targeted therapies.
- A shift toward value-based reimbursement for diagnostic tests and away from procedural cost-based pricing would incentivize test developers to conduct additional clinical utility studies to demonstrate the value of their tests. Higher value tests could in turn receive more favorable reimbursement than lower value tests. Implementing such a transition is a complex proposition, however, and would require deliberate consideration by all stakeholders.

The foregoing list is not exclusive but merely illustrative of policy and marketplace changes that could incentivize continued innovation in this area. We welcome an opportunity to discuss these and other ideas in greater detail with the Committee.

### **Conclusion**

GSK greatly appreciates your attention to the important issues of regulation of and payment for diagnostic tests, and we thank you for the opportunity to provide our perspective on these interrelated topics. We look forward to working with the Committee as you consider changes in policy to incentivize the development and use of diagnostic tests and, by extension, precision medicines. Please do not hesitate to contact us with any questions.



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Chairman Fred Upton  
Representative Diana DeGette  
House Energy & Commerce Committee  
2125 Rayburn House Office Building  
Washington, DC 20515

January 5, 2015

Dear Chairman Upton, Rep. DeGette:

Thank you for your bipartisan leadership in driving discussions to help accelerate the discovery, development and delivery of promising new treatments to patients. Healthcare innovation is a critically important national priority, and we appreciate your dedication to soliciting input to the Committee's recent white paper on the regulation of laboratory developed tests (LDTs) from as many stakeholders as possible.

Human Longevity, Inc. (HLI) is a human health information technology and health care company focused on extending the healthy, high-performance human life span. I and my co-founders, Robert Hariri, M.D., Ph.D., and Peter H. Diamandis, M.D., have a track record of setting and achieving bold goals in genomic science, biotechnology, stem cell therapy and disruptive innovation. As stakeholders committed to innovation in health care, we want to ensure that current regulation as well as future standards reflect and encourage the highly innovative direction in which genomic technology is rapidly evolving.

In particular, next-generation sequencing (NGS) technologies enable sequencing of whole human genomes that comprise 3 billion unique data points. It is also possible to link this information with a patient's clinical data. Using the combined strength of NGS and clinical information will radically change the way diseases are diagnosed and treated. Such data-intense approaches are already being implemented in certain clinical environments (neurologic conditions, newborn screening, cancer treatments, and other situations).

Our current laboratory test regulation was not designed to address this level of power and complexity and the meaningful regulation of the new tools that are available today requires a paradigm shift in our regulatory approach: we are no longer able to prospectively clinically validate every part of the information generated (for example the 3 billion data points generated sequencing a human genome) in these tests. As we move to better understand and integrate the increasingly complex data arising from multiple sources for each patient, we rapidly reach situations in which every patient requires a tailored approach (e.g., n of 1) that makes traditional placebo-controlled clinical trials impossible. When one considers a risk-based approach to regulation of

diagnostics, one must consider not only the risk of a diagnostic test that is not sufficiently predictive or reproducible, but also the risks associated with having a regulatory scheme that is too restrictive for these exciting advancements to make their way to the clinic.

Therefore, rather than commenting on the specific questions in the white paper, we'd like to encourage a broader and longer-term view as your team carefully evaluates and drafts legislative changes to FDA's regulation of LDTs or to the FDA's authorities that impact genetic testing and sequencing. Significant innovation with the potential to change and revolutionize health care and the practice of medicine could be stifled without sound policies and a vision for the future. As the debate over the right approach to regulate LDTs continues, it is important to note that all stakeholders share the same high level goals: we need reforms that advance public health, innovation and effective treatment for patients. Within this context, we want you to be aware of our vision, so that Congress and regulators are not inadvertently limiting innovation.

As you move forward, we stand ready to help inform your efforts as best as we can. The US desperately needs new pathways that facilitate the approaches not only of today, but also for the transformative ones coming in the immediate future.

Sincerely,



J. Craig Venter, PhD  
CEO and Co-Founder  
Human Longevity, Inc.