



Testimony of

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Committee on Energy and Commerce
Subcommittee on Health

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

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STATEMENT SUMMARY

Presented by Dr. Kathy Behrens Wilsey, co-founder of the Coalition for 21st Century Medicine and a life science venture capitalist, investor, board member and executive. Dr. Wilsey served on the President's Council of Advisors on Science and Technology (PCAST) as chairwoman of its Subcommittee on Personalized Medicine. A former director of the National Research Council's Board on Science, Technology and Economic Policy, Dr. Wilsey is a past director, president, and chairwoman of the National Venture Capital Association.

- The United States is at crossroads in the ongoing revolution of personalized medicine, and could fulfill the promise of “21st Century Cures”—early, rapid and comprehensive diagnosis, and individualized, targeted treatments against serious and life-threatening diseases—only if regulators and public and private insurers align toward the objective.
- The proposed regulation of laboratory developed tests, or LDTs, could either facilitate or choke off the current development of similar progress against various cancers, cardiovascular disease, deadly infectious diseases, and countless rare diseases and disorders.
- The Coalition is deeply concerned about how the uncertain regulatory environment has discouraged investment funding in, and development of advanced diagnostics. The lack of a clear path for innovative *in vitro* diagnostics under the current FDA regulations has been evident as FDA proposes and withdraws different proposals to roll back its historic, flexible approach to these innovative tests. We believe that prolonging the current regulatory limbo or, worse, implementing an incomplete or overly burdensome regulatory framework would result in the accelerating loss of investment in American companies and the movement of our innovative discoveries offshore.
- Continued innovation is only possible if the FDA provides clear and reasonable standards that permit physicians and patients to rely upon advanced diagnostics to better guide treatment, and does so before the deadlines and threatened risks of enforcement action under its proposed “framework” guidance take effect.
- FDA must provide detailed substantive guidance on many outstanding issues before its proposed “framework” is finalized, which starts a clock for compliance among affected laboratories: (1) identifying the “device” within the LDT service; (2) harmonizing FDA and CLIA quality systems regulations; which have different purposes; (3) providing clear guidance on requirements for obtaining labeling that is useful for clinicians and patients; and (4) accommodating medical communications between providers—laboratories and treating physicians—under an FDA regulatory framework that imposes substantial limitations on pro-active communications by medical product manufacturers.
- The framework put forth by the FDA is no doubt an improvement over the initial draft guidance published in 2006, but it still leaves far too many critical questions unanswered, and hoping that the agency appropriately resolves those questions in a final guidance presents too great a risk of stifling innovation at a crucial moment in the historic evolution of advanced diagnostics.
- We also encourage the Subcommittee to consider legislation, where necessary, to fill gaps in the regulatory framework and address potential inconsistencies and duplication across regulating authorities to ensure that the balance between advancing the public health and facilitating American innovation is maintained.

Good morning, Chairman Pitts, Ranking Member Pallone, and Members of the Subcommittee. I am Dr. Kathy Behrens Wilsey, co-founder of the Coalition for 21st Century Medicine. On behalf of the Coalition, thank you for convening today's hearing to address this critical issue in health care innovation.

The Coalition for 21st Century Medicine represents world renowned diagnostic technology companies, clinical laboratories, researchers, venture capitalists, and patient advocacy groups who are working to develop and promote high quality, innovative diagnostic tests. Founded in 2006, the Coalition has a successful history of working with lawmakers and policymakers to identify meaningful ways to balance regulation and innovation, and to ensure that regulatory policy promotes rapid access to new diagnostic information.

Development of and access to innovative molecular diagnostics is essential to enabling individualized treatment, and has the potential to revolutionize our health care system. However, the potential for advanced diagnostics to help patients has yet to be fully realized due in large part to the widespread perception by many companies and investors that the costs, risks, and barriers associated with diagnostic development outweigh the anticipated returns. This perception has been fueled by a variety of failed attempts to apply a regulatory framework that was not designed, nor is well suited for rapidly advancing *in vitro* diagnostics.

Advances in technology and genomic information are rapidly changing the commercial diagnostic landscape and opening up new opportunities for advanced diagnostic tests. There is perhaps no field in which government policies will play a greater role than in diagnostic

innovation, and have the potential either to slow such innovation or to help lower diagnostic development risks/barriers.

Today's hearing is exceptionally well-timed. It is no exaggeration to say that our country is at a cross-roads in the ongoing revolution of personalized medicine. Because of the success of the Human Genome Project (HGP) and related technologies, we are closer than ever to fulfilling the promise of what this Subcommittee calls "21st Century Cures"-- early, rapid and comprehensive diagnosis, followed by individualized, targeted treatments against the most serious and life-threatening diseases. We have the tests and technology to guide treatments to the right patients at the right time. We can make extraordinary advances in medical treatment, but only if government programs align toward this future.

For the past thirty years, I have been a venture capitalist, investor, board member and executive focused on the life sciences industry. I served on the President's Council of Advisors on Science and Technology (PCAST) from 2001 to early 2009, and was chairwoman of PCAST's Subcommittee on Personalized Medicine. I am a former director of the National Research Council's Board on Science, Technology and Economic Policy, and I was the director, president, and chair of the National Venture Capital Association.

In these and other roles, I have observed first-hand how investment in personalized medicine has produced tests that help inform medical decision making to provide more effective, safer, and more efficient care. However, I also have observed how antiquated government programs designed for a different era – whether they be regulatory oversight or payment – have not been

aligned to promote that progress and in many cases, impede such progress. It is with this in mind that I believe that the proposed regulation of laboratory developed tests, or LDTs, that is set forth in the FDA’s Anticipated Details of the Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories “Framework for Regulatory Oversight of Laboratory Developed Tests (LDT)” (the “Draft Guidance”) could either facilitate or choke-off the development of diagnostic tests for various types of cancer, cardiovascular disease, deadly infectious diseases, and countless rare diseases and disorders.

We have a keen interest in the extent to which the Food and Drug Administration (FDA) intends to regulate LDTs as medical devices. Since its inception, the Coalition has been working with FDA on developing a reasonable regulatory framework that would apply to all diagnostic testing—both *in vitro* diagnostic test kits as well as LDTs—and we remain committed to that effort. We acknowledge and appreciate the time the FDA has taken to meet and to engage with us over the years, and particularly since releasing this latest guidance, aiming to develop an appropriate regulatory model for advanced diagnostic tests that protects public health and promotes innovation.

Appropriate regulation of *in vitro* diagnostic testing is essential to assuring reliability and accuracy, and fostering public confidence. At the same time, continued innovation is only possible if the FDA provides clear and reasonable standards for test developers that permit physicians and patients to rely upon advanced diagnostics to better guide treatment, and only if the Agency implements such standards before the deadlines and threatened risks of enforcement action under its proposed ‘framework’ guidance take effect. The Coalition is deeply concerned

that investment in, and development of, advanced diagnostics have already declined as a result of the current, sustained period of regulatory uncertainty. The lack of a clear path for innovative in vitro diagnostics under the current FDA regulations has been evident as FDA proposes and withdraws different proposals to roll back its historic, flexible approach to these innovative tests. We believe that prolonging the current regulatory limbo or implementing an incomplete or overly burdensome regulatory framework would result in the accelerating loss of investment in American companies and the movement of our innovative discoveries offshore.

Eight years ago, I helped found this Coalition when the FDA proposed troubling draft guidance to newly regulate a group of novel LDTs under a previously unknown term “*in vitro* diagnostic multivariate index assay” (IVDMIA) tests. For years, the Agency had recognized that “the use of in-house-developed tests has contributed to enhanced standards of medical care ... and that significant regulatory changes in this area could have negative effects on the public health.”ⁱ But when the Agency proposed to reverse this position, stakeholders from across the spectrum of medicine and health care converged to defend the proposition that high quality, innovative diagnostic tests were essential to improving health care and that the draft FDA enforcement policy over so-called IVDMIA was likely to be more harmful than helpful to patients. Since then, we have worked with the FDA, Congress and the Administration to find the balance between regulation and innovation that bolsters public confidence while promoting rapid access to accurate and reliable new diagnostic information. Despite best efforts on the part of many, today, we are still too far away from finding that balance. The framework put forth by the FDA is no doubt an improvement over the initial draft guidance published in 2006, but it still leaves far too many critical questions unanswered, and hoping that the agency appropriately resolves

those questions in a final guidance presents too great a risk of stifling innovation at a crucial moment in the historic evolution of advanced diagnostics.

We consequently applaud the Subcommittee for exercising its oversight function by holding this hearing, and encourage Congress to continue to work with the FDA throughout the public comment process. We also encourage the Subcommittee to consider legislation, where necessary, to fill gaps in the regulatory framework and address potential inconsistencies and duplication across regulating authorities to ensure that the balance between advancing the public health and facilitating American innovation is maintained.

There is no question that we have already made enormous progress since 1987 when the Human Genome Project was initiated under President Reagan in the face of widespread skepticism against this unprecedented, multidisciplinary enterprise. But with the sustained vision and material support of this Committee, of Congress, and of successive Administrations, the scientific community and American companies struggled, collaborated, and succeeded—beginning what National Institutes of Health (NIH) Director and pioneering scientist Francis Collins describes as “the dawning of the genomic age.”

Since the human genome was unlocked, there has been an explosion of research and innovation dedicated to diagnosing and treating human disease better, sooner, and faster. According to the NIH, there are tests available for about 2,500 diseases, with many more in development.ⁱⁱ Today, the United States leads the world in translating “bench” science into new diagnostics and in forming early-stage companies that will develop paradigm-changing services and products. We

have already made great strides in understanding which patients will or will not benefit from specific drugs, and have seen some early achievements in tailoring drug treatment for individual patients.

Notwithstanding this progress, the Coalition believes that delivering further on the hopes for, and promise of personalized medicine hinges on settling two strategic issues that face this Congress and the communities of scientists, innovators, regulators, and patients you have convened today:

- For years, advanced diagnostics have been under a cloud of regulatory uncertainty created by changing federal proposals to regulate LDTs, and by doubts cast on the integrity and adequacy of existing federal standards under the Clinical Laboratory Improvement Amendments (CLIA) of 1988. Flexible standards must be established that allow reliable and accurate advanced diagnostics to guide treatment by informed physicians. The Coalition believes that the FDA can work in concert with Congress and stakeholders to create an appropriate and flexible system of regulation for all *in vitro* diagnostic testing.
- If a rigid regulatory system is established that does not provide for timely access to accurate and reliable tests with clear and meaningful labeling for physicians and their patients, public and private payers will resist the coverage of, and payment for, advanced diagnostics. Without meaningful labeling or insurance coverage for these tests, physicians in turn will remain reluctant to order tests that may be helpful in the management of their patients. Today, it literally takes years for payers to approve

coverage and payment for advanced diagnostics. If these tests are available only with labeling claims that do not support the use of the tests to assist patient management decisions and under a regulatory framework which severely hampers clinical laboratory service providers from interacting with treating physicians so they have a better understanding how to use their tests in patient management, the adoption and use of personalized medicine will be stymied. We will not see the improved patient outcomes and reduction in unnecessary treatment that otherwise are already being achieved.

We are committed to working with FDA to strike the right balance between assuring public health and facilitating innovation in promulgating flexible regulations for all diagnostic tests—LDTs and IVDs. However, the Coalition is concerned that the proposed framework is incomplete, creates substantial uncertainty, and does not reflect a careful and important balance that recognizes the value and benefits that advanced diagnostics offer to patients, providers, and payers. The Coalition believes strongly that any future regulatory framework must be premised on the understanding that clinical labs today are offering new and important tests to informed physicians who are sufficiently knowledgeable about their technology and their potential clinical utility to seek them out for their patients. Developing a balanced risk-based system of regulation is only possible if the benefits and value of reliable and accurate advanced diagnostics in guiding treatment is fully understood by the Agency.

In the spirit of striking this balance, the FDA should thoughtfully articulate the public health risk supporting this guidance, so that this risk can be more carefully balanced against the proposed regulatory framework. The framework and the specific proposal to mandate adverse event

reporting, for example, presupposes—without meaningful data or other analytical bases—that there are substantial safety risks affecting American patients from the use of LDTs. A reliable presentation and understanding of the potential risks is a key component of evaluating any regulatory action.

Additionally, the Coalition is greatly concerned that the FDA substantially underestimates the number of LDTs subject to its proposed premarket review requirements. Today, thousands of clinical laboratories perform LDTs to give providers access to data that enable the development of individualized, patient-specific plans of care. For example, certain LDTs are capable of identifying patients susceptible to disease(s) and/or patients that may respond (or not respond) to a particular treatment. According to the Centers for Medicare and Medicaid Services (CMS), there are over 11,000 CLIA-certified laboratories qualified to perform “high-complexity” testing, including LDTs. We estimate that many molecular markers are offered as LDTs by hundreds, if not thousands of laboratories across the country. This would translate into potentially tens of thousands of premarket submissions to the FDA. We believe that the proposed framework creates a meaningful possibility, even with a protracted timeframe for implementation, that the Agency could burden its limited staff with a growing backlog of premarket submissions, inhibit insurance coverage and payment, and restrict patient access to innovative tests.

We also have concerns that the FDA underestimates the challenges associated with translating regulatory processes developed to oversee diagnostic *products* that are designed for broad distribution and use in contrast to *services* performed by individual laboratories. Most venture

capitalists appreciate that there are significant differences between the two that could substantially risk the successful implementation of the FDA's plans

We continue to believe that appropriate regulation is possible that balances the need to ensure patient safety with the need for diagnostic testing to help physicians and patients make informed and timely decisions about patient care. Without this balance, continued development and investment in better, more useful, and even safer diagnostic testing will be in jeopardy—and the patients and providers who would benefit from such tests will experience significant, unnecessary delays in access to critical diagnostic information and appropriate life-saving therapy.

Most importantly, because the proposed framework focuses on procedural milestones, it leaves unclear many of the critical issues and questions that must be addressed well before any of its proposed deadlines take effect. Absent resolution of these questions before guidance is published in final form, clinical laboratories would be simply unable to comply with the new requirements when the framework guidance is finalized. While we understand that FDA intends to address the unanswered issues and inconsistencies in the proposed framework, and will receive extensive public comments, it is critical that the Agency answer these questions before publishing a final guidance. The critical balance that must be struck will be elusive if FDA publishes a final guidance establishing new regulatory requirements that do not satisfactorily and completely resolve these fundamental questions.

To that end, the Coalition strongly encourages the FDA to publish additional draft guidance for comment as well as FAQ documents similar to those issued by CMS so that stakeholders will be able to understand, anticipate and comply with the new regulatory requirements well in advance of any final guidance.

The substantive issues raised by the proposed framework, which must be answered before FDA proceeds further, range from fundamental concerns to technical questions. Following are just some of the significant and critical issues that urgently require answers:

Device or Laboratory Practice?

- How would FDA distinguish a regulable “medical device” from laboratory services in an LDT? The former are analogous to test “kits” currently manufactured then distributed to laboratories to perform, while the latter are the practice of laboratory medicine outside of the Agency’s statutory authority.

Labeling.

- How will FDA ensure that labeling is meaningful for physicians and reimbursable by third party payors for patients—an issue that applies to all *in vitro* diagnostic testing (IVDs, as well as LDTs)?
- How would FDA labeling requirements apply in the absence of a distributed or tangible “box” on which to put a label, or a person or entity to “receive” the “box” or the “labeling”?

Manufacturing and Harmonization with CLIA.

- Medical device Quality Systems Regulation (QSR) requirements would apply upon filing of a premarket submission with the Agency, but the Draft Guidance does not adequately tell clinical laboratories how to comply. As one example, what constitutes a malfunction of a finished device if the test is an LDT?
- How does FDA intend to apply its rules on test design and quality systems to laboratories, and how would such requirements be reconciled with laboratories' continuing obligation to comply with CLIA quality systems requirements on those same activities?

Communications with Laboratories and Providers.

- How would FDA manage conflicting requirements governing consultations with physicians about patient test results? Under the practice of laboratory medicine, CLIA requires disclosure of known information relevant to use of a test by certified laboratory to a treating physician—without regard to “labeling claims.” This pro-active approach to dissemination of information by a clinical laboratory may be inconsistent with the restriction on dissemination of information by a medical device manufacturer under FDA regulation.
- What types of diagnostic or patient treatment claims would be permissible, and what kinds of evidence would be required by FDA?

We recognize that the FDA will receive extensive feedback from stakeholders, and the process of finalizing the draft guidance may take many months, if not years, to complete. The Coalition plans to submit public comments as well, but our concern is that reprising the protracted and unsuccessful guidance development that took place over IVDMIAAs would prolong the existing regulatory uncertainty for clinical laboratories, providers, and health systems, with adverse implications for LDT coverage and reimbursement, patient access, and investment in personalized medicine. Ultimately, this Subcommittee may be called upon to assess the necessity of expanded FDA regulation and to establish through legislation clear regulatory standards to address what historically has been a grey area of the Agency's legal jurisdiction.

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Endnotes

ⁱ Medical Devices; Classification/Reclassification; Restricted Devices; [Analyte Specific Reagents](#). Washington, D.C.: Food and Drug Administration, 1997.

ⁱⁱ [Personalized Medicine: Matching Treatments to Your Genes](#), National Institutes of Health, December 2013.