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**LABORATORY TESTING IN THE ERA OF PRECISION
MEDICINE**

HEARING
OF THE
**COMMITTEE ON HEALTH, EDUCATION,
LABOR, AND PENSIONS**
UNITED STATES SENATE
ONE HUNDRED FOURTEENTH CONGRESS

SECOND SESSION

ON

EXAMINING LABORATORY TESTING IN THE ERA OF PRECISION
MEDICINE

SEPTEMBER 20, 2016

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LABORATORY TESTING IN THE ERA OF PRECISION MEDICINE

TUESDAY, SEPTEMBER 20, 2016

U.S. SENATE,
COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS,
Washington, DC.

The committee met, pursuant to notice, at 10:06 a.m., in room SD-430, Dirksen Senate Office Building, Hon. Lamar Alexander, chairman of the committee, presiding.

Present: Senators Alexander, Murray, Burr, Isakson, Hatch, Cassidy, Casey, Bennet, Baldwin, Murphy, and Warren.

OPENING STATEMENT OF SENATOR ALEXANDER

The CHAIRMAN. The Senate Committee on Health, Education, Labor, and Pensions will please come to order. This is our 45th hearing of the last 2 years, and virtually all of them have been what we call bipartisan hearings where we invite witnesses to help inform us about the issues rather than sit around and castigate each other. I thank Senator Murray for working in that way.

This morning's hearing is about laboratory-developed tests to help us understand and get a better understanding of how diagnostics and testing fit into the promise of personalized medicine that we hear the President talk about so much. Senator Murray and I will each have an opening statement. Then we'll introduce our panel of witnesses. After our witness testimony, Senators will have 5 minutes of questions.

Laboratory-developed tests are medical tests that are designed, manufactured, and used in a single laboratory. These are labs in doctors' offices, hospitals, universities, State public health departments, private companies—places where scientists both develop and use tests to determine whether you have a disease or whether a certain drug will work for you. There are more than 60,000 lab-developed tests available to Americans today to help screen for and diagnose diseases and conditions such as rare or emerging infectious diseases and different types of cancer.

As I will mention in a minute, these 60,000 laboratory-developed tests are regulated by a process that includes the Center for Medicare and Medicaid Services, CMMS, but they're not regulated by the FDA. Let me share two examples of lab-developed tests.

Last year, President Obama announced the Precision Medicine Initiative which will involve mapping 1 million genomes and has the potential to transform medical treatment in our country. I attended a summit the President convened on the topic in February.

There, he recommended expanding access to a breast and ovarian cancer test developed by a commercial lab called Color Genomics. To take this test, anyone can ask their doctor to order it, pay about \$250, provide a simple saliva sample, send the package back in the mail, and work with your doctor to understand your genetic risk for developing these cancers.

As part of the President's Precision Medicine Initiative, Color Genomics said it is going to double the number of free tests offered to women. This test is an example of a lab-developed test, in this case, one developed by scientists in a commercial lab regulated by CMMS, not by the FDA.

Here's another example: A woman in her 80's goes to Vanderbilt University Medical Center for care. At Vanderbilt, someone puts a needle in her vein, takes blood and sends it to Vanderbilt's laboratory. Four days later, her doctor gets the results back from the lab and finds out that a certain blood thinner won't work for this patient. The patient would respond poorly to it. He prescribes something different.

Using that one blood test, scientists at Vanderbilt can find out whether the patient has one of 184 changes within 34 genes that might affect the way their body absorbs, distributes, metabolizes, or excretes a drug. Through its award-winning PREDICT program, Vanderbilt has been able to put important drug interaction information into patients' medical records so that doctors can know how they'll respond to medication. The blood test they use for this is a lab-developed test, in this case, developed in the lab of an academic medical center, Vanderbilt. Again, this is a test regulated by CMMS, not by FDA.

Both of these examples involve the President's Precision Medicine Initiative. I visited Vanderbilt last month. The medical center has received a \$71 million, 5-year grant to store and help make useful all the data in the Precision Medicine Initiative. Dr. Zutter of Vanderbilt estimated that 95 percent of tests used in the practice of precision medicine or personalized medicine at Vanderbilt are their lab-developed tests. Let me emphasize that. She said that 95 percent of the tests they use in their practice of precision medicine at Vanderbilt are laboratory-developed tests regulated by CMMS, not regulated by the FDA.

I received a lesson on these tests on my tour there. It's a good place to learn. The doctors in Vanderbilt's lab run about 4 million individual tests annually. Of those 4 million, 80,000 are run using tests developed by the doctors in Vanderbilt's own lab. Vanderbilt has developed 105 of its own tests. Vanderbilt has 105 lab-developed tests which it uses 80,000 times on patients there. The rest of the 4 million are done using FDA-approved diagnostic kits that are developed by manufacturers and sold to laboratories in hospitals and doctors' offices where they are performed.

We're holding this hearing today to learn more about lab-developed tests and their importance to the advancement of medicine. We also want to discuss a draft guidance released in 2014 by the FDA that would require each of these 60,000 lab-developed tests to be individually approved by the FDA.

This would change things. It would change the way lab-developed tests are currently regulated. They're currently regulated at

the Centers for Medicare and Medicaid Services, as I mentioned, through something called CLIA, the Clinical Laboratory Improvement Act of 1988, which Senator Mikulski of this committee led. It was a bipartisan effort, and I want to recognize her for her leadership in that.

The FDA's guidance about regulating laboratory tests is a draft guidance, but it proposes that all of the lab-developed tests that are currently under the CMMS CLIA program also be submitted to FDA for approval before they can be used. That would appear to me to be double regulation. Tests would need to meet the CLIA regulations, and then each one would need to be individually approved by FDA.

So what would FDA approval mean for Americans relying on the more than 60,000 different laboratory-developed tests available in the country today, which each one would have to be approved by the FDA before they were used? First, patients might lose access to tests until they are approved by FDA. I don't know how many labs would have the resources to put their tests through that approval process.

For reference, as of 2010, it took about \$75 million to bring just one high-risk device to market through the FDA process. Vanderbilt, for example, has 105 tests. If just one, the PREDICT test, is high risk, that could cost Vanderbilt \$30 million to \$75 million. You can quickly see how costs just to that institution could add up to billions.

We've heard from infectious disease doctors who have said in comments to the FDA about this draft guidance that they were, "very concerned that this oversight currently proposed could impede patient access to existing high-quality or state-of-the-art tests and threaten needed innovation." The Chair of the Department of Laboratory Medicine at the University of Washington wrote Senator Murray and me, suggesting that the proper approach would be to modernize the CLIA system, the CMMS system, to, "promote continued patient access to affordable, high-quality tests without duplicative regulations." Under the draft guidance, the biggest loser, it seems to me, would be Americans who stand to benefit from the rapid pace of science and discovery.

The Vice President is leading the Cancer Moonshot. Lab-developed tests have enabled much of the progress made in cancer research, allowing physicians to practice at the speed of science rather than the speed of the FDA. In one example, doctors began testing for mutations in the KRAS gene in 2008–2009 using lab-developed tests. There wasn't an option approved by the FDA until 5 years later in 2013–14. I am concerned that the FDA already has a full plate of responsibilities, and the agency has said it needs more money to meet those responsibilities.

I look forward to hearing today whether additional or different regulation of laboratory-developed tests is necessary.

Senator Murray.

STATEMENT OF SENATOR MURRAY

Senator MURRAY. Thank you very much, Chairman Alexander, and thank you to all of our witnesses for being here today.

Maintaining our country's leadership in science and biomedical innovation is a top priority for all of us here. I'm excited about the President's Precision Medicine Initiative and the Vice President's Cancer Moonshot which can help ensure that the next generation of treatments and cures are developed right here in the United States. The promise of precision medicine and new targeted therapies for cancer hinge on doctors' ability to treat a patient with the right drug at the right time. That means they will rely on diagnostics and new innovative tests more than ever before.

I am proud to represent a State that leads in developing both cutting-edge therapies and tests. I'm inspired by the work they do, how far science has advanced, and the promise that the future of medicine holds. But that promise cannot be realized unless doctors and patients have the assurance that when a test result demonstrates risk of a disease, provides an early diagnosis, or suggests a treatment, that result is correct and reliable. I'm concerned that our regulatory system currently can't provide that assurance.

Before most drugs and devices come to the market, they've been reviewed by the FDA and meet the gold standard for safety and effectiveness, a standard that our patients and families have come to trust. But many of the lab tests on which medical decisions are based are not subject to FDA review, something that most Americans are not aware of when they go to a doctor.

While the labs themselves are regulated, as mentioned by our Chairman, thanks to important legislation that Senator Barbara Mikulski championed, that law does not require the tests to be clinically meaningful, and that law doesn't ensure that a patient will get the same result no matter what lab they go to.

Some tests are subject to FDA review—tests that are marketed by medical device companies or are used with a particular new drug. Developers of these tests must demonstrate to the FDA that they are accurate, precise, and clinically meaningful. This discrepancy has created an uneven playing field for innovative companies and laboratories, including many in Washington State, and uncertainty for patients and physicians.

It also presents potential risk for patients who may seek the wrong treatment or no treatment at all based on test results. Just this month, the FDA alerted women and their doctors that certain tests marketed as screening tools for ovarian cancer lacked evidence to support their use. We certainly need new ways to screen for ovarian cancer, but we don't need tests that offer false security or cause unnecessary worry.

More than ever, physicians and patients and their families must be able to rely on test results in making treatment decisions. And it's also important that patients can be assured that the test results will be the same whether their physician uses a laboratory across the street or across the country.

Nearly 2 years ago, in pursuit of these goals, the FDA proposed a new approach to regulating lab tests. I've heard views from a wide range of stakeholders about this proposal and how the FDA's policies would impact their work. I think that there are ways the agency's proposal could be improved. But even though everyone wants to make sure the tests offered to patients work as advertised and that we allow researchers and clinicians to continue to inno-

vate and advance precision medicine, there is not wide agreement about the best regulatory approach.

The two questions I'm most interested in exploring today are: How can we help make sure patients are getting the highest quality and most innovative tests possible? And how can we provide regulatory certainty and a level playing field for test developers? I look forward to hearing from our witnesses today. I'm confident that your insight today will help us inform some bipartisan efforts to make sure that the promise of precision medicine and the Cancer Moonshot are realized.

Thank you very much, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Murray.

I'm delighted to welcome our four witnesses. Thank you for taking the time to be here.

First, we'll hear from Dr. David Klimstra, Attending Pathologist and Chairman of the Department of Pathology at Memorial Sloan Kettering Cancer Center. He is Professor of Pathology and Laboratory Medicine at the Weill Medical College at Cornell University.

Next is Brad Spring, Vice President of Regulatory Affairs and Compliance at BD Life Sciences located in Sparks, MD. Mr. Spring has over 27 years of experience in the diagnostics industry and is responsible for executing global regulatory strategies, global product registration processes, and ensuring regulatory compliance.

We will then hear from Dr. Jeff Allen, President and CEO of Friends of Cancer Research. Friends of Cancer Research advocates for cancer patients, collaborating with all the healthcare sector to improve patient care. I thank Dr. Allen for working with this committee, especially with Senator Burr and Senator Bennet and Senator Hatch, to help pass the Breakthrough Drug Pathway, which has been a great success with over 100 drugs designated and 46 approved in a relatively short period of time since its enactment.

Last, we'll hear from Dr. Karen Kaul, Chair of the Department of Pathology and Laboratory Medicine at NorthShore University HealthSystem, Clinical Professor of Pathology at the University of Chicago Pritzker School of Medicine. She and her lab have been deeply involved in the development of laboratory tests for cancer, heritable conditions, and microbial diseases.

We thank the four of you for coming. If you would each try to summarize your comments in about 5 minutes, that will leave more time for the Senators to ask questions.

Dr. Klimstra, let's begin with you.

STATEMENT OF DAVID S. KLIMSTRA, M.D., ATTENDING PATHOLOGIST AND CHAIRMAN, DEPARTMENT OF PATHOLOGY, JAMES EWING ALUMNI CHAIR IN PATHOLOGY, MEMORIAL SLOAN KETTERING CANCER CENTER, PROFESSOR OF PATHOLOGY AND LABORATORY MEDICINE, WEILL MEDICAL COLLEGE OF CORNELL UNIVERSITY, NEW YORK, NY

Dr. KLIMSTRA. Good morning, Mr. Chairman, Ranking Member Murray, and committee members. My name is David Klimstra, and I'm Chairman of the Department of Pathology at Memorial Sloan Kettering Cancer Center in New York. I'm grateful for the opportunity to share our experience with molecular diagnostic testing in the era of precision medicine.

President Obama's Precision Medicine Initiative challenges pathologists to characterize each patient's cancer at a much more fundamental level than ever before, describing not only its origin and subtype, but also its genetic features, which make it unique to the individual patient. One way to do this is to sequence the cancer genes, which is now easier, faster, and cheaper. Specific genetic abnormalities can point to targeted treatments, ensuring that the most effective therapies are employed and treatments without benefit are avoided.

At MSK, we now routinely sequence most advanced solid cancers, like breast, prostate, colon, lung, and pancreas cancer, using an assay called MSK-IMPACT, which simultaneously studies 468 cancer related genes. Over the past couple of years, we've reported MSK-IMPACT results for nearly 12,000 patients, helping shape their treatment recommendations.

MSK-IMPACT is just one of approximately 350 laboratory-developed molecular tests we currently perform. We use LDTs because the tests can be customized to provide the specific information we need. They can be adapted to study a range of different types of specimens, and they can bring the tests to clinical care quickly, relative to FDA-approved tests which have been slow to come to market.

To help you understand how these LDTs become established at MSK, let me explain the basic process in our labs, which are regulated by New York State and subject to premarket approval. The concept for a new LDT begins with a clinical need. Appropriate testing methods are then developed by our 13 board certified molecular pathologists and laboratory scientists. The reliability of the methods is verified following standardized procedures to ensure sensitivity, specificity, and reproducibility. The tests are further validated using different testing methodology or using similar methods in a different laboratory.

Then a highly detailed description of the new test is submitted to the State for approval. The MSK-IMPACT submission was 535 pages long, for instance. Generally, the State raises some questions that require a revised submission or additional validation experiments. Approval of the revised submission allows the test results to be released to the medical record.

This approval process works reasonably well, although it can be slow. From the conception of a new test through submission to the State for approval can take 12 to 15 months. Formal State review can also take months. The very first complex sequencing assay we developed was submitted for State review in December 2012. Final approval was obtained in March 2014. But the review process has improved, based in part on the dialog we maintain with the State. MSK-IMPACT received final approval in 8 months, and the State provides even more rapid conditional approval that allows us to offer tests clinically before final review.

Once approved, all of our test results are reported by physicians with advanced molecular diagnostics training and interpreted in the context of the patient's entire medical situation. Further, LDT performance is monitored by participating and ongoing proficiency testing. There is also a formal quality assurance process, and any

test performance issues are subjected to rigorous review and reporting.

For these reasons, we believe that additional regulatory oversight of our labs, such as that proposed by the FDA in their draft guidance of 2014, would be duplicative and unnecessary. I would also raise concerns about the cost of additional regulations, both monetary and in terms of patient access to cutting-edge diagnostics. Maintaining a regulatory infrastructure is already costly, and additional costs of obtaining regulatory approval for individual tests may prohibit academic laboratories from developing LDTs.

The current cost of an FDA premarket approval submission is over \$260,000, and although a modified fee schedule could be developed, it is easy to see how a lab with dozens or hundreds of LDTs could not afford to obtain FDA approval. This could drive innovative molecular testing out of the academic environment and into only larger commercial labs which have the resources to maintain regulatory compliance.

But most importantly, I worry about the delays in test availability from overly stringent regulations. Many important cancer gene mutations, such as the EGFR mutations critical for the treatment of lung cancer, were being detected with academically developed LDTs 5 years or more before an FDA-approved assay became available. Can we afford to deny our patients access to practice-changing tests for years while their cancers progress?

Of course, it is critical to ensure that we have safe, reliable, and meaningful laboratory results, and rational regulation can help that. But we urge Congress and the FDA to create a flexible regulatory process that does not delay access to important treatment information and that does not impede significant contributions to precision medicine coming from academic institutions.

When Vice President Biden visited MSK to discuss the Cancer Moonshot, he asked for a decade's worth of advances in 5 years. Let's not throw an unnecessary roadblock in that path.

Thank you for providing me this important opportunity to present these views.

[The prepared statement of Dr. Klimstra follows:]

PREPARED STATEMENT OF DAVID S. KLIMSTRA, M.D.

SUMMARY

I am the chairman of the Department of Pathology at Memorial Sloan Kettering Cancer Center (MSKCC), where the Department of Pathology conducts a wide array of custom-developed molecular assays to characterize the genetic changes in patients' cancer tissues, and we have extensive experience with the development, validation, execution, and regulation of these laboratory-developed tests (LDTs).

Achieving the promise of the Precision Medicine Initiative requires characterizing cancers at the genetic level. Broad-spectrum genomic analysis performed using DNA and RNA sequencing technologies has been developed for clinical use in some of the top academic and commercial pathology laboratories. Many tests employed in molecular diagnostics are developed and validated within individual laboratories and are therefore regarded to be LDTs, which have been the subject of proposed enhanced regulation by the Food and Drug Administration (FDA).

LDTs at MSKCC are all initiated based on clinical needs, developed using standard, verifiable methods with a rigorous validation process, and interpreted by expert molecular pathologists.

Our laboratories are CLIA compliant and are inspected by the Joint Commission on Accreditation of Health Care Organizations (JCAHO) and the New York State

Department of Health (NYS DOH). LDTs we develop must undergo extensive pre-test review and approval by the NYS DOH prior to being offered to patients. The process of LDT development, validation, and approval can require 12–15 months to complete.

Additional regulation of our LDTs would be redundant and unnecessary; it would slow the process of test development, restricting availability of advanced diagnostic tests to patients; it would add significant cost and effort to the administration of pathology departments; it would stifle innovation of critical novel diagnostics; and it would threaten to preclude the involvement of academic pathology departments in molecular testing, driving these assays completely into the commercial sector where large companies isolated from the input of academic oncology would be the only adequately resourced entities capable of maintaining regulatory compliance. Rational regulation of LDTs requires assessment of the risks involved in the test but also the nature of the testing technology and validation process already in place, to ensure optimal patient safety as well as optimal patient access to practice-changing technology.

My name is David Klimstra, M.D., chairman of the Department of Pathology at Memorial Sloan Kettering Cancer Center (MSKCC) in New York City, and I am grateful for the opportunity to share our experiences related to molecular diagnostic testing in the era of precision medicine with the U.S. Senate Committee on Health, Education, Labor, and Pensions. At MSKCC, we are committed to exceptional patient care, cutting-edge research, and the rapid translation of scientific discoveries into clinical advances. The MSKCC Department of Pathology plays a central role in fulfilling this promise by ensuring precise and timely diagnosis through the use of state-of-the-art equipment and advanced diagnostic techniques to analyze more than 100,000 patient samples annually. My department conducts a wide array of custom-developed molecular assays to characterize the genetic changes in patients' cancer tissues, and we have extensive experience with the development, validation, execution, and regulation of these laboratory-developed tests.

The promise of precision medicine requires access to sophisticated molecular diagnostic testing.

In President Barack Obama's State-of-the-Union address on January 30, 2015, he stated,

“Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type—that was an important discovery. What if matching a cancer cure to our genetic code was just as easy, just as standard?”

This basic premise of the Precision Medicine Initiative is predicated on an enhanced understanding of the characteristics of each patient's individual cancer, including knowing not only the organ in which it arose and the specific subtype of the cancer but also its genetic characteristics—the features that distinguish it from other seemingly similar cancers arising in other patients. The technology to decipher the genetic abnormalities that uniquely characterize each individual cancer has become rapidly more accessible in recent years, allowing comprehensive genetic analysis as a routine test for patients with advanced cancers. Broad-spectrum genomic analysis performed using DNA and RNA sequencing panel technologies that assess 100's of genes simultaneously, termed “next-generation sequencing,” has been developed for clinical use in some of the top academic and commercial pathology laboratories and is now increasingly available, even outside of major centers. Thus, the field of molecular pathology has rapidly emerged as a critical cornerstone of cancer diagnostics.

Much of the technology employed in molecular diagnostics is developed and validated within individual laboratories, although sequencers, robotics, and other pieces of equipment employed in these multi-step assays are manufactured elsewhere. These tests are therefore regarded to be “Laboratory-Developed Tests (LDTs),” which have been the subject of proposed enhanced regulation by the Food and Drug Administration (FDA). At Memorial Sloan Kettering Cancer Center (MSKCC), our molecular diagnostics laboratories perform approximately 350 different tests that meet at least some interpretation of the definition of LDTs, provided in the FDA draft guidance of October 3, 2014. At MSKCC, our LDTs allow the rapid translation of impactful research findings to the clinic (“from bench to bedside”), meaning that patients can benefit from new types of predictive testing very quickly—even years before the appearance of an FDA-approved diagnostic test. Many of the more recently developed LDTs we perform are genomic sequencing tests, designed to provide a thorough genetic characterization of each individual patient's cancer, and

nearly 12,000 cancers have been subjected to clinical sequencing using our MSK-IMPACT™ assay, which currently analyzes 468 cancer-related genes. The results of MSK-IMPACT™ testing are used to better understand each patient's cancer, to aid in classification and prognostic stratification, and to identify genetic changes that predict the sensitivity—or resistance—of the tumor to specific therapeutic interventions. Ultimately the use of molecular pathology is reducing overall treatment costs as well as pain and burden for patients by ensuring that the “right” therapies (i.e., those therapies most effective for that individual) are employed as first-line treatments and therapies without efficacy are avoided.

One of the benefits of the current technology is the ability to analyze hundreds of genes simultaneously, without significantly increasing the cost of the test compared to single-gene or small panel assays. This provides a wealth of data regarding clinically actionable alterations but also a broad array of potential genetic targets that are the focus of active research. Accumulation of this valuable research data is essentially a byproduct of studying the known actionable genes, and having voluminous data from our Center and others will allow a much expanded understanding of the interplay of cancer genetic changes and the role of novel genes in tumor progression, therapeutic sensitivity, and treatment failure. Our data are being shared with numerous other investigators around the Nation through Project GENIE (Genomics, Evidence, Neoplasia, Information, Exchange) of the American Association for Cancer Research (AACR), and currently MSKCC is the largest contributor to this collaborative data base. It is essential that efforts to offer and further develop these assays are able to move forward quickly, as the technology is rapidly advancing, requiring continuous test development research to offer the most effective molecular testing to our patients.

Attention to the safety, accuracy, and reproducibility of our molecular diagnostic tests is paramount, and a well-established process exists to ensure that results are reliable. Our team of 13 board-certified molecular pathologists is involved in every step of the process, and they review and formally report the findings of every case, to ensure that the test worked properly, that all relevant genes were adequately analyzed, and that the genetic findings are interpreted within the context of the patient's clinical findings. We believe that the delicate balance between assuring quality in molecular diagnostics and moving forward cutting-edge advances as quickly a possible is being achieved. In order to meet the objectives of Vice President Biden's “Cancer Moonshot,” which he explained directly to us when he visited MSKCC last May, we hope to accelerate progress in cancer research—“to make a decade worth of advances in 5 years”—moving forward our molecular diagnostic technology without unnecessary impediments that would be caused by excessive or redundant regulation. This objective will not only allow important future research advances, but it will also more quickly deliver vital treatment information to aid cancer patients who are afflicted today.

A standardized process is in place to develop, validate, and release LDTs for clinical testing.

The development of a new molecular pathology LDT at MSKCC begins with the identification of a clinical need for additional data used to make patient management decisions. Academic oncologists work closely with our molecular pathologists to review new scientific findings—including many discovered at MSKCC—to recognize when additional molecular characterization of patient cancer samples may allow novel therapeutic options. Molecular methods are then developed that will permit the acquisition of the needed findings, and these methods are adapted by the molecular pathology service for use in a clinical diagnostic setting. A series of validation experiments is then performed in our Clinical Laboratory Improvement Amendments (CLIA) compliant laboratories to test the performance of the assay, using positive and negative controls that have been already studied using a different technology. This process ensures that the test is reliable, specific, and reproducible. The number of validation experiments varies depending upon the test parameters and the specific requirements of our regulatory agency, the New York State Department of Health (NYS DOH; see <http://www.wadsworth.org/regulatory/clip/clinical-labs/obtain-permit/test-approval/submission-checklists>).

Upcoming guidelines prepared by the Association for Molecular Pathology and the College of American Pathologists, written in collaboration with our own molecular pathologists, will help standardize the validation process for sequencing-based assays nationwide. Once the validation experiments are completed, a detailed description of the new test, including the specific conditions, reagents, and data analysis process, along with the results of the validation experiments, is prepared for submission to the NYS DOH. This process—from the conception of the new test through submission for NYS pre-test approval—takes up to 12–15 months depending on the

complexity of the test and the novelty of the technology employed. For example, assays developed in our labs over the past 3 years required 6–8 months—after all of the test conditions had been established—simply to compile sufficient validation data to submit the package for NYS DOH approval. Formal NYS DOH review can also take months. Generally, there are questions raised by the NYS DOH, requiring clarification or additional experiments, with resubmission of a revised document. Acceptance of the revised submission finally allows the test to be offered to patients, with release of the results to the medical record. The first next-generation sequencing assay developed at MSKCC was submitted for NYS DOH pre-test review in December 2012; final approval was not obtained until March, 2014.

Our current next-generation sequencing assay for solid cancers, MSK-IMPACT™, required 8 months for final approval. Other recent assays have also taken nearly a year or longer, but the NYS DOH provides more rapid conditional approval, given the long track record our laboratory has established with the agency, allowing us to offer the tests clinically pending final review, provided any concerns raised in that final review are addressed successfully within 60 days. All of the LDTs employed in our laboratories use well-established methods and technologies, which can be performed in other laboratories to verify their accuracy, and the results can also generally be confirmed using other technologies.

As part of the CLIA-mandated quality assurance program, test performance at MSKCC is assessed through annual participation in proficiency testing (e.g., conducted by the CAP), in which test samples with known findings are analyzed to ensure consistent and accurate results. Proficiency testing is one of the central safeguards of laboratory quality under the CLIA program. Furthermore, there is a strong institutional commitment to Quality Assurance, reflecting the National Patient Safety Goals, and test performance issues are subjected to rigorous review and reporting, with corrective measures instituted whenever systems issues may be discovered.

Through all of these measures, LDTs performed at MSKCC are subjected to substantial oversight to protect patient safety and ensure accurate results. The cost of these measures is challenging to assess but annual NYS DOH inspections cost \$140,000 per year and biennial JCAHO laboratory accreditation costs \$54,000 per year, and the Pathology Department devotes the aggregate time of approximately five full time faculty and administrators to maintaining regulatory compliance.

Nationwide, the CLIA program regulates laboratories that perform testing on patient specimens in order to ensure accurate and reliable test results. When a laboratory develops an LDT, the CLIA program prohibits the release of any test results for patient care prior to the laboratory establishing certain performance characteristics relating to analytical validity for the use of that test system in the laboratory's own environment [42 CFR 493.1253(b)(2)—establishment of performance specifications]. CLIA requires that laboratories performing LDTs and modified FDA-approved tests establish the same performance characteristics that are required for unmodified FDA-approved tests, as well as determining analytic sensitivity, analytic specificity, and any additional performance characteristics that may be important to establish (e.g., sample preparation, specimen stability, data analysis process). The details of these validations are carefully reviewed by outside inspectors as part of periodic CLIA-mandated laboratory inspections. Biennial inspections are completed by laboratory accrediting agencies with CMS deemed status, such as the Joint Commission (JCAHO) or College of American Pathologists (CAP).

Regulation of LDTs must protect public health but not deter innovation or patient access to testing.

Academic departments of pathology and associated clinical laboratories have been intimately involved in the non-commercial development and implementation of LDTs used for patients cared for in their institutions. Many of the scientific and clinical discoveries that underlie and allow the development of LDTs have been made first in academic departments of pathology, in close development and collaboration with clinical caregivers and cancer researchers.

Any oversight framework implemented by the Federal Government must be appropriate to the way modern clinical laboratories provide patient testing. LDTs include a vast range of tests—from minor modifications of FDA approved tests or kits to assays fully developed and performed in a single laboratory. The FDA should make a distinction between “black box” tests with proprietary algorithms provided by a single for-profit company, which may not adequately provide patient safeguards and cannot readily be verified by testing in other laboratories, versus tests that are interpreted by a physician, and the analytical and clinical validity of the test can be verified by an independent third party or an alternative methodology (i.e., the test does not use a proprietary algorithm or technology). A distinction must also be

made between assuring the diagnostic accuracy of a test (i.e., ensuring that the test result reflects the presence or quantity of the parameter being measured) versus the clinical utility of a test (i.e., ensuring that the information provided by the test is truly useful for clinical decisionmaking). Active engagement of clinicians in defining the need for specific tests is key to the latter metric.

LDTs have rapidly evolved with advances in technology and business models, resulting in tests that are more complex, have nationwide reach, are available for common diseases, and involve higher risks to patients if inaccurate. In some instances, LDTs are being marketed directly to the patients. Due to the increased application of LDTs for genetic testing and precision medicine, the use of LDTs outside of the physician-patient context, and the development of LDTs by larger corporations, there is a concern that some LDTs may not be properly validated for their intended use, putting patients at risk via inaccurate diagnoses and incorrect treatment decisions. The FDA, with its extensive experience in regulating IVDs, may be better suited to protecting patients especially for tests that may pose a “high risk.” In contrast, when LDTs utilize publicly available diagnostic technology and interpretation algorithms and are reviewed and reported by licensed medical professionals, FDA regulatory oversight is duplicative and unnecessary. The current cost of a Premarket Approval (PMA) submission, for a single LDT, is \$261,388 for a standard application, and \$65,347 for small businesses (<http://www.fda.gov/ForIndustry/UserFees/MedicalDeviceUserFee/ucm452519.htm>); busy academic molecular diagnostics laboratories currently offer dozens or even hundreds of different LDTs. The costs of FDA regulations, along with the delays they will entail, would simply prevent these types of laboratories from functioning, driving all of molecular diagnostics into the large commercial lab setting. An overbearing regulatory environment is highly likely to limit the significant innovation occurring in many academic diagnostic laboratories.

The FDA should limit duplication of regulatory efforts by not only utilizing third-party review, but also by granting deeming authority to agencies that have already established a formal pre-market review process, such as the previously mentioned NYS DOH’s Laboratory Specific Assay Validation Review and Approval Program. The longstanding NYS DOH approach to regulating LDTs is among the most rigorous in the country and may provide a framework to build on for enhanced FDA oversight of LDTs.

The key to effective test regulation is to recognize the diversity of testing currently defined as LDTs and the existing level of regulatory and quality assurance oversight, to assure that currently unrestricted LDT development has appropriate safeguards without subjecting well-regulated laboratories to additional costly and time-consuming regulations. If the entire LDT compendium is “painted with one brush” from the regulatory perspective, the result will likely be the constraint of many outstanding efforts, delaying delivery of practice-changing innovation to patients and hindering academic centers from participating in molecular diagnostic testing altogether.

The CHAIRMAN. Thank you, Dr. Klimstra.
Mr. Spring.

STATEMENT OF BRAD SPRING, VICE PRESIDENT, REGULATORY AFFAIRS AND COMPLIANCE, BD LIFE SCIENCES, BALTIMORE, MD

Mr. SPRING. Chairman Alexander, Ranking Member Murray, and members of the committee, I’m Brad Spring, Vice President of Regulatory Affairs and Compliance for BD Life Sciences based in Sparks, MD. I’ve worked in the in vitro diagnostic field for nearly 28 years, and I’m honored to have the opportunity to participate in today’s panel on behalf of BD.

BD is a U.S.-based global medical technology company that is advancing the world of health by improving medical discovery, diagnosis of disease, and the delivery of care. Diagnostic tests play an important role in the diagnosis of disease, genetic disorders, infection, and other health conditions. These tests may be performed in a clinical laboratory, a doctor’s office, hospital bedside, or in the home.

The issue of how to best regulate diagnostic tests to ensure the public's health while allowing for innovation and rapid access to these tests has been debated for many years. BD is grateful to the committee for taking time to study this complex issue very carefully. During my remarks, I hope to shed light on the regulatory process under which BD currently brings tests to market and to share a set of principles that could help guide future reforms.

Under current regulations, diagnostic test manufacturers like BD are required to provide data to FDA demonstrating how accurately and precisely a test measures an analyte or a target and how well it works in leading to a correct diagnosis. Diagnostic tests that are developed and used by laboratories are not regulated by FDA. CLIA provides CMMS the authority to regulate laboratory operations to ensure reliable test results by focusing on the quality of laboratory procedures and the competency of personnel.

FDA regulates diagnostic tests as medical devices based on the level of risk to patients and public health posed by their intended use. Class 1 tests are the lowest risk, and most are exempt from premarket review, but these tests are still subject to good manufacturing practices and other controls. Class 2 tests pose a moderate level of risk based on their intended use and require clinical evidence and extensive analytical testing. Class 3 tests, most of which go through the premarket approval or PMA process, require the greatest amount of analytical and clinical data as well as manufacturing information.

Over the past year, I have had the opportunity to collaborate with colleagues from the diagnostic industry, clinical laboratories, and academic institutions to gain consensus on a diagnostic regulatory construct that advances innovation, protects patients, provides a predictable and timely path to market, and ensures reasonable risk-based regulation. New insight from genomics and engineering fields has led to important advances in diagnostic test development.

Determining the appropriate regulatory oversight for cutting-edge diagnostic tests, whether they are produced by BD or another manufacturer or in a clinical laboratory, is critical for the future of medicine. While certain issues remain and additional stakeholder input is needed, our efforts have gone considerably farther than prior attempts at bridging differences between the manufacturing and the lab communities. Stakeholders, including BD, are beginning to coalesce around the following seven key principles of a comprehensive regulatory reform proposal, and I'll list those principles now.

(1) A new regulatory framework must protect patients and ensure timely access to innovative diagnostic tests.

(2) The framework needs to apply the same regulatory requirements for the same tests regardless of the entity type.

(3) Regulatory standards should be focused on test accuracy and reliability through evidence of analytical and clinical validity.

(4) The level of oversight should be based on the level of risk to patients and the public health.

(5) There needs to be a clear jurisdiction between FDA, CMMS, and the States.

(6) Improved transparency and predictability regarding approval requirements is needed.

(7) Expedited pathways should be created for tests serving unmet needs.

In conclusion, we offer these principles as a roadmap to help guide the committee's important work on diagnostic regulatory reform. While challenges remain, I firmly believe we can finally accomplish the mission of ensuring patients are getting accurate and reliable tests while still benefiting from the latest in innovative diagnostic technologies.

I greatly appreciate your commitment to public health, and I look forward to answering your questions.

[The prepared statement of Mr. Spring follows:]

PREPARED STATEMENT OF BRAD SPRING

SUMMARY

I appreciate the opportunity to appear before the committee to discuss "Laboratory Testing in the Era of Precision Medicine" on behalf of BD. BD is a U.S. based global medical technology company that is advancing the world of health by improving medical discovery, diagnosis of disease and the delivery of care. The company is a leader in patient and healthcare worker safety and technologies that enable medical research and clinical laboratory practices. We work in close collaboration with customers and partners to help enhance outcomes, lower healthcare delivery costs, increase efficiencies, improve healthcare safety and expand access to health.

Over the past year, I have had the opportunity to collaborate with colleagues from industry, labs, and academic institutions to gain consensus on a diagnostic regulatory construct that advances innovation, protects patients, provides a predictable and timely path to market, and ensures reasonable risk-based regulation.

In my testimony today I will discuss the following:

- The current regulatory process for diagnostic tests and BD's experience with the process.
- The need for regulatory reform focused on improving patient care and accelerating clinician access to new tests.
- Seven key principles of a comprehensive regulatory reform proposal, which are as follows:
 1. A regulatory framework that protects patients and ensures access to innovative diagnostic tests.
 2. An approach that applies regulatory principles regardless of entity type.
 3. Regulatory standards are focused on test accuracy and reliability through analytical and clinical validity.
 4. The level of oversight is based on level of risk to patients.
 5. There is clear jurisdiction between FDA, CMS and States.
 6. Improved transparency and predictability regarding approval requirements.
 7. Expedited pathways for tests serving unmet needs.

INTRODUCTION

Chairman Alexander, Ranking Member Murray and members of the committee, I am Brad Spring, vice president of Regulatory Affairs and Compliance for BD Life Sciences based in Sparks, MD. I am honored to have the opportunity to participate in today's panel on behalf of BD.

BD is a U.S. based global medical technology company that is advancing the world of health by improving medical discovery, diagnosis of disease and the delivery of care. The company is a leader in patient and healthcare worker safety and technologies that enable medical research and clinical laboratory practices. We work in close collaboration with customers and partners to help enhance outcomes, lower healthcare delivery costs, increase efficiencies, improve healthcare safety and expand access to health.

Scientific advances arising from the Nation's investment in biomedical research enable the development of new diagnostic tests that can prevent disease or detect it early when treatment is often more effective and less costly. Diagnostic tests play an important role in the diagnosis of disease, genetic disorders, infection or other

conditions. Depending upon the type of test, it may be performed in a clinical laboratory, a healthcare professional setting such as a doctor's office or a hospital bedside, or at home.

The issue of how to best regulate diagnostic tests to ensure the public's health while allowing for innovation and rapid access to these tests has been debated for many years. BD is grateful to the committee for taking the time to study this issue carefully, including holding today's hearing. During my remarks, I hope to shed light on the regulatory process under which BD currently brings tests to market and to share a set of principles that could help to guide future reforms.

CURRENT REGULATORY PROCESS FOR DIAGNOSTIC TESTS

Currently, the Federal Food, Drug and Cosmetics Act directs the Food and Drug Administration (FDA) to regulate diagnostic tests developed by manufacturers, like BD. For a diagnostic test to receive FDA clearance or approval, manufacturers are required to provide data demonstrating how accurately and precisely a test measures an analyte and how well it works in leading to a correct diagnosis.

There is also a second route to market for diagnostic tests that are developed by clinical laboratories. The Centers for Medicare and Medicaid Services (CMS) provides oversight over laboratory developed tests (LDTs). CMS has authority to regulate laboratory operations through the Clinical Laboratory Improvement Amendments of 1988 (CLIA). Under CLIA, CMS seeks to ensure reliable test results by focusing on the quality of the laboratory procedures and competency of personnel.

MANUFACTURER EXPERIENCE

Diagnostic tests developed by BD and other manufacturers are reviewed and either cleared or approved by the FDA before they can be provided to clinical labs, physician offices or directly to patients. The FDA regulates these tests as medical devices based on the level of risk to patients and public health posed by their intended use.

Class I tests are the lowest risk and exempt from pre-market review, but these tests are still subject to good manufacturing practices and other controls. Class II tests pose higher risks and require prospective clinical data and extensive analytical testing. Class III tests, most of which go through the premarket approval (PMA) process, require the greatest amount of clinical data and manufacturing information as part of a submission to the FDA.

REGULATORY REFORM IS NEEDED TO IMPROVE PATIENT CARE AND ACCELERATE CLINICIAN ACCESS TO NEW TESTS

New insights from genomics and engineering fields such as optics and fluid dynamics have led to important advances in diagnostic test development. Determining the appropriate regulatory oversight for cutting edge diagnostic tests, whether they are produced by BD or another manufacturer or in a clinical laboratory, is critical for the future of medicine.

Over the past year, I have had the opportunity to collaborate with colleagues from the diagnostic industry, clinical laboratories, and academic institutions to gain consensus on a diagnostic regulatory construct that advances innovation, protects patients, provides a predictable and timely path to market, and ensures reasonable risk-based regulation.

While unresolved issues certainly remain and additional stakeholder input is needed, our efforts have gone considerably farther than prior attempts at bridging differences between the manufacturing and lab communities. Stakeholders, including BD, are beginning to coalesce around the following seven key principles of a comprehensive regulatory reform proposal:

1. A new regulatory framework must protect patients and ensure access to innovative diagnostic tests.

2. The framework needs to apply regulatory principles regardless of entity type.

The current structure, under which regulatory requirements are tied to the type of entity (i.e., a manufacturer or a laboratory), results in different standards for accuracy and reliability for the same test and other discrepancies between the types of oversight.

In an approach that applies regulatory principles regardless of entity type, diagnostic tests would be regulated the same way regardless of whether they are developed by a manufacturer or a lab. This would allow for clear, consistent lines of jurisdiction. As noted earlier, clinical laboratories are regulated by CMS through CLIA

while manufacturers are regulated under FDA but the agencies regulate different aspects of the diagnostic test process.

3. Regulatory standards should be focused on test accuracy and reliability through analytical and clinical validity.

Any regulatory standard for a diagnostic test should focus on analytical and clinical validity to ensure that clinicians and patients are getting the most accurate result to make critical health care decisions.

Analytical validity considers the ability of the tests to identify measure or analyze one or more analytes, biomarkers, or substances.

Clinical validity evaluates the reliability and accuracy with which a test in a specific population identifies, measures, predicts, monitors, and/or assists in selecting treatment for a disease or condition, or characteristics related to an individual's clinical status.

4. The level of oversight should be based on level of risk to patients.

The higher the risk, the more evidence would be required to be reviewed and approved by FDA. All tests would be classified as high-risk, moderate-risk, or low-risk tests. The premarket, quality, and post-market requirements will vary by risk class.

High Risk: a clinically significant inaccurate result for the intended use would cause serious or irreversible harm, or death, to the patient or public based on failure to treat, incorrect treatment, invasive procedures, or prolonged disability if such inaccurate result were undetected when used as intended in medical practice.

Moderate risk: a clinically significant inaccurate result for the intended use would cause non-life-threatening injury, injury that is medically reversible, or delay in necessary treatment if such inaccurate result were undetected when used as intended in medical practice.

Low Risk: a clinically significant inaccurate result for the intended use would cause minimal or no harm, immediately reversible harm, or no disability if such inaccurate result were undetected when used as intended in medical practice.

There are other mitigating factors in risk classification. Among these are whether the technology and clinical use is well-characterized and whether there are other tests (confirmatory or adjunctive) used in the diagnosis.

5. There needs to be clear jurisdiction between FDA, CMS and States.

The following table illustrates a proposed jurisdiction of process activities by agency and level of government:

Test Development	Design, Development, Validation, Preparation of Reagents, Platform manufacturing.	FDA
Laboratory Operations	Reagent Preparation, Run tests, Report results	CMS
Medical application	Practice of medicine (interpret and consult on results)	States

6. Improved transparency and predictability regarding approval requirements is needed.

7. Expedited pathways should be created for tests serving unmet needs.

CONCLUSION

We offer these principles as a road map to help guide the committee's important work on diagnostic regulatory reform. While challenges remain, I firmly believe we can finally accomplish the mission of ensuring patients are getting accurate and reliable tests while still benefiting from the latest in innovative diagnostic technologies. I greatly appreciate your commitment to public health and look forward to answering your questions.

The CHAIRMAN. Thank you, Mr. Spring.
Dr. Allen.

**STATEMENT OF JEFF ALLEN, PH.D., PRESIDENT AND CEO,
FRIENDS OF CANCER RESEARCH, WASHINGTON, DC**

Mr. ALLEN. Chairman Alexander, Ranking Member Murray, and members of the committee, I'm Jeff Allen, President and CEO of Friends of Cancer Research. It's an honor to testify before you today and provide the perspective of my organization on behalf of patients as you continue this committee's effort to examine how

laboratory testing can best support the future of medicine and patient care.

The therapies patients have access to today to treat many different diseases are far more effective but are also more complex than their predecessors. Adding to this complexity is the increased reliance on molecular tests to provide optimal medical care. The development of new drugs that are targeted toward specific alterations has resulted in numerous compelling examples of more effective treatments. In fact, nearly two-thirds of the drugs that have received a Breakthrough Therapy Designation have a biomarker associated with their research program.

Given the role that medical tests play in determining patient care, it's imperative that the accuracy of these tests be well characterized. The ramification of inaccuracy can be quite significant. An inaccurate test could result in a patient not receiving the most appropriate treatment or expose them to a potentially harmful one.

When a patient is told that they have cancer or any other debilitating disease, they are flooded with confusion, fear, anger, and the thought oftentimes of losing the life of a loved one or their own. While their journey will undoubtedly include periods of confusion and uncertainty, they shouldn't be left to wonder if the results of a test which their physician used to decide their course of treatment was right or not.

Molecular tests may, indeed, be the key to precision medicine. I and millions of people across this country hope that the work of this committee will be a catalyst to accelerating getting the right medicines to the right patients at the right time. In order to achieve this goal, the approach to regulating these tests needs to be realigned. Tests manufactured and sold as diagnostic kits undergo premarket review by the FDA. Conversely, those made and performed within a single laboratory, or LDTs, have historically not had FDA premarket review.

The laboratories that perform LDTs are subject to oversight established by CLIA, but this assessment focuses on laboratory processes and personnel, not on analytical and clinical validity to determine if the test actually performs as claimed. The presence of two separate regulatory processes and incongruent requirements has resulted in a system where certain tests with known high quality that ought to be trusted exist alongside a vast array of tests that remain relatively uncharacterized. This is not the reliable path to precision medicine.

Today, due to great advancements in science and technology, clinical laboratories and commercial manufacturers are developing molecular tests that may have the same use. In a recent study that we published with the Deerfield Policy Institute, we audited hundreds of medical records from across the country to explore the use trends of molecular tests that assess two critical alterations in lung cancer known as ALK and EGFR. The results of this audit showed that 49 percent of patients tested for ALK alterations and 87 percent for EGFR mutations were evaluated with an LDT, despite the availability of an FDA-approved assay.

Given the large number of tests currently in use, there exists a potential for wide variability in test performance and claims. Any test that produces a result intended to be used to guide medical de-

cisionmaking should be evaluated in its clinical context for risks that may be incurred. For patients, consumers, and healthcare providers, it's the result of the test that's important, not where it's manufactured.

Without a uniform regulatory approach for molecular tests, variability is likely to be exacerbated by rapidly advancing technology. This is further complicated by the fact that the traditional approach of developing a single drug with an individual test is becoming obsolete. Next-generation sequencing and other genomic platforms can analyze hundreds of genetic markers from the same sample and are being developed by different institutions around the country. Steps should be taken to understand variability and improve consistency.

As members of this committee decide how best to address the regulation of molecular tests, I believe that we can find common ground. First, the primary basis for regulating molecular tests should be what medical decision the test is used to inform. Tests that are used to guide medical decisionmaking, LDT or diagnostic, ought to be subject to the same regulatory oversight and requirements.

Second, the FDA should work with the laboratory and diagnostic industry to standardize techniques to characterize variability between tests. And, third, advanced genomic screening may require a regulatory framework of its own, taking into consideration the rapid pace of technological advancement, in ensuring that patients have access to high-quality, reliable testing. The future of precision medicine in the health and lives of patients depends on the accuracy of these tests.

Thank you, and I look forward to your questions.

[The prepared statement of Mr. Allen follows:]

PREPARED STATEMENT OF JEFF ALLEN, PH.D.

SUMMARY

The therapies patients have access to today to treat many different diseases are far more effective, but also more complex than their predecessors. Adding to this complexity, and the more exacting nature of science today, is the increased reliance on molecular tests for providing optimal medical care. Molecularly defining diseases and developing new drugs that are targeted toward specific alterations has resulted in numerous compelling examples of new and more effective treatments for previously untreatable conditions. This provides the motivation and rationale for researchers to pursue new potential drug targets, and great hope for patients waiting for potential cures.

It's not unusual for a variety tests to be used by healthcare providers to help identify elevated risks, diagnose certain conditions, inform the best treatment option, or even measure if a treatment is working. In some cases, entire treatment regimens are being prescribed based upon the results of such tests. Given the role that medical tests play in optimizing and determining patient care, it's imperative that these tests' performance and accuracy be well characterized before placing important treatment decisions on the results that they provide.

The ramifications of uncertainty or inaccuracy can be quite significant. An inaccurate test could result in a patient not receiving the most appropriate treatment or expose them to an unnecessary or potentially harmful treatment.

Regulatory oversight of tests has been inconsistent, and puts patients at considerable risk as tests evolve and become more complex. Tests manufactured and sold as "diagnostic kits" undergo premarket review by the Food and Drug Administration (FDA). Conversely, those made and performed within a single laboratory, called laboratory developed tests (LDTs), have not historically had FDA premarket review, as the Agency has generally exercised enforcement discretion. The laboratories that perform LDTs are subject to oversight established by the Clinical Laboratory Im-

provement Amendments (CLIA), but this assessment focuses on laboratory processes and personnel—not on premarket assessment of analytical and clinical validity to determine if they actually perform as claimed. The presence of two separate regulatory processes and incongruent requirements has resulted in a system where certain tests with known high quality, that ought to be trusted, exist alongside a vast array of tests that remain relatively uncharacterized. This is not the reliable path to precision medicine.

Today, due to great advancements in science and technology clinical laboratories and commercial manufactures are developing molecular tests that may have the same use. In a recent study, we explored the use trends for molecular tests that assess two critical alterations in lung cancer, *EGFR* and *ALK*. It showed that 87 percent of patients tested for *EGFR* mutations and 49 percent for *ALK* alterations were evaluated with an LDT, despite the availability of an FDA approved assay. Given the large number of tests currently in use, some which have been subjected to pre-market review by FDA while others have not, there exists the potential for wide variability in test performance and claims. Any test that produces a result that is intended to be used to guide medical decisionmaking should be evaluated in its clinical context for risks that may be incurred. For patients, consumers, and healthcare providers it is the information provided by the test that is important, not the place it is manufactured or how it is distributed.

Good morning, Chairman Alexander, Ranking Member Murray, and members of the committee. I am Dr. Jeff Allen, President & CEO of Friends of Cancer Research, an advocacy organization that drives collaboration among every healthcare sector to power advances in science, policy, and regulation that speed life-saving treatments to patients. I would like to thank all members and the staff of this committee for putting together this important hearing. It is an honor to testify before you today and provide the perspective of my organization, and on behalf of patients, as you continue this committee's efforts to examine how laboratory testing can best support the future of medicine and patient care.

Advancements in basic science have never been more profound. The remarkable advancements being made at the National Institutes of Health (NIH), at medical and academic centers all across the country and within private sector industry are rapidly changing how we look at disease, and are in some cases leading to new and markedly improved treatments for patients. Exciting new initiatives like the President's Personalized Medicine Initiative (PMI) and the Vice President's Cancer Moonshot are important opportunities to continue along this promising trajectory and build on the remarkable progress to date.

The therapies patients have access to today to treat many different diseases are far more effective, but also more complex than their predecessors. Adding to this complexity, and the more exacting nature of science today, is the increased reliance on molecular tests for providing optimal medical care. It's not unusual for a variety of tests to be used by healthcare providers to help identify elevated risks, diagnose certain conditions, inform the best treatment option, or even measure if a treatment is working. In some cases, entire treatment regimens are being prescribed based upon the results of such tests.

Given the role that medical tests play in optimizing and determining patient care, it's imperative that these tests' performance and accuracy be well characterized before placing important treatment decisions on the results that they provide. The ramifications of uncertainty or inaccuracy can be quite significant. An inaccurate test could result in a patient not receiving the most appropriate treatment or expose them to an unnecessary or potentially harmful treatment. A recent report from the National Academies concluded that diagnostic errors, including some from molecular tests, account for 6–17 percent adverse events in hospitals, and played a role in 10 percent of patient deaths.¹ I don't raise these statistics to be alarmist, to suggest that medical tests are not vital to the future of patient health, or to ignore that there are currently numerous, highly beneficial tests that facilitate the use of life-saving treatments. But as this field rapidly moves forward and becomes more complex, it is important to create policies that can help patients and medical professionals be confident in the results that a test provides.

When a patient is told that they have cancer, or any other debilitating disease, they are flooded with confusion, fear, anger, and the thought, often times, of losing the life of a loved one, or their own.

¹Balogh, EP et al. Improving Diagnosis in Healthcare. Committee on Diagnostic Error in Health Care; Board on Health Care Services; Institute of Medicine; The National Academies of Sciences, Engineering, and Medicine. 2015.

While their journey will undoubtedly include periods of confusion and uncertainty, they shouldn't be left to wonder if the results of a test, which their physician used to decide the course of their treatment, was right or not. Molecular tests may indeed be the key to precision medicine. I, and millions of people across this country, hope that the work of this committee will be a catalyst to accelerate getting the right medicines to the right patients at the right time.

SCIENTIFIC PROGRESS FACILITATED BY MOLECULAR TESTS

Past scientific and technological advancements have helped to demonstrate the potential promise of precision medicine in oncology. For example, decades ago many hematologic malignancies were classified as either simply leukemia or lymphoma. At that time the 5-year survival rate for patients diagnosed with those diseases was in the single digits. Through the advancement of microscopy techniques, researchers and physicians are now able to identify different cells and unique characteristics of cells that contribute to their abnormal growth and reclassify specific diseases. Today, there are nearly one hundred different histologically defined leukemia and lymphomas. This ability to identify different subsets of diseases allowed for treatments to be developed that were in some cases more tailored toward those specific cells and were more effective in the subgroup. Today, the number of patients that are still alive 5 years after their highly specified diagnosis is greater than 70 percent.²

While the technology is more complex, today a similar phenomenon is occurring based on the improved ability to identify molecular alterations and in some cases to develop treatments to target them accordingly. Many cancers and other diseases that had previously been grouped together are now being characterized based on the presence or absence of different molecular indicators, or biomarkers. The identification of certain biomarkers may indicate elevated risk for developing a disease, the presence of a disease, or the likelihood (or not) of responding to a treatment. In most cases, the assessment of a biomarker requires the use of a molecular test. As more and more reliance is placed upon molecular tests, both in research and routine clinical care, the importance of their accuracy cannot be understated.

MOLECULAR TESTS ARE CHANGING THE APPROACH TO R&D

The rapid evolution of precision medicine through the identification of biomarkers and the increased utilization of molecular testing has brought a paradigm shift to the biomedical research enterprise. Molecularly defining diseases and developing new drugs that are targeted toward specific alterations has resulted in numerous compelling examples of new and more effective treatments for previously untreatable conditions.

Products such as imatinib for patients with Ph+ chronic myelogenous leukemia, trastuzumab for treating patients with HER2+ breast cancer, and crizotinib or other inhibitors toward ALK-translocated non-small cell lung cancer are all examples of targeted therapies that have transformed different types of cancers. This provides the motivation and rationale for researchers to pursue new potential drug targets, and great hope for patients waiting for potential cures. In a relatively short period of time, the movement toward precision medicine has resulted in the rapid expansion of a high-quality diagnostic testing industry, impacted care delivery practices in terms of tests that are provided to patients, changed patients' awareness of their health data, are affecting economic models for payment for medical services, and significantly shifted both the opportunities and challenges associated with developing and regulating new medicines.

It has been estimated that 87 percent of the oncology research pipeline is devoted to targeted therapies, of which a large proportion are used with a biomarker test.³ Among some of the most potentially transformative new therapies—those that have received FDA Breakthrough Therapy Designation—64 percent have a biomarker associated with their research program.⁴ Among some of the most transformative therapies in recent years—those that have been approved after being designated as

²Allison, M. Is Personalized Medicine Finally Arriving? *Nature Biotech.* Vol. 26 N. 5; May 2008.

³IMS HealthGlobal Oncology Trend Report 2015: https://www.imshealth.com/files/web/IMSHpercent20Institute/Reports/Global_Oncology_Trend_Report_2015_2020/IMSH_The_Oncology_Pipeline.pdf. Accessed 9/14/16.

⁴Brookings Center for Health Policy—Breakthrough Therapy Designation: Exploring the Qualifying Criteria 4/24/15: <https://www.brookings.edu/wp-content/uploads/2015/03/Breakthrough-therapy-slide-deck.pdf>. Accessed 9/14/16.

a Breakthrough Therapy—38 percent have biomarker selection criteria as part of their indication.⁵

While the shift toward a more personalized approach to medical research and care has been enabled by molecular diagnostics, it has also presented challenges that require modifications to traditional R&D. For example, by identifying molecularly defined subsets of disease, it is hoped that tailoring treatment to these subsets rather than the broader disease will result in the reduction of non-responders to treatment. However, due to the increasing number of disease subsets that have been identified, many of which represent less than 5 percent of patients with a particular cancer, this significantly reduces the number of patients who are eligible to receive a targeted therapy. When a molecular subset of a disease is a small fraction of the total number of patients, it requires broad screening to identify the patients for existing targeted treatments and novel approaches to study new drugs in those settings.

To begin to address this issue directly, drawing on advances in molecular testing that enable researchers to identify clinically meaningful alterations in dozens of genes, Friends of Cancer Research is currently working with a large, diverse set of partners from academia, industry, government and advocacy to develop a modern day, innovative precision medicine clinical trial. In this project, called Lung-MAP, a “master protocol” governs how multiple drugs, from multiple companies, each targeting a different biomarker, are tested as potential treatments for lung cancer. Each arm of the study tests a different therapy that has been determined to target a unique genetic alteration. Lung-MAP utilizes cutting-edge screening technology to help identify which patient may better match each arm. This trial is creating a rapidly evolving infrastructure that can simultaneously examine the safety and efficacy of multiple new drugs.⁶ Lung-MAP provides a model for future research designs that can efficiently incorporate cutting-edge molecular testing and facilitate clinical trials that support the future of personalized medicine. This approach will have the ability to improve enrollment, enhance consistency, increase efficiency, reduce costs, and most importantly improve patients’ lives.

CURRENT REGULATION OF MOLECULAR TESTS

In the case of new therapies, the Food & Drug Administration (FDA) is responsible for regulatory oversight of new drugs and to approve them before they enter the market. For molecular tests, however, the regulatory paradigm is more complex. Two broad categories of tests—those manufactured and sold as “diagnostic kits” by companies and those made and performed within a single laboratory, often called laboratory developed tests (LDTs)—have historically been treated differently by regulatory authorities. Since the 1970s, the FDA has provided regulatory oversight for kits that are manufactured and sold by companies to health professionals. Conversely, the Agency has exercised enforcement discretion in requiring premarket review for LDTs. For much of the period of FDA’s enforcement discretion, LDTs were typically manufactured in small volumes and used by laboratories housed within the same institution where patients were treated. They were largely intended for rare diseases and were a lot less prevalent in the healthcare system.

Laboratories themselves are subject to CMS regulation under the Clinical Laboratory Improvement Amendments (CLIA).⁷ The FDA approval process is designed to ensure that individual tests are properly designed and validated so that they are accurate, reliable, and clinically valid, before they are used in clinical practice whereas CLIA is designed to assure that tests are properly performed, largely through the oversight of laboratory personnel and procedures. Although both rigorous in their oversight processes, FDA and CLIA regulations serve very different purposes and so have different sets of regulatory requirements addressing different aspects of the quality of tests.

When this division of responsibility was set up, the methodologies and intended use of the data generated by tests regulated by FDA and those under CLIA was different.⁸ More recently, with the expansion of molecular testing and increased technical capabilities, the breadth of analytes and biomarkers for which there are

⁵Breakthrough Therapy Designations: <http://www.focr.org/breakthrough-therapies>. Accessed 9/14/16.

⁶Herbst, RS, et al. Lung Master Protocol (Lung-MAP)-A Biomarker-Driven Protocol for Accelerating Development of Therapies for Squamous Cell Lung Cancer: SWOG S1400. *Clin Cancer Res.* 2015 Apr 1;21(7):1514–24. doi: 10.1158/1078-0432.CCR-13-3473. Epub 2015 Feb 13.

⁷Weiss RL. The Long and Winding Regulatory Road for Laboratory-Developed Tests. *Am J Clin Pathol.* 2012; 138: 20–6.

⁸US Food and Drug Administration. Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs). October, 2014.

LDTs and manufactured kits continues to grow. The intended use of the information generated from different tests has also evolved. Any test that produces a result that is intended to be used to guide medical decisionmaking should be evaluated in its clinical context for risks that may be incurred. For patients, consumers, and healthcare providers it is the information provided by the test that is important, not the place it is manufactured or how it is distributed. The regulatory framework and standards used to ensure the safety and quality of tests should reflect this principle. It is important to acknowledge concerns that have been raised about the potential consequences of an increase in oversight of molecular testing. These concerns raise the possibility that small laboratories will not have the means to handle the administrative burden of complying with new regulations. However, it is worth noting that many molecular tests are not subject to a full FDA pre-market approval application (PMA) and instead go through the FDA de novo process, which provides significant flexibility. Moreover, patients and healthcare providers need to confidently rely on a tests' results, no matter the test's origin. The presence of two separate regulatory processes and incongruent requirements has resulted in a system where certain tests with known high quality, that ought to be trusted, exist alongside a vast array of tests that remain relatively uncharacterized. This is not the reliable path to precision medicine.

USE TRENDS OF MOLECULAR TESTS

An additional challenge encountered as use of molecular testing expands is the growing number of cases in which analytes being assessed by LDTs developed and performed in single labs may be identical to the analytes assessed with kits manufactured to be marketed. To better understand this current landscape, our research team, in conjunction with the Deerfield Policy Institute, conducted a study to examine trends in molecular testing of non-small cell lung cancer (NSCLC) patients with advanced-stage adenocarcinoma, with a focus on testing to detect *EGFR* mutations and *ALK*-rearrangements. Testing for these alterations is recommended by medical guidelines and both LDTs and FDA-approved tests are available. The study was just published yesterday and provides several key findings. Overall rates of testing of patients with advanced non-small cell lung cancer (NSCLC) were high: 95 percent (550 of 579) of patients were tested for *EGFR*, and 84 percent (489 of 579) were tested for *ALK*. Our study also showed that large number of patients who underwent molecular testing were tested with a non-FDA approved test. Specifically, 87 percent (369 of 424) for *EGFR* and 49 percent (195 of 399) for *ALK* were tested with an LDT, despite the availability FDA approved assays for those alterations.

While our study was not intended to assess any differences between FDA-approved tests and LDTs that are used to detect *EGFR* or *ALK* alterations, it does reveal a high prevalence of use of tests that have not been subject of FDA review. There are pros and cons to the widespread use of LDTs. On the one hand, LDTs may offer rapid technical advances and facilitate innovation in molecular testing, and have been demonstrated in some cases to offer advantages beyond existing FDA regulated alternatives.^{9 10} On the other hand, concerns exist that LDTs are not currently subjected to pre-market review by the FDA and thus are not required to meet the same evidentiary standards as FDA regulated tests. Additionally, LDTs have in at least some instances been reported to perform poorly, as noted in a report of case studies released by the FDA.¹¹ The FDA's most recent safety communication warning against use of ovarian cancer screening tests is one more case where FDA pre-market review would have been critical to prevent women from being exposed to tests that simply do not perform as claimed.¹² Given the large number of tests currently in use, some which have been subjected to pre-market review by FDA while others have not, there exists the potential for wide variability in test performance

⁹ Association for Molecular Pathology: Facts FDA Ignored: An analysis of the FDA report, "The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies" (2015). <http://amp.org/emails/documents/AMPRresponseFDACaseReportFinal.pdf>. Accessed 9/15/16.

¹⁰ Evans J, Watson M. Genetic testing and FDA regulation: overregulation threatens the emergence of genomic medicine. *JAMA*. 2015; 313: 669–70.

¹¹ US Food and Drug Administration: The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies. <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM472777.pdf>. Accessed 9/15/16.

¹² FDA Safety Communication: <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm519413.htm>. Issued 9/7/15. Accessed 9/15/16.

and claims, and the reality that some patients making major medical decisions based on inaccurate test results.^{13 14 15}

Without a uniform regulatory approach for molecular tests, the potential for uncharacterized variability is likely to be exacerbated by rapidly advancing technology. This situation is further complicated by the fact that the traditional approach of developing a single drug with an individual test may be becoming obsolete. Testing many analytes simultaneously on a single platform is greatly preferred to testing one analyte at a time due to limitations in the quantity of patient tumor tissue available for testing and the potential for streamlining previously separate workflows. Indeed, next-generation sequencing (NGS) technology and other genomic analysis platforms that can analyze hundreds of genetic markers from the same sample are being developed and widely used at hospitals around the country. The information generated by NGS testing in clinical laboratories may be used to identify potential risk factors, prognostic information, or predictors of adverse reactions to drugs, all of which may contribute to a larger body of evidence used by physicians to manage patient care. These powerful NGS technologies are being developed and performed in clinical laboratories whose operations are subject to oversight and accreditation, but are not subject to FDA review, meaning that a thorough review of the accuracy and reliability of the test results is not performed.

While NGS and other emerging technologies present transformational opportunities, steps should be identified to understand variability and improve consistency among different testing platforms. Several studies have shown that different platforms can frequently yield different results.^{16 17} Due to technological capabilities and expertise residing at clinical laboratories, numerous institutions are developing and utilizing their own genetic screening platforms. While this may present the opportunity to improve time and resource efficiencies, there currently is no requirement to assess inter-institutional variability of genetic platforms. Therefore, the results of tumor molecular analysis may differ from hospital to hospital. Without new approaches to oversight it will remain difficult to assess and optimize clinical outcomes. Therefore, appropriate standards and requirements should be identified and implemented to ensure that patients are being tested with high-quality, reliable tests regardless of where the test are performed.

FDA has taken steps to begin to work with stakeholders to identify new approaches and explore how data obtained from different genetic screening platforms may be able to be compared and potential variations between platforms be better understood. This effort is part of the Obama administration's Personalized Medicine Initiative and two draft guidance documents were recently made available for public comment.¹⁸ The agency plays a critical role in PMI; its flexible approach on NGS and work to convene all sectors of the community will support advancing the science so innovative new NGS tests come to market, and have accurate results for patients.

CONCLUSION

As the members of this committee decide how best to address the regulation of molecular tests, I would like to lay out a few points that I believe are important to consider. First, the primary basis for regulations governing molecular testing should not be where a test is performed but rather what medical decisions the test is used to inform. Thus, tests that are used to guide the same medical decision-making ought to be subject to the same regulatory oversight and requirements no matter where they are developed or performed. Second, medical professionals need to be able to compare the strengths and weaknesses of tests that claim to measure the same analyte(s). Currently there is no means for them to complete this task. The FDA should work with the laboratory and diagnostics industry to standardize techniques to characterize variability between tests. Third, advanced genomic screening technologies may require a regulatory framework of their own, which takes into consideration the rapid pace of technological advancement and ensures

¹³ Conway P: Congressional Testimony before the Committee on Energy and Commerce, Subcommittee on Health U.S. House of Representatives. "Examining the regulation of diagnostic tests and laboratory operations." Nov. 17, 2015.

¹⁴ Yorzcyk A, Robinson LS, Ross TS. Use of panel tests in place of single gene tests in the cancer genetics clinic. *Clin Genet* 2015; 88: 278–82.

¹⁵ Polley MY, Leung SC, McShane LM, et al: An International Ki67 Reproducibility Study. *J Natl Cancer Inst* 2013; 105: 1897–906.

¹⁶ Boland, JF et al. *Hum Genet* 2013; 132: 1153–1163.

¹⁷ Dickson, DJ, Pfeifer JD. *Clin Pharmacol Ther* 2016 Feb; 99(2): 186–97. Epub 2016 Jan 12.

¹⁸ FDA Draft Guidances Designed to Streamline Regulatory Oversight for Next-Generation Sequencing Tests: <http://www.fda.gov/ScienceResearch/SpecialTopics/PrecisionMedicine/ucm510027.htm>. Accessed 9/15/16.

that patients have access to high quality, reliable testing. The future of precision medicine and the health and lives of patients depends on the accuracy of these tests.

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For more information, please contact: Ryan Hohman, JD, Managing Director, Policy & Public Affairs, Friends of Cancer Research at rhohman@focr.org or 202.944.6708.

The CHAIRMAN. Thank you, Dr. Allen.
Dr. Kaul.

STATEMENT OF KAREN L. KAUL, M.D., PH.D., CHAIR, DEPARTMENT OF PATHOLOGY AND LABORATORY MEDICINE, DUCKWORTH FAMILY CHAIR, NORTHSORE UNIVERSITY HEALTHSYSTEM, CLINICAL PROFESSOR OF PATHOLOGY, UNIVERSITY OF CHICAGO PRITZKER SCHOOL OF MEDICINE, EVANSTON, IL

Dr. KAUL. Thank you, Chairman Alexander, Ranking Member Murray, and Senators. I very much appreciate the opportunity to participate in this morning's hearing on an important topic that is the focus of my life's work, pathology and laboratory medicine, and, specifically, how we support precision medicine.

I'm a pathologist, a medical professional who provides results and consultation to other physicians, and I also oversee testing services that touch every patient in our healthcare system. I'll mention that the assays that we're talking about this morning are not performed in doctors' offices. We're not manufacturing kits, or manufacturing at all, but instead are optimizing procedures that we can use as part of our delivery of care to provide the best information to take care of patients. This is my practice of medicine.

The regulatory oversight of testing must make these new tests available safely and expeditiously, and we need to carefully consider the roles of CLIA and the FDA, how they'll be optimized and how they will work together to support precision medicine. The FDA requires prospective clinical trials and review. I've served on an FDA panel and see the value in this. However, the investment required drives IVD test kit manufacturers to choose what to submit for approval. They must recover the cost in the market in the end, and the menu of FDA-approved test kits we have reflects this.

We currently have two FDA-approved kits for BRAF mutations for melanoma, but nothing approved for the other tumors that require BRAF testing to optimize treatment—thyroid, brain, colorectal, and others. In order to serve those patients, we must treat the kit as a lab-developed test, repeat all of the validation as now is required under CLIA because we're using it for a non-FDA cleared purpose, even though this is a purpose recognized in national consensus treatment guidelines.

Another example is the KRAS gene mutation which you've already heard about from Senator Alexander, which predicts response to targeted therapy. Laboratories banded together in order to respond a decade ago when it became clear that this was needed for optimal patient care, worked across the country to ensure that

the results arriving in one test matched those in another, and put together an enormous effort to make sure this truly worked, all done under CLIA.

As we have heard, the test kit finally did become available. But, unfortunately, by the time this was the case, new information indicated that KRAS testing alone was not enough, and the test kit was obsolete. These 6 years caused a great delay for patients and indicate that an inadvertent outcome of the FDA review process is to delay necessary testing to patients as well as to increase costs, because the kit, as it did become available, was severalfold more expensive than the procedures we had been using with great success for a decade.

A similar story is that of chronic myelogenous leukemia, or CML, and the BCR-ABL translocation that is causative of the disease. Identification of this abnormality has been a valuable diagnostic tool in labs for decades. Many labs set this testing up around 1990. In fact, we were doing precision medicine even back then. Methods developed by the lab have been incorporated in clinical management to monitor patients for years.

The first FDA-approved kit for BCR-ABL was just approved this past summer in 2016. It's not approved for diagnosis but only monitoring, and it doesn't cover all the chromosomal translocation breakpoints that we need. For those purposes, we need to continue to use lab-developed tests, all performed under CLIA.

DNA-based testing has also saved thousands of lives through rapid diagnosis of infections. Testing for microbes using DNA can allow results in hours rather than days or weeks. An excellent example is HSV encephalitis, a life-threatening infection that can cause death within hours. Previous diagnostic methods include virus culture from cerebrospinal fluid, which was slow and often failed, or a brain biopsy.

A landmark study in 1995 demonstrated that DNA detection provided superior results for patients, and, again, labs rallied together to set up assays, compare results, set standard protocols, proficiency testing—all the things that we do regularly under CLIA. And I'll add that CLIA does look at the results of our validation studies and does look at the performance of the lab, so it's an important part. It's not just the processes in the labs. At any rate, PCR became the standard of care.

Twenty years later, an FDA-approved assay finally became available for HSV detection. So during those 20 years, should we have waited for the kit and not performed this testing? This would have required that many patients who did have the disease got treatment much later, too late to save their lives, and many patients who didn't have the disease would have stayed in the hospital on IV antiviral agents at great cost when they didn't need to be treated. We think this makes a big difference for patients.

There are many examples of other infectious diseases for which molecular assays have had an enormous benefit for rapid detection as well as characterization of antimicrobial resistance genes, important now in the battle against superbugs, hospital-acquired infections, and new agents threatening our public health.

The overarching goal for all of us is the safety and efficacy of our lab tests and procedures. Labs have a history of operating success-

fully under CLIA, and there's published data to support this. CLIA does need expansion and modernization, however. Goals for test performance can be defined by clinical groups prior tests being launched, and we do need an expanded review of data coming out of labs who are performing this testing.

We also need very desperately appropriate reference materials for labs to demonstrate their quality before the testing is launched to the public. Labs that are not able to meet these quality goals, whether they choose to use a kit or an in-house procedure, should not be allowed to do the testing, period.

Labs currently have the infrastructure to support an expanded CLIA program without expensive additional programs. But this is not so for FDA oversight. FDA has an important role, but only for those products that are truly IVD kits manufactured to work in an array of settings across the country.

Thank you.

[The prepared statement of Dr. Kaul follows:]

PREPARED STATEMENT OF KAREN L. KAUL, M.D., PH.D.

SUMMARY

I am a pathologist, a medical professional who provides results, consultation and guidance to other physicians, and I oversee testing services and procedures that touch every patient in our health care system. Lab results constitute the majority of data in a patient's electronic medical record, and our procedures dictate the majority of downstream medical decisions for patients. We have a great responsibility to patients who deserve the most accurate and up-to-date information so that they receive the most appropriate, complete and efficient course of care. We owe this to our patients, and to our physician colleagues who care directly for them.

We find ourselves in an interesting and exciting time with an explosion of knowledge and technology that can revolutionize patient care; this is the promise of precision medicine. We must bring this to the clinic with safety and accuracy, while also faced with demands to lower the cost of medical care in the U.S. We are talking today about the regulatory oversight of laboratory developed testing procedures (LDPs), the extent that medical practice should be regulated, and what models will balance the needed accuracy with ensuring new tests are made available to patients safely and expeditiously. Oversight provided by the Clinical Laboratory Improvement Amendments (CLIA) and the Food and Drug Administration (FDA) currently both exist in the lab, and appropriately so. We need to carefully consider their best roles and how they will affect testing to support and facilitate precision medicine. I will provide real examples of the impact of these two pathways for oversight:

1. The FDA approval process is expensive, leading manufacturers to submit those assays for which they can recover cost afterward, to submit certain sample types but not others (leaving labs perform these off-label IVDs as LDPs under CLIA. Examples of BRAF and BCR-ABL testing are provided)

2. The FDA approval process is slow, making many tests obsolete by the time they are offered (KRAS example) so that LDPs are still needed to provide the information needed for standard patient care.

3. There are many examples of critical lab tests in cancer and infectious disease that have been performed with great benefit to patients as LDPs under CLIA for years to decades (BCR-ABL, HSV and many tests for infectious diseases, KRAS and other gene mutation tests). For a few of these, FDA-approved tests were developed much later, based on the body of knowledge and literature produced by the labs, and were ultimately more expensive to purchase and perform. Often, these tests do not fully serve the needs of the labs, physicians and patients.

4. Next generation sequencing methods have replaced single gene tests in many labs as they provide needed data more efficiently and reliably, with the flexibility to incorporate new gene targets as needed. Performance standards have already been developed, along with lab inspection checklists and proficiency testing samples.

5. CLIA modernization would be beneficial to expand its scope and include defined standards and reference materials for labs to use to demonstrate their performance and quality *before* offering a new clinical test.

6. Getting a correct, complete and timely answer from the lab is the most important outcome for patient care.

It is often thought that when “lab tests” are done to reach a diagnosis, they are done with a kit or on a machine, but in fact, most are done with the direct involvement of a laboratory professional or physician, with years of specialty training after medical school. We have had ACGME certified fellowships and board certification in Molecular Genetic Pathology for nearly 20 years. And what we do in the lab is generally not encompassed by a “test kit,” but starts with the pathologist examining the tissue section, or bone marrow aspirate, or gram stain, and determining what additional studies are needed to provide the complete package of information to the clinician so that patient can be treated appropriately. Some of these will be FDA cleared kits, and others will be LDPs performed under CLIA; both have their place. And when performed locally, these procedures can be integrated, interpreted as a whole, completed in a timely fashion, and used for training of the next generation of physicians, for whom we hope, maximal use of this genomic information will be a way of life as they treat human disease. *That is the promise of personalized medicine!*

Chairman Alexander, Ranking Member Murray, and other members of the committee, thank you very much for the opportunity to participate in this morning’s hearing on a very important topic that is the focus of my life’s work: Pathology and laboratory medicine, and specifically how we support precision medicine.

The field of pathology offers the opportunity to understand the science of disease, to lead innovation and quality efforts, and to have enormous impact on the lives of patients every day. I most often interact with ordering physicians, and I am your doctor’s specialist: a medical professional whose testing services and procedures touch every patient in our health care system. Patients benefit from laboratory medicine throughout their life beginning with newborn screening. Lab results constitute the majority of data in a patient’s electronic medical record, and our procedures dictate the majority of downstream medical decisions for patients. Medical professionals in clinical laboratories have a great responsibility to patients to provide the most accurate and fastest information so that they can have the most appropriate and most efficient course of care. We owe this to our patients, and to our treating physician colleagues who care directly for them.

We find ourselves in an interesting and exciting time. The human genome has been sequenced and we are seeing an explosion of knowledge and technology that we can apply to patient care; this is the promise of precision medicine, and we need to continue to innovate and integrate it into the clinic. This has been most evident in oncology—every cancer patient should have access to the testing needed to best guide their treatment, as early as possible in their treatment planning. As always, we must provide highest level of safety and accuracy. At the same time, we are faced with growing demands to lower the cost of medical care in the U.S.

We are talking today about the regulatory oversight of laboratory developed testing procedures (LDPs), the extent that medical practice should be regulated, and what models will balance the needed accuracy with also ensuring new tests are made available to patients safely and expeditiously. Oversight provided by the Clinical Laboratory Improvement Amendments (CLIA) and the Food and Drug Administration (FDA) currently exist in the lab and are not mutually exclusive options, but we need to carefully consider their best roles and how they will affect testing to support and facilitate precision medicine.

The FDA traditionally requires prospective clinical trial data and a lengthy review process—I have served on an FDA panel as an expert, and there is value in the process. However, the investment required drives in vitro diagnostic (IVD) test kit manufacturers to carefully choose what tests, what applications, and even what sample types to submit for FDA approval—a company will rarely go through this process unless the costs can be recovered at the end, and the cost of a prospective clinical trial will understandably influence the trial design and breadth. As a result, physicians in laboratory medicine have access to two FDA-approved IVDs for BRAF oncogene mutation testing, important in determining treatment, that can be used for melanoma samples, but nothing approved for analysis of thyroid, glioma, colorectal or other cancers for which the BRAF gene mutation is needed. In order for us to serve our patients, we are required to turn the IVD into an LDP, since we are using it for a non-FDA-cleared purpose, and thus it will be regulated under CLIA. Alternatively, we could better utilize our limited resources by developing and validating a laboratory testing procedure capable for testing all sample types while providing high quality, accurate testing to our patients. In fact, labs are doing that through the implementation of gene panels analyzed by next generation sequencing.

Lab testing done under CLIA has been extremely beneficial to patient care. An illustrative example is testing for the KRAS gene, known for several years to predict which patients with metastatic colorectal cancer will respond to targeted therapy. Testing has been standard for several years, since a landmark study was presented at the American Society of Clinical Oncology (ASCO) meeting in 2007.¹ I clearly recall the deluge of requests we had from oncologists and patients following that meeting because the treatment, used for appropriate patients defined at the gene mutation level, made a difference in outcome. However, there were no clinical tests, no kits, nothing available at that time to test for mutated KRAS gene. In molecular pathology labs across the country, we had a great deal of experience detecting single mutations in human DNA and had been doing so for other genes and purposes for quite some time, all done under the quality standards as defined by CLIA. Labs across the country quickly shared information and protocols, debated at length as to the details of reliable assays, and shared samples and data to define the best approach and to ensure that test results done in one lab matched those done in another.² Hours were spent on conference calls and at professional meetings debating and comparing details, and one might argue, examining a breadth of information not seen during the FDA review of a single manufacturer's assay. After a few months, several labs were able to offer fully validated KRAS assays that worked reliably and were safe for patient care. Under CLIA, the validation data collected by these labs was subject to ongoing peer review, and labs participate in ongoing proficiency testing to demonstrate assay quality.

In less than a year, the profession was able to translate a meaningful and significant scientific discovery into a well validated clinical tool for oncologists. Yet, it took fully 6 more years for the first FDA-approved KRAS mutation kit to hit the market, at a cost severalfold higher than the LDP assays we had been using for several years. Unfortunately, by the time this FDA approved kit reached the market, new data demonstrated that KRAS analysis alone was not enough; mutation analysis of other RAS family genes was necessary, and the FDA-approved assay was largely obsolete. Thus, an inadvertent outcome of the FDA review process is to delay or make necessary testing unavailable to patients, as well as to increase cost, neither of which are good for patient care. The tests that go through this process do not keep up with the standard of care as dictated by nationally accepted NCCN guidelines and are essentially frozen in time at the time of FDA approval.

Another clear illustration of both the innovation occurring within the lab, and the significant benefit to patient care is the story of chronic myelogenous leukemia, or CML, and the Philadelphia chromosome causing the BCR-ABL gene translocation. The abnormal chromosome was first described and characterized in the 1960s, and the genes affected by the translocation were identified in the 1980s. Identification of this gene translocation at the molecular level gave hematopathologists a definitive tool to use when making a diagnosis of CML, and testing was set up in my lab around 1990. Truly, even then this was precision medicine! Over time, as targeted therapy (Gleevec) became available, we developed assays that could quantify the abnormal genes in blood, allowing the monitoring a patient's response to treatment and detection of early relapse, and this was included in the consensus guidelines for clinical management. This work was all done by hospital labs, molecular pathologists, hematopathologists and lab scientists, working together in every setting from their labs to national meetings to international consensus conferences. Reams of documentation, study data, comparisons and peer-reviewed literature have been published, transparency being important to all.^{3,4} Clearly, this work has had a major clinical impact, has been good for patients, and has served as a model for precision medicine in general! The first FDA approved kit for BCR/ABL became approved this past summer, 2016, and is ONLY approved for monitoring, not diagnosis, and does not include the entire spectrum of breakpoints. For initial diagnosis, we must continue to use the necessary in-house procedures, all performed as procedures under CLIA.

The Clinical Laboratory Improvement Amendments (CLIA) provide for oversight of clinical laboratories, and defines extensively the details for laboratory operation, assay validation, reagent quality and testing, staff requirements and training, and much more in an effort to ensure that lab results are accurate, reproducible and reliable. The checklists and details are developed and reviewed via consensus of laboratory experts, and constitute hundreds of pages of requirements and data points. In the lab, we think about the patient everyday, and are well aware of the impact our work has on their lives. CLIA for us is a way of life, and we have built into our lab operations, mechanisms for data collection, training, proficiency testing and other processes to ensure our compliance with CLIA. We are subject to unannounced inspections, and must demonstrate satisfactory performance characteristics for any test that we offer in the lab to ensure that our results are accurate. For testing not

reviewed by the FDA, we go through an even more rigorous validation process before offering the test for clinical use. CLIA works, and the outcome of published laboratory comparisons demonstrate the quality results achieved under CLIA regulations. However, the science of laboratory medicine has advanced dramatically in the almost three decades that CLIA was enacted, and it's time to modernize the CLIA regulations. Personally, I would like to see consensus goals for test performance—such details as what percent tumor cells should an assay be able to detect, what mutations should be included, and what sample types should be tested—that would be defined by professional expert groups early in the process as labs begin to design an validate assays for a newly relevant gene. Labs would work toward these quality goals, and any lab not able to meet them should not offer the assay for clinical use. Ideally, we would also have available an appropriate set of reference materials for labs to demonstrate the ability of their assays to perform well—this is a major need and would be of great benefit, but will require funding. Currently a multidisciplinary pilot is being organized to test this strategy: the Tapestry pilot.⁵ In this model, labs would be allowed to utilize assays that best served the needs of their patients and needs of their labs, with the most important endpoint being getting the correct answer!

In fact, this is how it works for most testing in the clinical laboratory—labs generally have a variety of assays to choose to implement, so they base that choice on clinical need and fit with the lab—it is not critical that labs all use the same assay or platform, provided that all are able to get the correct answer. Ongoing proficiency testing (the testing of unknown samples at intervals during the year, another use for reference materials) is used to demonstrate the ongoing quality in the lab.

Now, however, most of our single gene and small gene panel assays for cancer are becoming obsolete. Thanks to testing that looks at a larger number of genetic mutations in tumors, an oncologist has an arsenal of information to help design a treatment plan specific to the complex nature of that patient's tumor. Many labs have implemented Next Generation Sequencing (NGS) which looks at larger panels of genes relevant in cancer, has a very high degree of sensitivity and reliability, and is less expensive than individual gene analysis approaches. Labs performing this testing onsite can maximize the benefit to patients by providing results rapidly and integrate the data and professional consultation into interdisciplinary treatment-planning conferences. Consensus laboratory guidelines, inspection checklists and proficiency materials have already become available to clinical laboratories, under CLIA. With proven proficiency in this method, labs will be able to respond quickly to clinical needs as new gene mutations are found to make a difference in patient care. In that model, the strength of the data supporting the clinical use of that gene will be the key challenge and target for medical professional consensus discussions.

While most of the conversation regarding precision medicine focuses on cancer testing, it is equally important to highlight that DNA-based diagnostic testing has saved thousands to millions of lives through rapid diagnosis to determine appropriate treatment in infectious disease. Nearly all testing for viruses is done using DNA and RNA-based methods, for the simple reason that this allows labs to get more information, often much faster. Viruses grow slowly in laboratory culture, and may require weeks for a diagnosis, far too long for patient care. However, detection of the viral nucleic acid can be done in hours. An excellent example of this is Herpes Simplex virus. HSV can cause a life-threatening infection of the brain, and without rapid identification and treatment with IV antiviral agents, a patient could die within 48 hours. Older diagnostic options included viral culture from cerebrospinal fluid, which was slow and often grew no virus, or a very invasive brain biopsy. A sentinel study was published in 1995 demonstrating that PCR technology could be used for HSV detection with superior results.⁶ Labs rallied to develop and validate assays, define needed detection limits, set up standard protocols and proficiency testing, all the usual things we do, and PCR quickly became the standard of care. Twenty years later an FDA approved assay finally became available—Should we have withheld testing during those years, waiting for an FDA approved test kit? Rapid and accurate diagnosis using an LDP validated and performed under CLIA allowed many patients who did not have HSV infections to go home, rather than remain in the hospital on IV drugs (a great cost savings!) and those who did have an infection were able to get the needed treatment started within hours. There are many other examples of microbes for which molecular assays have had an enormous benefit, both in terms of rapid detection as well as characterization of antimicrobial resistance genes, important in the battle against spread of superbugs and hospital-acquired infections.

Labs are often faced with new infectious agents threatening our public health, as we currently are with Zika. While testing for these agents is often developed and performed under the auspices of the CDC and public health labs, hospital labs at

academic centers and in the community are often on the front lines in these outbreaks. Programs coordinating broader access to testing would be greatly beneficial.^{7,8} Recall the H1N1 swine flu epidemic in 2009, for example—our emergency rooms were swamped, our State public health labs buried in samples they were unable to test, hospitals and physicians were trying to determine who to treat, who to isolate, who to hospitalize . . . We happened to have been studying Tamiflu resistance in seasonal influenza at the time using a lab developed procedure that detected flu A, and fortunately differentiated the swine flu type; as this test was validated under CLIA, we were able to use it to our patients' advantage.⁹ Whether confronted with another respiratory virus, or Ebola, or Zika, or something else, a more coordinated effort between the public health and hospital labs would be beneficial for all. We simply cannot be satisfied with the current situation with pregnant patients waiting weeks for viral test results!

To close, the overarching goal for all of us is the efficacy and safety of our lab tests and procedures for patients. We are physicians and healthcare providers and our focus is on the patient at all times. Labs have a long history of success operating under CLIA, which allows a greater flexibility and faster responsiveness to new tests that are needed to improve patient care. This process would benefit from some expansion, particularly to define pre-launch consensus performance guidelines and provision of reference materials. Labs currently have the infrastructure to support even an expanded CLIA compliance program without extensive additional expense. FDA has an important role in the lab as well, but one limited to those products that are truly IVD test kits and instrumentation which are designed to work in multiple labs and settings across the country.

It is often thought that when “lab tests” are done to reach a diagnosis, they are done with a kit or on a machine, but in fact, most are done with the direct involvement of a laboratory professional or physician such as myself. Anatomic and Clinical Pathology residency training is 4 years in length (after medical school) and our residents go on to do at least 1, and sometimes 2 or 3 year-long subspecialty fellowships. We have had ACGME certified fellowships and board certification in Molecular Genetic Pathology for nearly 20 years. We train to do this, just as surgeons train for 5 years to do surgery. And what we do in the lab is generally not encompassed by a “test kit,” but starts with the pathologist examining the tissue section, or bone marrow aspirate, or gram stain, and determining what additional tools are needed to provide the complete package of information to the clinician so that patient can be treated appropriately. Pathologists need the best and most up to date tools to do their jobs, and they are doing this for patients. Some of these will be FDA clears kits, and other will be lab procedures performed under CLIA; both have their place. As much as possible, these capabilities need to be onsite to insure that the results can be integrated, interpreted as a whole, completed in a timely fashion, and also for training of the next generation of physicians, for whom, we hope, maximal use of this genomic information will be a way of life as they treat human disease. *That is the promise of personalized medicine!*

REFERENCES

1. Di Fiore F, Le Pessot F, Lamy A, et al. *KRAS* mutation is highly predictive of cetuximab resistance in metastatic colorectal cancer. *Journal of Clinical Oncology*, 2007 ASCO Annual Meeting Proc.; Vol 25, No 18S (June 20 Supplement), 2007: 10502.
2. Kamel-Reid S, Zhang T, Persons DL, et al. (Molecular Oncology Resource Committee of the College of American Pathologists) Validation of *KRAS* testing for anti-EGFR therapeutic decisions for patients with metastatic colorectal carcinoma. *Arch Pathol Lab Med*. 2012;136:26–32. doi:10.5858/arpa.2011-0220-OA. <http://www.ncbi.nlm.nih.gov/pubmed/22208484>.
3. Kantarjian HM, Talpaz M, Cortez J, et al. Quantitative polymerase chain reaction monitoring of BCR-ABL during therapy with imatinib mesylate (ST1571, Gleevec) in chronic phase chronic myelogenous leukemia. *Clinical Cancer Research* 2003; 9: 160–166. <http://clincancerres.aacrjournals.org/content/9/1/160.full-text.pdf>.
4. Hughes TP, Branford S. Molecular monitoring of BCR-ABL as a guide to clinical management in chronic myelogenous leukemia. *Blood reviews* 2006;20:29–41. <http://www.tapestrynetworks.com/initiatives/healthcare/onco-logy-therapeutics-and-diagnostics/diagnostic-quality-assurance-pilot.cfm>.
5. Lakeman FD, Whitely RJ, and the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Diagnosis of Herpes Simplex Encephalitis: Application of Polymerase Chain reaction to Cerebrospinal Fluid from Brain-

biopsied Patients and Correlation with Disease. *Journal of Infectious Diseases*, 1995;171:857–63.

7. Nowak J and Kaul KL. The role of community molecular diagnostics labs in the H1N1 Pandemic. *Journal of Molecular Diagnostics* 2009;11:366–370. [http://jmd.amjpathol.org/article/S1525-1578\(10\)60253-X/pdf](http://jmd.amjpathol.org/article/S1525-1578(10)60253-X/pdf).

8. Crawford JM, Stallone R, Zhang F, et al. Laboratory Surge Response to Pandemic (H1N1) 2009 Outbreak, New York Metropolitan Area USA. *Emerg. Infect. Dis.* 2010. DOI 10.3201/eid1601.091167.

9. Kaul KL, Mangold KA et al. Influenza A subtyping: Seasonal H1N1, H3N2, and the appearance of novel H1N1. *Journal of Molecular Diagnostics* 2010; 12:664–669. DOI: 10.2353/jmoldx.2010.090225.

The CHAIRMAN. Thank you very much for the terrific and very helpful testimony. We'll now go to a series of—a round of 5-minute questions.

Dr. Klimstra, in my short 5 minutes, I'm going to acknowledge the incongruity of kits being regulated one way and laboratory tests being regulated another way. But I'm interested in the consequences to patients of what happens if we regulate laboratory-developed tests the way we regulate kits today. My information says there are about 60,000 laboratory-developed tests in the country. Am I correct that the 2014 guidance proposed by the FDA would require each one of those 60,000 tests to be individually approved by the FDA?

Dr. KLIMSTRA. Thank you for the question. I believe the—

The CHAIRMAN. Can you give me a yes or no?

Dr. KLIMSTRA. Maybe, unfortunately.

[Laughter.]

The CHAIRMAN. Most of the 60,000 tests?

Dr. KLIMSTRA. A large number of them, depending upon how—

The CHAIRMAN. Tens of thousands of tests?

Dr. KLIMSTRA. Tens of thousands.

The CHAIRMAN. Tens of thousands would have to be regulated by the FDA. Price Waterhouse did a study that showed that the cost of such FDA approval might be in the range of \$30 million to \$75 million for each test. Does that sound plausible to you?

Dr. KLIMSTRA. That sounds a little high to me, but I believe if you add all of the costs of the experiments together with the charges that would be incurred for undergoing the review, it will certainly be a substantial amount of money.

The CHAIRMAN. At Sloan Kettering, you said that you have 350 laboratory-developed tests.

Dr. KLIMSTRA. That's correct.

The CHAIRMAN. You engage in a lot of what we call personalized medicine. Is that correct?

Dr. KLIMSTRA. Yes, it is.

The CHAIRMAN. At Vanderbilt, the head of personalized medicine told me that 95 percent of their personalized medicine practice used their own laboratory-developed tests. Is that comparable to what you do?

Dr. KLIMSTRA. Yes, it is.

The CHAIRMAN. What would happen if you had to submit each of the 350 laboratory-developed tests that you have to the current FDA approval practice?

Dr. KLIMSTRA. We would close the lab. There's no way that the institution could afford the cost associated with formal FDA review

and approval of all of those tests. It would simply be economically impossible.

The CHAIRMAN. Did you testify that one of those 350 tests had helped 12,000 cancer patients?

Dr. KLIMSTRA. That's correct.

The CHAIRMAN. You are already regulated by CMS and the State of New York, you testified. If you were then to be also regulated by the FDA, that would be triple regulation, if I understand it correctly.

Dr. KLIMSTRA. That's right.

The CHAIRMAN. Dr. Kaul, in your practice of personalized medicine, what percent of your institution's personalized medicine practice relies on your own laboratory-developed tests?

Dr. KAUL. We're a somewhat smaller institution but also have a big investment in personalized medicine and have been developing tests for several decades. If there is an FDA-approved assay that works well and is affordable and is not a test that we've already had in-house for several years, we certainly look at that very seriously. But in many situations where we have a test that appropriately covers the mutations needed, we'll stick with an in-house test. So the majority of our personalized medicine tests—

The CHAIRMAN. Majority is the answer. Is that right?

Dr. KAUL. Majority.

The CHAIRMAN. The majority of your personalized medicine practice uses laboratory-developed tests.

Dr. KAUL. Yes.

The CHAIRMAN. You're at the University of Chicago. Is that correct?

Dr. KAUL. Yes, an affiliate of the University of Chicago.

The CHAIRMAN. An affiliate of the University of Chicago. What would happen to your laboratory if the FDA required you to—how many laboratory-developed tests do you have at your institution?

Dr. KAUL. In personalized medicine, I would say we have 50 or 60. But there are lab-developed tests across the lab in other areas, not just personalized medicine.

The CHAIRMAN. More than 50 or more than 100?

Dr. KAUL. Many more. Hundreds.

The CHAIRMAN. Hundreds of tests. What would happen if the FDA required FDA approval in addition to CMS approval in your institution?

Dr. KAUL. I think the regulatory and expense burden would be such that we wouldn't continue in personalized medicine, and I think it would have a big impact on the way that medical care is delivered today for testing in general.

The CHAIRMAN. To be specific about that, what would the effect be on patients at your institution?

Dr. KAUL. They would not get the care they need. And I believe this care, as much as possible, needs to be delivered onsite so that we can put together all of the information, deliver it at multidisciplinary tumor boards, discuss with the clinicians, and teach our residents and fellows. This would all go away.

The CHAIRMAN. I'm sure questions will be directed to Mr. Spring and Dr. Allen. But just my observation is that we're in a rapidly changing world here, but it's been changing longer than for the last

year or two. Laboratory-developed tests are well established, and it's clear that we have, in the case of Sloan Kettering, two areas of regulation already. It doesn't make much sense to me to solve the problem by slowing down the use of laboratory tests so they can be at the same slow pace of kits. I recognize that those may be two different kinds of regulation.

But I think our goal is to speed up the development of safe and effective tests so that institutions may use them to help patients while the patients are still alive. I'm delighted that we're having this hearing and hope to learn from it.

Senator Murray.

Senator MURRAY. Thank you very much.

As I mentioned in my opening statement, in a recent announcement, FDA stated that lab tests marketed as screening tools for ovarian cancer were not supported by definitive evidence and results from that unproven test may have led women to delay or forego treatment or undergo unnecessary treatment. As we move toward a greater emphasis now on precision medicine in our healthcare system, patients and their physicians are going to be relying on these types of tests more and more to guide their own treatment.

Dr. Allen, I wanted to ask you: How do we know that claims made by labs about cancer screening tests or other tests are supported by strong scientific evidence?

Mr. ALLEN. Unfortunately, particularly when they are for newly discovered markers, I don't think we do know what evidence is behind them if they don't go through the FDA process.

Senator MURRAY. Dr. Klimstra, the tests that are offered by Memorial Sloan Kettering—they do have to be reviewed by New York State Department of Health if they're not reviewed by the FDA. So patients in New York can be assured that their test results are accurate and that results are clinically meaningful. But do patients in other States across the country have that same assurance?

Dr. KLIMSTRA. If patients are in other States, not being tested in New York, they don't have the same pre-test review requirements. No, they do not.

Senator MURRAY. Dr. Allen, in your experience, are patients outside of New York State told or even generally aware that their tests may not have been reviewed by FDA or any external organization to assure that their test results are meaningful?

Dr. ALLEN. I think that's probably a difficult number to assess. But as a supplement to the publication that I mentioned, we conducted a survey of national oncologists to see what they knew about their test status, and one in five practicing oncologists did not know whether their tests that they ordered were FDA approved or not. So I strongly suspect patients do not.

Senator MURRAY. Mr. Spring, before you market a test, what studies do you need to perform to demonstrate to the FDA that your tests work and are clinically meaningful?

Mr. SPRING. It depends on the risk of the test and the classification of the test. But the majority of our tests will go through what we call analytical testing, some sort of bench testing that challenges the ability of the test to detect the analyte or target. We'll

look at things like what substances might interfere with that test and so forth.

Then we take it out, say, into the real world and do some sort of clinical testing, either prospectively on patients or, in the cases of maybe rare disease or low-prevalence diseases, we'll go to some sort of tissue bank or a specimen bank to do that testing. It's a balance of analytical and clinical testing.

Senator MURRAY. After all of that work, is there anything preventing a lab without FDA review from marketing a test making those very same claims?

Mr. SPRING. No, there's nothing preventing them today.

Senator MURRAY. I think that is what sets up the uneven playing field that actually undermines public trust in the sustainability of innovators in this diagnostic field. It kind of seems like to me if we want precision medicine to advance, we need to make sure we are incentivizing innovation and assuring patients' tests will work as promised. Right?

Mr. SPRING. Exactly.

Senator MURRAY. Dr. Kaul, let me move to you. In your testimony, you spoke about your work to ensure the tests you offer are accurate and give meaningful information to doctors and patients. In this era of precision medicine, patients' treatments may vary widely, depending on test results, and that's why it's so important that patients get the same result regardless of the lab that their doctors use.

Tell me what safeguards are in place to ensure that the results from your lab would match the results from, like, Dr. Klimstra's lab or a lab in my home State of Washington?

Dr. KAUL. I'll make a couple of comments here. No. 1, the CLIA lab validation process requires that labs take their lab-developed procedures through the same protocols that happens at the FDA. We don't go through the FDA review, but we're doing the same quality assessment of the effectiveness of those tests up front. This data can be collected over CLIA. I think we need some broader oversight here. But right now, that is reviewed when we have lab inspectors dropping in unannounced to look at our validation data, and if they're not happy with it, we can't offer the testing. I think some of this activity could be moved proactively.

But we do have assurances because of the CLIA process currently. We're also required for all of these to participate in proficiency testing, so we get unknown samples multiple times a year that the labs are asked to test, return the samples to CAP—CAP is the purveyor of CLIA oversight in this situation—and we get extensive and detailed publications looking at how our results compared to those of other labs. Much of this has been published, and the quality is there. There's not so much variation in these assays that we're talking about.

We can look to see how the in-house tests stack up against the results of a test kit manufactured that did go through the FDA, and, again, there's generally no difference. The lab tests perform well, and there's published data to support this.

I'll also add that we are concerned about screening tests. Those are not the tests that Dr. Klimstra and I are talking about. I think there's a big difference between the validity of a test looking at a

gene mutation where there's extensive published literature about the value of that mutation in determining treatment response in a patient and looking ahead at who might produce ovarian cancer and needs to be treated differently down the road, and that does need a higher level of scrutiny as well. But those are not the tests we're talking about today.

Senator MURRAY. My time is up. Thank you.

The CHAIRMAN. Thank you, Senator Murray.

Senator Burr.

STATEMENT OF SENATOR BURR

Senator BURR. Thank you, Mr. Chairman.

Dr. Kaul, thank you for that last comment, because I think you draw a big distinction. We're trying to put all these things in one bucket and they don't belong in one bucket. I'm just going to turn to you as a pathologist with a lab. How many times do you do an LDT knowing that the LDT isn't going to prove—isn't going to identify what you're looking for?

Dr. KAUL. I'd say we don't. We have LDTs that we have never launched because they didn't make our quality guidelines, and we don't put those in practice.

Senator BURR. My point is you're a healthcare professional that's making a healthcare decision—

Dr. KAUL. Yes.

Senator BURR [continuing]. Based upon the tools that are available for you. It's somewhat shocking to me—I'm sitting here almost having an out-of-body experience, because we're having a debate about whether we set up a regulatory architecture that makes it slower and more costly to determine a diagnosis, yet all the diagnoses that we're looking for—every medical professional would agree that if we find it earlier, we have more options to treat. If we identify it earlier, we have the ability on a longer glide path to customize the treatment to the particular condition that we find.

Isn't our responsibility here as policymakers and as healthcare professionals to do whatever is in the best interest of the health outcome of the patients, regardless of the territorial battles that we fight up here?

My question would be to anybody that would like to take a stab at it: I've heard everybody agree that technology's pace is beginning to increase, that what took us 6 years maybe to accomplish before, we're doing it in 6 months. What's taking us 6 months today, Mr. Spring, is going to take us 1 month down the road. Is there anybody here that believes that the FDA architecture or the FDA talent exists today to be able to handle an approval—a process of an application or an approval 3 years from now?

Mr. SPRING. I can take a stab at that.

Senator BURR. Sure. Go for it.

Mr. SPRING. I think that the current framework does need to change. I'm not going to comment on the talent that FDA has, but I think they've shown innovation in addressing some of these needs through issuance of recent guidance such as the next-gen sequencing guidance as well as reliance on existing evidence that's out there, such as literature and so forth. I don't think the current construct and framework will work in this situation. We do need to see

legislative reform, and following the principles I outlined, I think we can get there.

Senator BURR. I'll tell a story—go ahead, Dr. Klimstra.

Dr. KLIMSTRA. Thank you. I'd just like to respond as well. I think one of the critical points to keep in mind relates to the comment Dr. Kaul made a few minutes ago, that there are vastly different types of LDTs that are being considered under this legislation. The idea of risk stratification, not only for the impact of the results of the test on the patient, but for the nature of the technology being employed, whether it can be validated with other types of technology in other laboratories or not, whether it uses proprietary algorithms that cannot be validated by others. These are critical points to consider in deciding which tests are highest risk, and if we are to institute additional regulatory structure, it should focus on those very high-risk tests.

Senator BURR. Dr. Allen.

Mr. ALLEN. I think what we're looking for here in terms of predictability is assurance that tests are safe and clinically valid. How to get there is up to the developer. We're looking from a regulatory standpoint at the floor—

Senator BURR. Do you trust Dr. Kaul to make that decision in her lab as a pathologist on a laboratory test?

Mr. ALLEN. I would absolutely trust Dr. Kaul to make those calls as a medical professional. But I think what we're looking for is assurance that the tools she's using to make those calls have the same predictability no matter where they're developed.

Senator BURR. So a quick story. I've got 33 seconds. In the mid 1990s, we created a new diagnostic tool called contrast imaging. The only problem was it didn't have a reimbursement code. And I remember calling Dr. Hatch, who was then the director at CMS, and I explained this to him. Contrast imaging gave us the ability to actually diagnose on the first guess versus to do non-contrast and have 17 options as to what we can do after that—more precise.

After 2 weeks of deliberation, he came back and he told me that he had solved the problem. He was going to give a 20 percent bonus to non-contrast imaging to make up for the lack of reimbursement that contrast imaging was going to get. I started a very elementary point at seeing how government looks at technology and advancement. It played no role—there was no role that was played about the quality of care that could be provided. It was about how we fit something in an old architecture.

I'm going to be fascinated as we go through this. I think all of you said we can reach an agreement. I think we can. But understand that if we don't do this in an organic way, we will be back here 12 months from now when technology has changed, where the capability to do even further lab-developed tests is that much greater, and where the challenges that are faced in a PMA or in a trial are so great that the talent may not be there or the architecture may not be there to allow that to happen in a way that impacts positively patients' lives, and we cannot take that out of the equation. That should drive the discussion we have.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Burr.
Senator Baldwin.

STATEMENT OF SENATOR BALDWIN

Senator BALDWIN. Thank you, Mr. Chairman and Ranking Member. This is a really great panel and an opportunity to delve into this topic, and I know we'll return to this in the future, in part because this has been a key focus of the HELP Committee, the idea of encouraging more advanced cures, and we know the first step to that is the precise diagnosis and screening of a condition to help best target and inform therapy.

My home State of Wisconsin has seen notable progress in this field, from things like critical antibody tests for transplant patients developed at the University of Wisconsin's academic laboratory to the first FDA-approved stool-based DNA test for colorectal cancer developed by a Wisconsin company called Exact Sciences. I will say, however, I am concerned that the growth of the laboratory-developed test industry—with that growth, there is too much that we still don't know, and it's an entire sector of the diagnostic set of tests that patients rely on.

So I have a couple of questions. If a patient doesn't know if, say, their cancer test or their Lyme's Disease test is an LDT, which has, say, not been FDA approved, or even if it hasn't been subject to the type of examination that shows that it's been proven to work, but they have this expectation, of course, as patients that that test is accurate, because of this uneven oversight, we might not know or find out too late whether a test is harming patients or giving them false hope or a wrong diagnosis.

Dr. Allen, I want to hear from you, first, the impact on patients when they don't have information about their tests. I'm not even talking about the test results yet, but sort of what sort of review that test has had that they're relying on.

Mr. ALLEN. I think there's an expectation that when you go into your doctor's office, you're going to get told the best information that that medical professional can provide to you based on a whole host of tests, of analyses, their medical interpretation of the symptoms that you're describing to them, and, frankly, patients shouldn't have to worry about this. If there's one thing that we can take out of the challenges that they're facing, could it be the evenness around the tests so that they have at least one portion of their care that they can be confident in and can expect are giving them the best possible information without variability.

This isn't about the competence of the individual who is interpreting the test or using it, because they're extremely educated, extremely talented. But they may not even know if there's variability in a test that they're using, and that's what we're trying to reduce here and have a level playing field for all of these tests, because complex decisions are made upon them.

When you think about, PSA tests, for example, this spurs a conversation between men and their doctors about what options they should be pursuing. Let's reduce some of the variability and make sure that those tests are producing the same result no matter who's performing the test or providing the information back to the patients.

Senator BALDWIN. Thank you. I want to talk a little bit about the CMS overseeing CLIA process. Throughout 2015, the Milwaukee

Journal Sentinel published a watchdog report entitled “Hidden Errors,” and it revealed deficiency in lab testing procedures across the country. It showed that our current system to regulate labs under CMS has gaps that we need to address, and the series outlined a number of specific instances where patients received incorrect results from individual labs to larger lab companies and their practices.

They outlined examples, of course, to readers which were quite shocking, incorrect paternity test results, false HIV test results, issues due to technician mistakes, or machines that were simply not properly calibrated. Many of these labs had been inspected and accredited under CMS guidelines. I’m concerned about the gaps that may exist.

Dr. Klimstra, you’ve mentioned this already. But I wonder if you could explain some of the important lab quality control differences that exist in a State like New York, whether it’s State law that requires robust lab inspection and oversight. These laws differ from State to State. What protections do New Yorkers have that others might not?

Dr. KLIMSTRA. I think the key difference in New York is the requirement for premarket approval in which the tests and the validation experiments done in order to establish them must be submitted for State approval before the tests can be offered. In other States, the mandate to maintain that regulatory level falls on the directors of the laboratories, and to the extent that they are medical professionals and they have an enormous investment in accurate results, I believe many of them are maintaining the same level of compliance. But the actual validation experiments would not be reviewed until after the test has been released. That’s the fundamental difference between New York and other States.

The CHAIRMAN. Thank you, Senator Baldwin.
Senator Hatch.

STATEMENT OF SENATOR HATCH

Senator HATCH. Thank you, Mr. Chairman.

I want to thank all of you for being here and for the excellent testimony.

In today’s ever changing healthcare landscape, clinicians and patients need stability and a clear process to feel confident about the tests influencing their healthcare decisions. I’m not certain that the current FDA structure could provide that stability.

We have great clinical and diagnostic test companies in Utah. These thought leaders have been at the forefront of molecular testing for decades, from the BRCA gene to the response to the H1N1 outbreak, bringing hundreds of tests to market.

A more recent and pressing example involves ARUP Laboratories with infectious disease experts at the University of Utah and other test developers around the country. This past winter, as the FDA and CDC were seeking to prepare for Zika outbreaks at the Rio Olympics and in the United States, infectious disease experts around the country were working diligently to complete EUAs or Emergency Use Authorizations with the FDA.

Several excellent reference tests were developed by labs and manufacturers in the spring and were able to detect Zika’s pres-

ence in blood. ARUP and others also worked to validate testing for urine testing general guidance specified in the FDA's EUA document. These groups were able to develop sensitive and robust Zika tests early in the spring using Zika sequences widely available to developers at that time.

A major barrier for all test developers has been the EUA validation requirement, requiring clinical samples from infected patients that have a medical history. These samples have been extremely challenging to obtain, and Brazil, which has been at the center of the outbreak, has prohibited the export of Zika genetic materials. In addition, new tests must be compared to existing EUA-approved assays, and these have limited availability, especially in the early days of the Zika outbreak.

This has impeded timelines for rapid test validation and approval, which is the goal of an emergency test initiative. The Utah team finished prescribed FDA requirements at the end of the summer but was recently asked to perform almost 500 additional development tests using FDA-developed Zika validation material. This requirement was not included in the original EUA guidance document issued by the FDA, and it is not clear if such testing has been a requirement for all test submissions.

None of this is to say that the FDA has been anything but thoughtful and flexible toward the research team. But it appears to me that there is no clear and expeditious process to follow in this situation. Test developers have been confronted with new requirements during the development window, and while flexibility matters, so does a clear process to ensure proper oversight of LDTs. Based on this example, I have basically two questions.

Dr. Kaul, have you experienced standards changing in this way during your career? Again, the FDA leads have been considerate scientists, so this is not an attack on the people working there, but an inquiry into the process for approval of clinical diagnostic tests.

Dr. KAUL. I'd like to answer this in two ways. You mentioned the EUA and the influenza outbreak, and, actually, our laboratory found ourselves in the midst of this in 2009 because we had a lab-developed test that was extremely effective at detecting swine flu. We had validated it for other purposes but worked with our public health lab, and within the space of a few weeks, because the sequences were published, this assay worked beautifully, and I can't say we missed a single case.

We did then go on to help two other companies develop their own EUA reagents, and 10 months later, the EUA approval was received after the outbreak was over. So I think there are some concerns here. Lab-developed tests, I think, provided a service, and it would be a lovely thing to allow those labs who are on the front lines of these outbreaks to work in a more integrated fashion with the public health labs and the CDC.

I do think the other comment you're mentioning is the need for reference materials, and labs struggle for this, whether they are trying to validate a new assay—which is why the two companies trying to develop swine flu assays turned to us in the labs because we had characterized samples we could share with them to validate their FDA assay.

But it's a struggle, and oftentimes it slows this process, not only in assay development, but I think also—as I mentioned earlier, we really need well characterized reference materials in cancer and infectious disease to help labs be able to demonstrate, pre-offering the test, that they can hit certain quality targets. There's a group called Tapestry that's working on a pilot project in cancer, and this is an area that would benefit us all.

In the end, it shouldn't matter what test kit we're using or what procedure as long as we can get the right answer for patients. That's the truth we're all after in the end.

Senator HATCH. Thank you.

Mr. Chairman, may I ask just one more question?

The CHAIRMAN. Sure.

Senator HATCH. Dr. Klimstra, you've seen the impacts of changing guidance practices over time, and separately from this Zika example, it would seem to me that the FDA believes these tests can be regulated as devices using existing authorities. But these tests are not all the same, and they are certainly not devices, in my opinion. Legislative solutions that incorporate all stakeholders are more transparent and could be more appropriate to ensuring oversight for high-risk tests.

In your opinion, would it be wiser to delay finalizing this LDT guidance in favor of discussing whether the FDA needs the authority to provide proper oversight for these tests?

Dr. KLIMSTRA. Yes. I think this is obviously a very complex issue with different types of tests, with different risks to patients, and different testing scenarios. I think that a thorough consideration of all of the options and the practical ramifications of certain choices needs to be carefully discussed. I fear that, as has been intimated, the current review process that the FDA has would not be adequate to accommodate all of the tests that fall under their definition of LDTs, and that without further refining the highest risk tests, there would not be an adequate infrastructure to expeditiously review these tests, delaying diagnoses and delaying innovations reaching the clinic.

Senator HATCH. Thank you so much.

Thanks, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Hatch.

Senator Bennet.

STATEMENT OF SENATOR BENNET

Senator BENNET. Thank you, Mr. Chairman. Thank you very much for holding this hearing.

And thank you to all the witnesses for being here today.

Just for the benefit of the committee, I'd love to go down the line here and ask you what the one or two things are that you would like us to keep in the forefront of our minds as we think about and as we consider legislating in the area of lab-developed tests.

Dr. KLIMSTRA. Thank you, Senator Bennet, for that opportunity. The key point I would like to make is that you've heard throughout the panelists that we all agree that safe, effective, reliable diagnostic testing is very important. But it's also critically important to keep in mind the ramifications and the process for additional regulation to ensure that we don't inadvertently remove these tests

from the hands of academic institutions and that we don't delay access of patients to valuable innovative testing.

Senator BENNET. Mr. Spring.

Mr. SPRING. Thank you, Senator. I'm going to echo what Dr. Klimstra said. We do need to ensure that these tests are accurate and reliable. But with that said, we have to assure that the same test follows the same regulatory framework, and the same level of evidence for that test should apply, no matter where that test is developed or implemented.

Second—and we heard this from Senator Hatch—we need a more predictable and transparent process. We don't like to see surprises halfway through the validation of our tests, and we need to improve upon that. Those are the two areas I'd like to see.

Senator BENNET. Thank you.

Dr. Allen.

Mr. ALLEN. Any test that is used to guide medical decision-making should be held to the same standards, no matter where it's developed. It's important in that context to explore flexibility in demonstrating safety and accuracy, but the standards should be the same.

Senator BENNET. Dr. Kaul.

Dr. KAUL. Thank you again for the question. We're all on the same page that we want safe and effective testing for patients and that it needs to be regulated. The key is the pathway to regulation, and whether that is the FDA that will create some considerable challenges, as we've heard, in terms of time and expense, or CLIA, where the labs already have a significant infrastructure and are already reporting information required by CLIA, is the decision that needs to be made.

I obviously believe the CLIA course with necessary expansion, premarket approval, those sorts of things, would be most useful and less onerous to the laboratory and would allow us the flexibility to get these very much needed assays out to patients to cover the mutations and the testing that they need as we move forward under personalized medicine.

Senator BENNET. Along those lines, for anybody on the panel who would like to answer, what do you think the implications are for the President's vision of precision medicine in light of the FDA's proposed guidance?

Dr. KAUL. I will take a crack at that. As enthused as I am about the President's endeavors, how we bring that to clinical care in a responsible way with the FDA proposal leaves me puzzled.

Senator BENNET. Anybody else?

Mr. SPRING. Yes, I'll comment on that and I think echo some of the comments made earlier. If you look at precision medicine, we're looking at a number of tests that are addressing unmet needs. We need to find a way to rapidly get these tests to market but still follow the same standards of ensuring accuracy and reliability.

Senator BENNET. Dr. Allen, I have one other question for you. Since we signed the Breakthrough Therapy—or the President signed it about 4 years ago, we've seen more and more therapies using a diagnostic tool. I wonder if you have a view about how important it is to have a regulatory structure around tests and how

what we're discussing here would specifically affect breakthrough drugs.

Mr. ALLEN. First, let me thank you and Senator Hatch and Senator Burr and the committee for really jump-starting the Breakthrough Therapy Designation and getting it passed into law. It certainly had a profound effect on the current State of drug development. In fact, as you mentioned, the use of molecular diagnostics is really critical to the effective implementation of the designation. In fact, 18 of the 48 drugs that have been approved with a breakthrough designation had a test associated with their use.

It's important, with the Breakthrough Therapy Designation, the underlying safety and efficacy standard for the drug does not change. It's the flexibility and the collaboration and how to demonstrate that. We have an opportunity here on the testing side to make sure that the development of the tests is not the rate-limiting step to making sure that breakthroughs reach patients, but also that there is flexibility in demonstrating the safety and accuracy of the tests in that expedited context so that you're still reliable in the test and providing timely access to both the test and the effective drug.

Senator BENNET. Thank you to the panel.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Bennet.

Senator Cassidy.

STATEMENT OF SENATOR CASSIDY

Senator CASSIDY. Dr. Klimstra, now, I gather that in New York, you get this approval pretty quickly, and it is not that expensive. Is this better than what CLIA does? Not to put you on the spot, but—

Dr. KLIMSTRA. Is it better? I can speak to the second part of the question. In New York State, we pay an annual fee to New York to provide our laboratory inspections. It's based on our gross billings. And in addition to that, the costs of premarket review for each LDT that we develop and submit to them are zero. There's no added expense to us—

Senator CASSIDY. And what's their turnaround time?

Dr. KLIMSTRA. The turnaround time at this point—because we have a well established relationship with the State and they recognize the quality of our lab and we already have hundreds of LDTs approved by them, within several weeks of submission, they give us conditional approval, and then they—

Senator CASSIDY. This is true for Memorial Sloan Kettering, which is famous, interstellarly, for your abilities.

Dr. KLIMSTRA. Thank you.

[Laughter.]

Senator CASSIDY. What would it be for a lab less well known?

Dr. KLIMSTRA. It would depend on the complexity of the test. New York State is in the process of putting forward a revised structure of test complexity—

Senator CASSIDY. Go back to CLIA. I don't mean to interrupt. I've just got limited time. Go back to CLIA. Do you feel if CLIA is looking for clinical and analytic validity, do they provide that adequately? Because I think that's one of the questions here.

Dr. KLIMSTRA. I think the pretest review is an added layer of protection. We are allowed to offer our tests with conditional approval pending final review. There's a period of time when we are offering clinical tests—

Senator CASSIDY. Moving beyond Memorial Sloan Kettering into a startup lab, which may be really good—some post doc who left your place. But there is not a history with CLIA. Would they have this effective, low-cost turnaround time?

Dr. KLIMSTRA. I would not think so.

Senator CASSIDY. If they did, are you as confident that if they were not very good, that the detection of a not very good product would be—that it would be detected, be it CLIA or be it New York State?

Dr. KLIMSTRA. I think that if there were high-quality people who have maintained the standards that CLIA mandates, they would detect their own quality issues before releasing—

Senator CASSIDY. But if they are not, would CLIA have sufficient mechanisms to say, "Ah, you are not maintaining high-quality X, Y, and Z. Therefore, we are not going to approve you and have further review."

Dr. KLIMSTRA. Under their current structure, prior to release of the test, the answer is no.

Senator CASSIDY. Under their current structure, no.

Dr. Allen, I looked at your paper that you quoted—I think I got the right one—and I'm struck. Twenty-seven percent of the people tested for the pertinent mutation had the test before an FDA test was approved. Now—and I see Dr. Kaul back there nodding her head. Her thing about the herpes simplex virus is dramatic. We would have—years treating HSV.

Are you advocating that until the FDA comes out with a product that we do nothing, knowing that herpes simplex virus—people would have been getting Acyclovir for many days at a time—and/or for the cancer, 27 percent of the people had not got the testing prior to the FDA approval? How do you balance that?

Mr. ALLEN. The facts that have been shared today in terms of the overlap between the availability of an LDT for tests like EGFR and KRAS are accurate. They were available as an LDT before a manufacturer brought a test to the FDA in order for it to be reviewed. That's because there's no requirement for them to do so. It's almost a voluntary nature for them, if they want to develop it as a kit, to take it to the FDA rather than perform it in their single lab.

I think we absolutely need to acknowledge what these research institutions and universities are doing in terms of being the driver and the engine of—

Senator CASSIDY. But, again, my point being that 27 percent of the people tested were tested before there was an FDA-approved test in your paper. So do we put on hold that testing until we have the FDA, through its laborious—oh, my gosh, how long does it take to brew a cup of coffee—

Mr. ALLEN. We need to think about some transitional period to go through—those that are discovered in terms of—as an LDT. But how do we then make that LDT that was developed at a single institution—how do we make that test available beyond patients that

are just treated and tested at that one institution? That may require the FDA to have oversight to make sure that those tests are clinically valid before they go into widespread use.

Senator CASSIDY. Mr. Chairman, can I ask one more question, please?

The CHAIRMAN. Of course.

Senator CASSIDY. Thank you. It helps being the last guy here.

Dr. Kaul, I really enjoyed your testimony. First, you made some summary points at the end which I did not see in your testimony. So either I was gathering wool or you slipped them in. But if you could submit those for the record, I would appreciate that.

Dr. KAUL. Absolutely.

Senator CASSIDY. Second, you kind of point maybe to a resolution. It seems like you have a crowd sourced approach, different labs collaborating to come up with something which is, if you will, Memorial Sloan Kettering and the University of Chicago writ large, everybody participating, and you check each other. Is that a fair way to depict it?

Dr. KAUL. Not being a millennial, I won't opt to use the word, crowd sourcing, but that's exactly what happens. We have a very active list serve. We sit at our professional meetings and talk like lab—

Senator CASSIDY. OK. Let me interrupt you. So how do you handle the IP?

The CHAIRMAN. Go ahead and take your time, Senator Cassidy.

Dr. KAUL. How do we—

The CHAIRMAN. Go ahead and ask your question.

Senator CASSIDY. Thank you.

Dr. KAUL. How do we handle the—

Senator CASSIDY. Intellectual property.

Dr. KAUL. For the most part, we don't, because we are doing this for patients. We're not doing this to make money and patent a gene or a test kit for our laboratories. We are in this to do the right thing for patient care.

Senator CASSIDY. As a physician, I applaud you. But is your medical school provost as high-minded as you?

[Laughter.]

Dr. KAUL. I think that there is—they have never approached me and pushed the things that we're doing in the labs, because it does offer the best thing for patients, and that's why we're doing it.

Senator CASSIDY. Let me ask is that the way forward? Because I'm just nihilistic about the FDA's ability to do anything in a timely fashion. And, frankly, what happens in New York—it is your reputation that precedes you, but if you're the smart post doc with a paradigm shifting whatever, you're much less likely to be approved in a timely fashion. But the smart post doc would post, and everybody would look at what she had done and be envious and offer a big contract, but they would approve and vet. Make sense?

Dr. KAUL. Makes sense. And that's essentially what we're doing already at national meetings. We all publish our data in peer review journals. We're presenting it at meetings where people can pick it apart, come up with the best assay, and in the BCR-ABL example, this was the basis for what then became and FDA-approved kit. There's a lot of work going on. I think we do need to

tidy up our quality standards and the process for pre-review, as you've heard. But I think that this is already happening under—

Senator CASSIDY. There is a technology, and sometimes technology becomes—and I'll ask my two clinicians, if you will. If you're doing PCR, polymerase chain reaction, you can put herpes simplex virus out there, and you can—that's a pretty standard test.

Dr. KAUL. Yes.

Senator CASSIDY. So everybody can make HSV. But some of this, for example, the tumor markers—it really would require not just conceptually how to do it, but actually validating that the person has implemented the concept correctly, and I think this is where everybody has a common ground. How do you, through the crowd source, if you will, also ensure that the implementation is as accurate as done at one of your institutions?

Dr. KAUL. I can take a crack at that. I think we already share a lot of samples amongst labs to make sure that the correct answers are given by all parties, and when we find something that's discrepant, we spend a lot of time trying to figure out why. But I think this can be baked into a little bit more formal process where the answer that's most important to patients is getting the correct answer, and it shouldn't matter if it's in my lab or David's lab or whatever. We all need to drive toward that level of quality for patient care.

Senator CASSIDY. Last, as we know, publication cycles can be prolonged, and abstracts may be published, but abstracts may not, as it turns out, be exactly the way you would publish. Is there a way to speed up the cycle in which the research—going back to online crowd sourcing—granted, you want a peer review, but in a sense, when you put it up there, everybody's going to peer review it. Right? Is there a way to shorten that cycle time? Because I think if we go to precision medicine, we really need a faster and faster cycle time than next year's convocation in the Netherlands.

Dr. KLIMSTRA. Yes, I think we're moving toward real-time data sharing. Another point made by Vice President Biden when he spoke about the Cancer Moonshot was the difficulty in exchanging data among cancer researchers and the need to accelerate that. The data from our sequencing assays is released in publicly available form very quickly after it's generated, allowing novel findings to be shared with cancer researchers around the world, and I think this has enabled the kind of contacts that were described in terms of sharing validation samples and other things to help people move their assays forward very quickly.

Senator CASSIDY. Is the path forward—actually, to ask you all—and I'm going to continue to use it, although, obviously, I'm not a millennial—is the path forward crowd sourcing with FDA or CLIA plugged into that which is taking place so that on a real-time basis, they have some scientists saying, "Yes, this really works," but in the meantime, it's all of you plugging it in, and at the end, they put the FDA seal of approval, with a few caveats for the attorneys, but on the other hand, people can begin to use? Would that be a way forward?

Dr. Allen, you're nodding your head.

And, Mr. Spring, do you feel like that would be a way forward?

Mr. SPRING. I think there are elements of what you've mentioned, as well as what we've heard about New York State, that that can be adopted by FDA. I think the current framework can't exist as it is and get these unmet-need tests out as quickly as possible. What you're suggesting is certainly one option I think we should look at.

Senator CASSIDY. Thank you all—very provocative. Thank you all.

The CHAIRMAN. Thanks, Dr. Cassidy.

As far as the data sharing goes, that's one more reason why we need to pass the 21st Century Cures legislation that we've been working on for 2 years and that the President is interested in. The Vice President is interested in it, and it's part of Speaker Ryan's agenda, and Senator McConnell said it's the most important bill of the year, if we pass it. It includes a requirement that NIH researchers must publicize their data, and the Vice President has made that point.

Dr. Allen, what did you think of that crowd sourcing exchange?

Mr. ALLEN. I think there are some elements of that that have been captured in even some of the things that the FDA is working on in a couple of guidance documents that they put out recently. Everyone is progressing in this direction, and it could be a very worthwhile exercise to discuss what different pathways could be made available, particularly for these different tests that may be developed in different places that are intended to do the same thing. We wouldn't want necessarily every single test to have to start completely from scratch if there's a way for them to collaborate better.

The CHAIRMAN. There are 60,000 existing laboratory-developed tests, none of which are regulated by the FDA, correct?

Mr. ALLEN. Correct.

The CHAIRMAN. What do we do with those? Stop them until they spend \$30 million or \$75 million and get each one approved? What do we do about that?

Mr. ALLEN. One, I think we certainly have to start with those that are presenting the highest risk to patients as the priority ones. And while the discussion most recently was about more advanced technology and large-scale genomic screening, a similar pathway could be constructed for older tests that potentially are reported to do the same thing. Not to say that 60,000 tests are going to be required to have a full FDA PMA in order to be used, but could they show that they are analytically equivalent to something that has already demonstrated clinical validity or an accurate reference material that they could compare back to and make that be a much faster process that labs could—that some labs are already doing, but perhaps not all labs are doing, as a way to validate those tests.

The CHAIRMAN. Let me ask this question while Senator Cassidy is here. Sometimes, if you own an old house and you invite the contractor in, he looks the house over and says, "You know, it would be easier and cheaper and quicker to tear it down and start over than it would be to try to remodel it." So you've got Sloan Kettering going to CLIA, then going to New York, and now the FDA says

“Come to us as well,” and Dr. Klimstra says, “If that happens, we’ll close down our lab.”

If I have lymphoma, and I want to check myself into Sloan Kettering, that’s not a result I really want to happen. I’d like to trust the doctors there to take their experience with whatever test they’ve cooked up, and I wouldn’t know anything about the test, even if you told me, but I would like for them to know about the test, and I would assume they did, and I agree it’s an unusual place, but, still, we don’t want that result.

How much regulation is enough regulation? Do we want to have CLIA plus the FDA plus a State regulation? Or do we want to create a new regulatory agency and phase it in over time so that we meet all of our objectives of patient access, safe, and effective?

Let me add that CMS is already so busy that it has no business making all the decisions it makes today. I do not see how anybody does that job. I’ve told them all that. We have far too many decisions made at CMS that need to be decentralized in this country. FDA is literally overwhelmed. They’ll be asking us to appropriate billions of dollars next year to help them meet the existing responsibilities they have.

In this really exciting area that affects so many people, why not start from scratch and create the ideal regulatory framework and phase it in over time so we meet those three objectives?

Mr. ALLEN. I’m not a lawyer, and I’m not sure I can advocate for tearing down the existing laws that have been in place for many years. Having said that, I completely agree that we should look at efficiencies and processes and limit to the extent possible any duplication. We should start from the core tenet of what type of oversight do we need for these tests so that we can reasonably assure that they’re safe and clinically valid as they go into use.

Personally, I would advocate that the FDA have a critical role in these tests, because they do have the medical personnel there that have an understanding of the underlying disease. For example, both in the Cancer Moonshot and through the work of this committee, there’s been steps that have been taken to direct the FDA to move toward a direction of establishing an FDA Oncology Center of Excellence to try and align the clinical expertise and the communication across that agency around all cancer products, including therapeutics and diagnostics, so compared to some of these other agencies—

The CHAIRMAN. Why wouldn’t that be a new regulatory agency if it’s an independent Center of Excellence?

Mr. ALLEN. Within—separate from the FDA?

The CHAIRMAN. Maybe it is. Maybe it isn’t. Dr. Califf says his biggest problem is he doesn’t have the medical personnel. He has wonderful people, but what he has asked us for is more authority to pay more money to more talented people because he has so many vacancies and they can’t get their work done.

Here we give them 60,000 laboratory-developed tests and say, “OK. Everybody stop while the FDA makes it way through 60,000 laboratory-developed tests,” at a time we’re hearing from Sloan Kettering that it would close their laboratory, and Vanderbilt—that 95 percent of its personalized medicine is conducted by its own lab-

oratory-developed tests. We don't want that result, I don't think, do we?

Mr. ALLEN. We absolutely don't want that result.

The CHAIRMAN. But you've been a leader, actually, in speeding things up with your breakthrough—I'm not picking on you. I'm really trying to take advantage of the work you've done with this committee to help us find ways to mobilize broad public support for getting these tests in the hands of doctors and patients more rapidly at a lower cost.

Mr. ALLEN. And I don't want to speak for everyone here, but I hope we all can continue to work with this committee, who also has taken a leadership role in expediting access, accelerating innovation, and protecting safety around this topic.

The CHAIRMAN. Let me ask any of you—could you give Senator Cassidy and me an update on private discussions that are going on about how to solve this challenge? Is there some consensus developing? Is there an organization that is working on this? Or is everybody just spouting off ideas and waiting for us to come up with some solution?

Dr. Klimstra.

Dr. KLIMSTRA. Of course, there's been a lot of discussion since the release of the draft guidance a couple of years ago among individual institutions, local regulatory groups, and professional organizations. The Association for Molecular Pathology and the College of American Pathologists have been working hard on developing validation guidelines for next-generation sequencing assays, for instance, that would allow prospective labs developing these LDTs to follow a very standardized process and to meet very specific analytic requirements for the test to be validated.

I think that there is an enormous amount of expertise vested in the academic institutions and the commercial laboratories in doing this, and we really need to pull all of that together. I like your idea to develop something novel, whether it's put on top of the FDA or put on top of CLIA or even New York State. But I think we need to start from scratch in a sense and reevaluate this entire new climate using the experience of people who have been in the field for a long time.

The CHAIRMAN. Mr. Spring, any concluding remarks?

Mr. SPRING. Yes. To answer your earlier question, we have, and I've been part of, discussions with the laboratories, academic institutions, and other manufacturers. To answer your earlier question about these 60,000 tests out there, we have to have some sort of grandfathering involved in that. You can't just automatically take them off the market.

I think what we'd be looking at is—Dr. Allen mentioned some sort of—what are the higher risk tests, how do we address those, and then looking forward to the future tests and how we bring these products to market as quickly as possible. I think FDA has come up with some innovative ideas, as an example, relying on analytical bench testing, releasing the product while you gather the clinical evidence, and that depends on the risk of the test. There's some innovation out there and some recent guidance that will help us get there.

To conclude, I won't re-read all seven principles that I spoke to, but I think these principles work for all stakeholders, the patients, the labs, industry, and others that may be involved in this. I think as we continue to look at these principles and use them in our discussions, we will find a path forward. But I do agree that FDA should be the body regulating these LDTs, just not under the current framework. We have to change it.

The CHAIRMAN. That means CMS would be out of the business. Is that right?

Mr. SPRING. No. There has to be a clear line of jurisdiction where CMS would still look at lab operations. Even if I make a test at BD and sell it, they have to ensure that the lab is using that test appropriately.

The CHAIRMAN. You'd still have CMS, New York State, and FDA? Mr. SPRING. Not necessarily New York State.

The CHAIRMAN. You would in New York.

Mr. SPRING. If you look at the Wadsworth Center and the role they play today, under new construct, they can still play a role that's not duplicative. They could assist either CMS or FDA in their roles. But lab operations is different, in my view, than developing a test. Lab operations is implementing the test.

The CHAIRMAN. I see what you're saying.

I see Senator Warren has arrived, and we'll go to her. But Dr. Allen and Dr. Kaul, I'll let you make a comment on that question, although you may have already done that, Dr. Allen.

Dr. KAUL. Thank you again for the opportunity. I think a number of key points just bear reiterating. The labs are not boxing and shipping kits out for others to be running. I think that's a key difference between what Mr. Spring and many of us in the clinical laboratories are doing.

Yes, CLIA addresses lab operations, safety, refrigerators, all those sorts of things that are part of operations. But they're also collecting a great deal of quality data, and this is inspected and reviewed at the time we have an onsite inspection. I think that this mechanism can be expanded. We've heard a variety of proposals that I think about today that have gone forward calling for CLIA modernization, and I think for the laboratory perspective, it fits more nicely into CLIA than into FDA, because we're already collecting a lot of this information already.

The CHAIRMAN. Thanks, Dr. Kaul.
Senator Warren.

STATEMENT OF SENATOR WARREN

Senator WARREN. Thank you very much, Mr. Chairman, and I apologize. We're trying to cover multiple hearings here all at once.

Lab tests are a cornerstone of precision medicine, and there's been a lot of innovation over the last several years. Most labs and most companies are doing amazing work that helps patients get diagnosed earlier and gets the best medications in at the right time.

But, as you've noted, most tests aren't regulated by the FDA, and most tests aren't reviewed by any external party to make sure that their results are accurate. I'm concerned that that means a lot of uncertainty for patients and doctors who are making important decisions based on these test results. So let me start there.

Dr. Allen, if a patient is offered a test to determine whether they are at a higher risk for cancer, can they be sure that the results they get are accurate?

Mr. ALLEN. Unfortunately, currently, not in all cases.

Senator WARREN. The answer is no.

Mr. ALLEN. The answer is no.

Senator WARREN. You can't know whether you're one of the—yes, it was accurate, or, no, it's not. The answer is just no. You can't be sure of that.

Mr. ALLEN. If the test has gone through FDA, I think you can have greater confidence in some of the information that has been provided in terms of evidence behind the test.

Senator WARREN. Do tests that haven't been demonstrated to be clinically valid come with some sort of disclosure so that patients and their doctors know—don't rely on these tests?

Mr. ALLEN. Not that I'm aware of.

Senator WARREN. In other words, all the tests look the same.

Mr. ALLEN. Correct.

Senator WARREN. The good ones and the ones that aren't so good. All right. It's great that our academic medical centers, like the ones in Massachusetts, are on the cutting edge, but not everyone can get to these centers. How do we ensure that you're getting the same results for a test done in Alaska as, say, a test done at Massachusetts General Hospital?

Dr. Allen.

Mr. ALLEN. That in some ways has been the subject of a discussion that we were just ending up—if there are processes that can be put in place rather than having every single test that is being offered have to go through their own individual pathway through the FDA in order to demonstrate validity, or is there a way for the different test manufacturers or the labs performing them to work together to demonstrate that there is some degree of concordance or at least understand the variability that may exist between different tests intended to do the same thing.

Senator WARREN. The best way I can understand this at this point is that we have identified a problem, and that is that we're not getting the same kind of results, they're not reliable, and that that means we have got to hammer out a way to make sure that if you get the test done in Alaska, the odds are at least above 99 percent that you're going to get the same kind of result if you had that test done in Massachusetts.

I appreciate your doing this. I just want to make the point that the best personalized medicine in the world won't work if it's given to patients who are unlikely to benefit from it because the treatment was based on bad lab results. The best personalized therapies won't work if patients are skipped over for treatment based on bad lab results.

Some of my Republican colleagues have suggested that we choose between innovation and verifying whether or not the tests are accurate. But innovation without proven accuracy is not a medical advance. I believe that we can have sensible oversight that will encourage more innovation, innovation that truly saves lives, and I look forward to working with you, Chairman Alexander, and with the committee to try to accomplish that goal.

Thank you all very much.

Thank you, Mr. Chairman. I appreciate you holding this open.

The CHAIRMAN. Thank you, Senator Warren.

Thank you to the witnesses. This has been very helpful. As I mentioned when we began, this is the 45th hearing we've had, and I think almost every single one has been bipartisan, as this one has been. I think every Senator who came learned something today from the four of you, so thank you for your time.

The hearing record will remain open for 10 days. After you leave, if you think of points you wish you'd made or solutions that you think would be helpful to us, we'd like to have them. We'd like to have them. And despite our different points of view, we work together reasonably well here in this committee.

The HELP Committee will meet again on Thursday for a hearing on the regulation of cosmetics, on the 22d.

Thank you for being here today. The committee will stand adjourned.

[Additional material follows.]

ADDITIONAL MATERIAL

RESPONSE BY DAVID S. KLIMSTRA, M.D. TO QUESTIONS OF SENATOR MURRAY,
SENATOR ENZI, SENATOR ISAKSON, AND SENATOR CASEY

SENATOR MURRAY

Question. Your testimony discussed the close working relationship staff in your labs have with the healthcare providers within your institutions, such as an oncologists making treatment decisions for patients. That communication seems to be critical to making sure that doctors understand what tests mean and how they make treatment decisions. If a healthcare provider outside of your system orders that same test, what level of interaction do you have with those providers?

Answer. It is indeed critical that ordering healthcare providers understand the indications for testing and the significance of results. Different tests provide different types of information, such as supporting a specific pathology diagnosis, predicting the clinical course of a disease, suggesting the use of a certain type of treatment, or raising the level of risk a patient may contract a specific condition. The last of these may not suggest that intervention is indicated but rather that other, more specific tests should be conducted. Direct communication with the professionals in the lab performing the test is essential to communicate the subtleties of test interpretation. In our department, the vast majority of molecular diagnostics tests are ordered by providers within our system, on patients under active treatment at our institution. There is close interaction between our molecular pathologists and the treating clinicians, including through tumor boards, conferences, and other meetings. Thus, our treating physicians are well aware of the indications for testing and the interpretation of the results. Unusual cases sent to us from outside institutions come as consultation cases, sent by physicians to one of our pathologists, who will convey the results along with information about their significance.

SENATOR ENZI

Question 1a. In the hearing panelists testified that if the regulatory guidance concerning Laboratory Developed Tests (LDTs) is finalized many labs would be forced to close given a nearly impossible financial burden to meet compliance. Similarly, members of the panel also testified that a vast majority of their personalized medicine practices rely on in-house LDTs.

Please describe what impact lab closures would have on availability of diagnostic tools for physicians, particularly those in highly specialized or rare diseases.

Answer 1a. The majority of LDTs currently in use have been developed in not-for-profit academic centers, purely to support advances in patient care. If FDA pre-market approval were to be required for all LDTs, under the current cost structure, the costs would quickly exceed what academic labs could afford, forcing the labs to stop developing LDTs. The impact would be twofold. Innovative research, bringing new tests quickly to clinical use, would stop in academic centers, delaying patient access to practice-changing test data. Testing would therefore be driven into large commercial laboratories, which would have the resources to maintain this new, considerably more burdensome and costly regulatory compliance. This would sever the interactions between the treating clinicians and their molecular pathologists, which are critical both to the proper use and interpretation of molecular tests and to the ongoing development of future tests tailored to meet the diagnostic needs defined by the clinical care team.

Question 1b. In your view, would there be consolidation among commercial laboratories? If so, what would you anticipate repercussions of that change, specifically related to the availability of new or more specialized diagnostic tests?

Answer 1b. In all likelihood, only the largest commercial labs would have the resources to function in a stringent and costly regulatory environment, forcing smaller operations (whether academic or commercial) out of the test development arena. This could limit the availability of tests for rare diseases or for uncommon alterations in common diseases, which lack the commercial market to justify the development costs involved.

Question 2. What types of evidence or studies do your laboratories conduct and assemble to show both analytical validity and clinical validity for a new LDT?

Answer 2. Details about our test development and validation process can be found in my previously submitted written testimony. Analytic validity (meaning accuracy, reproducibility, sensitivity and specificity of the test) is established via rigorous experiments, following guidelines established by the New York State Department of

Health. Specifically for next-generation sequencing assays, our laboratory directors are also participating in the development of test validation guidelines being proposed by the College of American Pathologists and the Association of Molecular Pathologists. The analytic validation experiments vary depending on the test but generally involve repeated testing of control samples with known alterations, to demonstrate consistent test performance; verification of test results in another laboratory; and verification of test results using a different testing platform or technology. The results of these validation studies, including the raw data, are submitted to NYS as a premarket approval package, and the test is not offered to patients until approval is obtained. Prospective test performance after launch is assessed with quality control at every step of the procedure, by participating in proficiency testing of control samples provided by the College of American Pathologists, and by review of test results in the context of all relevant clinical findings for each patient.

Clinical validity has been established for some tests by the performance of extensive peer-reviewed, published research, with recommendations incorporated into standard treatment guidelines such as those of the NCCN. For less well-established tests, the results are integrated into clinical management along with all other test results and other data. The utility of the results is the subject of ongoing outcomes research, generally conducted at the same academic institutions where the tests are performed. Indeed, these studies ultimately inform the standard treatment recommendations described above, as the data mature.

Question 3. How frequently are human clinical trials utilized to prove clinical validity for an LDT? If utilized, please describe typical format for clinical validity clinical trials.

Answer 3. Clinical trials are the best way to establish clinical validity for a biomarker detected by an LDT and should be performed before a molecular diagnostic biomarker is incorporated into routine use. Clinical trials are increasingly biomarker-driven and are designed in part to test the utility of the biomarker to guide therapy. As such, the size of the trial, outcome measures, and expectations from molecular diagnostic testing are determined during the development of the trial to ensure the clinical validity of the biomarker can be established once the research is conducted. However, it is important to note that several LDTs typically exist for a given biomarker. The analytical performance of individual LDTs can be readily validated against each other, and this occurs routinely in clinical practice. Requiring that every individual LDT (as opposed to the biomarker tested by the LDT) should undergo separate clinical validation in a separate clinical trial is simply unrealistic given the costs and the limited numbers of clinical trial patients available.

Question 4. Would default requirements for clinical trials to prove clinical validity potentially create barriers to developing new LDTs?

Answer 4. In short, yes. It is necessary to develop the new LDTs *first* to perform the trial testing their clinical validity. Without the laboratory test, clinical trial biomarker data cannot be generated. Establishment of clinical validity through clinical trials conducted primarily in academic institutions should be the first step before the novel test is offered generally to patients outside of the clinical trial setting.

Question 5. Please describe the current approval standard your laboratory relies on for determining whether to widely offer a new LDT to patients. Does the standard originate from a government body or from a peer-review authority, such as the College of American Pathologists and what is the scope of that standard?

Answer 5. See answer #2, above.

Question 6. What portion of your laboratory's test menu are LDTs as compared to FDA approved or cleared IVD test kits?

Answer 6. Over 99 percent of molecular diagnostics tests performed in Anatomic Pathology at MSKCC are LDTs. The Department of Laboratory Medicine at MSKCC uses mostly FDA-approved assays. The proportion of LDTs versus FDA-approved tests offered in other labs varies widely depending on the size of the lab, whether it is academic or commercial, and whether the focus is on innovative molecular diagnostics or more routine testing. The high proportion of LDTs used by the Molecular Diagnostics Service of the MSKCC Department of Pathology reflects its focus on being at the forefront of translating discoveries into cancer care by testing for critical new biomarkers, at the request of our oncologists, well before corresponding FDA-approved assays are available or in the continued absence of such assays.

Question 7. What are the most common modifications made to an LDRT or FDA approved or cleared test kits?

Answer 7. In Anatomic Pathology at MSKCC, we do not modify FDA-approved tests when they are utilized. In Laboratory Medicine, and in diagnostic labs at other institutions, FDA-approved assays are modified usually to allow their use on a specimen type other than that approved on the FDA application. For example, testing for human papilloma virus on anal tissue, looking for circulating tumor cells in CSF, and testing amylase levels on pancreatic cyst fluid all involve using an FDA-approved assay on a biospecimen not included in the approval application. These tests then become LDTs based on these modifications.

Question 8. How many “new” LDTs are a result of modification within your laboratory?

Answer 8. None in Anatomic Pathology; Laboratory Medicine at MSKCC has 20–30 LDTs based on modifications of FDA-approved assays.

Question 9. How many modifications result in a significant clinical impact for a patient receiving the test?

Answer 9. All modifications have a clinical impact, because the tests are modified to provide information requested by treating clinicians to help care for their patients.

Question 10. How many modifications change or expand the intended use of an LDT?

Answer 10. All modifications expand the use of the test. In New York State, any modifications to improve or expand an LDT trigger a round of analytical re-validation experiments to confirm that the changes have not altered the performance characteristics of the LDT, and a summary of these re-validation experiments must be submitted to the NYS DOH for approval prior to clinical use of the modified LDT. As FDA-approved tests are generally only intended to be used on a single or small subset of specimen types, the modifications that convert such assays to LDTs expand the range of specimen types that can be tested to help establish a diagnosis or guide treatment.

SENATOR ISAKSON

Question. In your testimony, you explained that additional regulation of our LDTs would restrict availability of advanced diagnostic tests to patient and add significant cost. As you know, the Emory University Genetics Lab in Atlanta is at the forefront of diagnostic genetic testing. Many academic centers operate clinical laboratories to better serve their patients, but they are not large organizations and don't have the budget to handle mountains of regulatory red tape. I worry if we add too much regulatory burden, that we will create a backlog of applications at FDA that cannot be kept up with.

What do you see as the unintended consequences on Emory and other academic medical centers if FDA takes a larger role in regulating LDTs?

Answer. The answer to this question is detailed in my prior written testimony. In short, burdensome and costly regulation of LDTs will drive molecular testing out of the academic environment at leading centers such as Emory and our own, among many others, reducing innovation and slowing the delivery of novel diagnostic testing to patients, especially for rare diseases or rare alterations in common diseases. The cost of offering molecular testing to patients would likely rise in the end as well.

SENATOR CASEY

Question 1a. Under the current system, it's possible for both an FDA-approved diagnostic and one or more LDTs to be available to patients and providers at the same time. I have several questions about what happens in these situations. How does a health care provider or a patient know if the test being ordered is FDA-approved or if it's an LDT?

Answer 1a. Since there is no current requirement for FDA approval for LDTs, it may not be necessary for laboratories to indicate that a given test is not FDA-approved. In our lab, however, we include a standard statement on all reports indicating that the test is not FDA-approved, but that it has been performed in a CLIA-compliant laboratory and has been approved by the New York State Department of Health.

Question 1b. Does the existence of an FDA-approved test raise questions about the validity or accuracy of other LDTs testing the same thing?

Answer 1b. It is not necessarily true that an FDA-approved test is more accurate than an LDT testing the same thing; in fact, a number of FDA-approved tests are

clearly inferior to LDTs. Examples include KRAS mutation testing, which only detects some of the currently recommended mutations, and *BRAF* mutation testing which is only approved for limited disease types. Given the long delay in developing FDA-approved assays, some have become obsolete by the time they are available, given the rapid pace of technological advancement now occurring in molecular diagnostics. Also, some FDA-approved tests are for a single analyte, or only to be used for limited indications (such as specific disease types). Contemporary multi-analyte tests allow much more comprehensive analysis of many genes at once, maximizing the use of patient biopsy tissue to obtain comprehensive molecular information.

Question 1c. If you were a patient and were given the choice of either an FDA-approved test or a laboratory-developed test, with no difference in cost, which would you choose?

Answer 1c. Depending upon the specific test result needed, current LDTs are superior to FDA-approved tests as discussed above. Only careful consideration of the testing options and indications would allow an informed choice.

RESPONSE BY BRAD SPRING TO QUESTIONS OF SENATOR CASEY

Under the current system, it's possible for both an FDA-approved diagnostic and one or more LDTs to be available to patients and providers at the same time. I have several questions about what happens in these situations.

Response. Yes, it is true in the current system both FDA approved IVD's (manufacturer) and LDTs (labs) can be and are available at the same time. LDTs are currently regulated by CLIA and not by FDA. CLIA reviews the testing process that is used to perform the LDT on a biennial basis (not prior to the test being offered), but the LDT is never reviewed to determine whether it is clinically valid. The same test produced by an IVD must be reviewed and approved by FDA to establish analytical and clinical validity before it can be marketed.

Question 1a. How does a health care provider or a patient know if the test being ordered is FDA-approved or if it's an LDT?

Answer 1a. They don't. Patients or Healthcare Providers are not provided the FDA approval status of a test, unless they ask. A majority of patients either assume all tests are FDA approved or they don't even think to ask if the tests are an FDA approved or an LDT.

Question 1b. Does the existence of an FDA-approved test raise questions about the validity or accuracy of other LDTs testing the same thing?

Answer 1b. There is no transparency as to how LDTs are analytically or clinically validated whereas information on the validations conducted by diagnostic manufacturers is publicly available on the FDA website. The lack of transparency for LDTs raises questions on the level and rigor of testing conducted by the laboratory to demonstrate clinical and analytical validity.

Question 1c. If you were a patient and were given the choice of either an FDA-approved test or a laboratory-developed test, with no difference in cost, which would you choose?

Answer 1c. I would choose the FDA-approved test because it has been through rigorous testing. Also, I could look up the performance of such tests and if there are any adverse events associated with the test on the FDA's website.

Question 2. The fact that some test developers have gone through the FDA approval or clearance process for their tests seems to indicate that they see a benefit to doing so. What is that benefit?

Answer 2. A test that has gone through the FDA approval process provides the public with more confidence that the tests accurately identifies or predicts the target disease or condition.

RESPONSE BY JEFF ALLEN, PH.D. TO QUESTIONS OF SENATOR ENZI AND SENATOR CASEY

SENATOR ENZI

Question 1. In the hearing panelists testified that if the regulatory guidance concerning Laboratory Developed Tests (LDTs) is finalized many labs would be forced to close given a nearly impossible financial burden to meet compliance. Similarly, members of the panel also testified that a vast majority of their personalized medicine practices rely on in-house LDTs.

Please describe what impact lab closures would have on availability of diagnostic tools for physicians, particularly those in highly specialized or rare diseases.

In your view, would there be consolidation among commercial laboratories? If so, what would you anticipate repercussions of that change, specifically related to the availability of new or more specialized diagnostic tests?

Answer 1. The primary goal for any new regulatory approaches for LDTs should be to ensure that patient safety is protected by understanding the characteristics of a test before it is widely administered. While access to tests is an important component of providing optimal care in many cases, access to an inaccurate test may be as harmful as providing a patient access to a drug that doesn't work. If laboratories that are unable to be compliant and demonstrate the clinical validity of the tests they are performing it would be in the best interest of the patients that could be exposed to misleading results for those labs not to be utilized.

In oncology, labs that offer tests that have been approved by FDA could be relied upon by shipping tumor samples or other specimens to those facilities for analysis. This occurs frequently today. This may result in fewer hospitals or facilities having in-house departments that are performing certain tests, but patient safety can be protected by relying on tests that have been shown to work and access can be maintained through mechanisms that can support remote testing. If a clear regulatory approach is developed, there may be a consolidation of labs toward those that are able to maintain compliance, but this could help support a guaranteed high-quality industry which will lead to higher quality healthcare. And this will bolster innovation overall by ensuring patients, their physicians, and test developers are making decisions based on good information.

Question 2. What types of evidence or studies do your laboratories conduct and assemble to show both analytical validity and clinical validity for a new LDT?

Answer 2. Friends of Cancer Research is not a clinical laboratory, and I personally have never worked in a clinical laboratory performing or evaluating LDTs, so it would be difficult to answer several of these questions that quantify aspects of clinical lab processes with any direct relevant experience.

Question 3. How frequently are human clinical trials utilized to prove clinical validity for an LDT? If utilized, please describe typical format for clinical validity clinical trials.

Answer 3. Although I am not certain how often clinical trials are used to establish clinical validity for LDTs, laboratories have stated that a host of other forms of evidence have at times been used to establish clinical validity for LDTs. Owing to the expense of clinical trials and the less expensive nature of some of the other methods cited, it may be fair to assume that, in some circumstances, clinical trials are not the only source of evidence that can be used infrequently to establish clinical validity of LDTs.

Question 4. Would default requirements for clinical trials to prove clinical validity potentially create barriers to developing new LDTs?

Answer 4. Clinical trials could be one way to develop evidence to demonstrate clinical validity, but there may be situations for which a clinical trial may not be necessary and evidence from other types of analysis could be sufficient. For example, if a test exists that has been shown to be clinically valid (and approved by FDA) a subsequent diagnostic test for the same intended use may not need to repeat clinical trials if it shown to meet a determined level of equivalency. An abbreviated approach could be developed where a follow-on diagnostic test demonstrates a high level of analytical concordance (or improvement compared to validated reference material) to an approved diagnostic device. If analytical concordance is high, the clinical outcomes of the drug/diagnostic would be expected to be highly similar to the earlier approved device that was FDA approved to guide the use of the drug.

Question 5. Please describe the current approval standard your laboratory relies on for determining whether to widely offer a new LDT to patients. Does the standard originate from a government body or from a peer-review authority, such as the College of American Pathologists and what is the scope of that standard?

Answer 5. Many of the current oversight mechanisms, such as CLIA or peer-reviewed certifications, focus on laboratory processes rather than the clinical validity of the test itself. The College of American Pathologists (CAP) does conduct proficiency testing, wherein it provides individual laboratories with unknown specimens for testing and participating labs analyze the specimens and return the results to CAP for evaluation. However, this proficiency testing is not done prior to patients receiving the test. An important component of any new regulatory approach is the requirement for pre-market demonstration of analytical and clinical validity. If tests

are being evaluated for the first time based upon their post-market use and outside of a research setting, it places patient safety at risk to inaccurate tests that could have been previously identified through sufficient pre-market review. This is one reason we support FDA premarket review for LDTs, as they are the only entity that assesses analytical and clinical validity before patients are exposed to tests.

Question 6. What portion of your laboratory's test menu are LDTs as compared to FDA approved or cleared IVD test kits?

Answer 6. While I can't comment on a specific laboratory, we recently published a study that explored the broad use of LDTs versus FDA-approved tests with the same intended use. For this research we audited hundreds of medical records from across the country to explore the use trends of molecular tests that assess two critical alterations in lung cancer, *ALK* and *EGFR*. The results of this audit showed that 49 percent of patients tested for *ALK* alterations and 87 percent for *EGFR* mutations were evaluated with an LDT, despite the availability an FDA approved assay.¹ Given the large number of tests currently in use, there exists the potential for wide variability in test performance and claims. Any test that produces a result intended to be used to guide medical decisionmaking should be evaluated in its clinical context for risks that may be incurred. For patients, consumers, and healthcare providers it's the result of the test that's important, not where it's manufactured.

7. What are the most common modifications made to an LDRT or FDA approved or cleared test kits?

8. How many "new" LDTs are a result of modification within your laboratory?

9. How many modifications result in a significant clinical impact for a patient receiving the test?

10. How many modifications change or expand the intended use of an LDT?

[Responses were not available for questions 7-10 above.]

SENATOR CASEY

Question 1a. Under the current system, it's possible for both an FDA-approved diagnostic and one or more LDTs to be available to patients and providers at the same time. I have several questions about what happens in these situations.

How does a health care provider or a patient know if the test being ordered is FDA-approved or if it's an LDT?

Answer 1a. In many cases, it is unlikely that the healthcare provider who orders a test for their patient is aware of whether the test performed is FDA-approved or an LDT, in instances where an FDA-approved and LDT intended for the same use exists. In our research, we found that 21 percent of oncologists who had ordered tests used in determining treatment for lung cancer reported that they did not know what type of test was used when asked to identify whether the test was a single-gene assay or multi-gene panel. Moreover, when respondents were able to identify the brand name of the test or the name of the lab offering it, they often incorrectly reported labeled the tests they used as lab-developed or FDA-approved. If the healthcare provider isn't aware of the type of test being used it is of even greater likelihood that the patient doesn't know.

Question 1b. Does the existence of an FDA-approved test raise questions about the validity or accuracy of other LDTs testing the same thing?

Answer 1b. The existence of an FDA-approved test does raise questions about potential variability between LDTs and the approved version. The extent of that variability is usually unknown because the FDA-approved test and existing LDTs are typically not directly compared. However, they are held to different standards in terms of their performance. FDA-approved tests are subject to pre-market review of data demonstrating their analytical and clinical validity. LDTs are not. Yet, the only difference between the FDA approved tests and most LDTs is where they are manufactured. This presents the potential for wide variability in test performance and claims, and the reality that some patients making major medical decisions based on inaccurate test results as they may receive different information depending on if their hospital or doctor's office is using an FDA approved test, or not.

Question 1c. If you were a patient and were given the choice of either an FDA-approved test or a laboratory-developed test, with no difference in cost, which would you choose?

¹ Audibert, CM, et al. *Use of FDA-Approved and Laboratory-Developed Tests in Advanced Non-Small Cell Lung Cancer: Results of a Retrospective Market Analysis*. Personalized Medicine in Oncology. Vol. 5 No. 7. 278-84. September 2016.

Answer 1c. If given the choice between an FDA-approved version of a test and an LDT alternative, I would opt for the test that had been reviewed and approved by the FDA. FDA pre-market review provides a greater assurance of the analytical and clinical validity of the test. Particularly for tests that measure relatively new markers, the clinical relevance and potential risks of an LDT may not be as well characterized as tests reviewed by the FDA.

RESPONSE BY KAREN L. KAUL, M.D., PH.D. TO QUESTIONS OF SENATOR MURRAY,
SENATOR ENZI, SENATOR ISAKSON, AND SENATOR CASEY

SENATOR MURRAY

Question 1. Your testimony discussed the close working relationship staff in your labs have with the healthcare providers within your institutions, such as an oncologist making treatment decisions for patients. That communication seems to be critical to making sure that doctors understand what tests mean and how they make treatment decisions. If a healthcare provider outside of your system orders that same test, what level of interaction do you have with those providers?

Answer 1. Pathologists provide consultative services for health-care providers who have privileges at our hospital, regardless of whether they are employed by the system, or are independent physicians associated with the hospital or system. All patients treated within our system are given the same level of care, which includes (for cancer patients) review of pathology, molecular findings, radiology and clinical details at multidisciplinary treatment conferences. Each hospital or system conducts its own series of such treatment planning conferences, which are based on published consensus treatment guidelines such as those from the NCCN; this provides continuity and consistency between treatment and care at different institutions. We generally would not provide consultative services for physicians who are not affiliated with our hospital or who do not use our laboratory services. Reference laboratories that test samples from physicians in a variety of settings may rarely provide limited consultation, but not at the level of hospital lab based pathologist who attends the multidisciplinary conferences, and is deeply involved in diagnosis and care.

Question 2. Our country's public health labs play a key role in helping our communities deal with disease outbreaks, prepare for emerging infections like Zika, and screen our newborns. How do lab developed tests help meet these challenges? What do you think is the best way to balance the necessary rapid evolution of tests with assurances that the tests work as intended?

Answer 2. Labs have historically developed many tests and procedures to provide diagnosis of emerging infections. Our lab successfully utilized an in-house influenza assay during the 2009 H1N1 (swine pandemic), and again when certain commercially available assays were found to miss some cases of the virus as it underwent its usual seasonal DNA evolution. More recently a lab-developed assay for Zika virus was launched to provide much needed diagnosis in the Houston area. In many locations, patients are waiting weeks for test results, an unacceptable situation, especially for pregnant patients. Hospital laboratories are on the front lines of these epidemics and emerging infections, and need to be able to provide correct and timely diagnoses for patients, and also to limit the spread of infections. Better coordination with the public health system labs would be beneficial. Labs need access to tests early in an outbreak, either via access to the CDC test assays (because the public health labs capacity to test samples is rapidly overrun) or by a mechanism to utilize acceptable in-house-developed tests that meet quality and performance standards. The FDA emergency use approval program is too slow to be effective in making test reagents available in outbreak situations.

SENATOR ENZI

Question 1. In the hearing panelists testified that if the regulatory guidance concerning Laboratory Developed Tests (LDTs) is finalized many labs would be forced to close given a nearly impossible financial burden to meet compliance. Similarly, members of the panel also testified that a vast majority of their personalized medicine practices rely on in-house LDTs.

Please describe what impact lab closures would have on availability of diagnostic tools for physicians, particularly those in highly specialized or rare diseases.

In your view, would there be consolidation among commercial laboratories? If so, what would you anticipate repercussions of that change, specifically related to the availability of new or more specialized diagnostic tests?

Answer 1. Labs develop test procedures to provide needed services to clinicians and patients, to maintain a level of care in keeping with consensus guidelines and the evolution of medicine. Hundreds of LDTs are performed across all divisions of the lab, and range from validating the use of a sample type or collection media that was not part of the FDA approval, to different diagnostic approaches that provide needed diagnostic information that is not otherwise available, or is more complete or faster than traditional approaches. The vast majority of lab testing needed to support personalized medicine falls into this LDT category.

If labs were not able to offer such testing, there would be an enormous impact on patient care. In some cases, there would be simply no way to attain a diagnosis. In other cases, relying on older methods would be too slow, too insensitive, or would simply not provide the needed information for appropriate care. In general, only the largest commercial labs would be able to afford to submit LDTs to the FDA (and unlikely all LDTs: labs would be driven by commercial concerns rather than patient's needs), limiting patient access and slowing results, and preventing the local consultation that is so critical to patient care. Limiting provision of these tests to only reference labs would also impede education of pathologists as well as oncologists and other physicians, not to mention removing competition to lower charges. This would also create a significant barrier to the innovation arising from academic labs that has led to advances in patient care.

Question 2. What types of evidence or studies do your laboratories conduct and assemble to show both analytical validity and clinical validity for a new LDT?

Answer 2. Labs focus on analytic validity, and do examine clinical validity insofar as to prove correct identification of the clinical condition. Clinical utility is generally established in studies reported in the literature, with labs moving to establish the needed testing in-house as an LDT when it is not otherwise available. Extensive details for analytic and clinical validation is outlined by CLIA procedures, and labs are required to demonstrate accuracy, reproducibility, sensitivity and specificity, reportable range, reference intervals and interfering substances, and define calibration and control materials, as well as participate in ongoing proficiency testing programs to demonstrate quality.

Question 3. How frequently are human clinical trials utilized to prove clinical validity for an LDT? If utilized, please describe typical format for clinical validity clinical trials.

Answer 3. It is unusual for a lab to do a traditional clinical trial independently, as this is generally done to establish the need for the analyte. As part of a CLIA validation the lab will always examine a set of samples already with a diagnosis to demonstrate clinical validity of the test. There is a great need for more samples to aid in test validation, and high quality reference materials would be of great value in allowing to objectively assess the analytic and clinical validity and performance of their LDTs.

Question 4. Would default requirements for clinical trials to prove clinical validity potentially create barriers to developing new LDTs?

Answer 4. Clinical validity can be demonstrated with a set of well-characterized blinded samples that labs would be able to access (purchase) for this purpose. Clinical trials are needed to demonstrate clinical utility—i.e., to establish the value of a new test to improve care. In many cases, labs are developing assays for assessment of gene mutations, markers, or analytes that are already known to be associated with a clinical condition, so a clinical trial is not needed.

Question 5. Please describe the current approval standard your laboratory relies on for determining whether to widely offer a new LDT to patients. Does the standard originate from a government body or from a peer-review authority, such as the College of American Pathologists and what is the scope of that standard?

Answer 5. Currently we watch medical literature, professional meetings, engage in discussion with colleagues to assess the need for a new LDT. When a new test is noted to offer an advantage, labs will develop an LDT if a high quality FDA approved assay is not available (note that the LDTs are most often developed years in advance of the FDA approved kit, to fill a clinical need). Often LDTs are developed to provide care consistent with national treatment guidelines. There is no formal national approval body. Many academic centers and laboratory departments have internal committees to review data and approve the assay (similar to institutional review boards for approving research studies). CAP does define in detail what data labs need to collect to validate a lab-developed test, and this data is reviewed by inspection teams at the time of onsite inspections. We carefully define perform-

ance requirements, collect data, do a statistical evaluation, and review with our lab and clinical colleagues prior to launching an LDT.

Question 6. What portion of your laboratory's test menu are LDTs as compared to FDA approved or cleared IVD test kits?

Answer 6. The proportion of LDTs on a lab's test menu varies widely: hospital labs offer a mix, with smaller community hospital labs offering primarily FDA approved testing and sending the more esoteric testing, such as that needed for personalized medicine, to an external lab. However, all but the smallest labs offer LDTs, many of which have been in use for decades, with extensive data to demonstrate their quality collected under CLIA. I would estimate that we run hundreds of LDTs.

Question 7. What are the most common modifications made to an LDRT or FDA approved or cleared test kits?

Answer 7. Modifications may be made to an FDA-approved test to accommodate specific sample types or tumors that must be tested but were not included in the original FDA approval. Similarly, use of new collection media, or other extensions of the clinical use of an FDA-approved test are frequently needed, and are common reasons that cause a lab to collect additional validation data and essentially treat the FDA-approved test as an LDT.

Question 8. How many "new" LDTs are a result of modification within your laboratory?

Answer 8. It is difficult to accurately estimate how many FDA-approved tests are modified. Some test kits in chemistry and hematology are likely to never be modified. However, with the speed with which DNA-based testing needed for personalized medicine is evolving and improving, most of the FDA-approved tests are behind the treatment standards and need modification, or are simply not adequate.

Question 9. How many modifications result in a significant clinical impact for a patient receiving the test?

Answer 9. Labs would not modify an FDA-approved test unless there was a significant clinical need, such as a sample type or collection media that was not covered by the FDA approval. However, this happens frequently, so labs are often faced with the need to modify or extend the intended use of an FDA approved assay. These actions would improve or broaden the impact of the test for patient care.

Question 10. How many modifications change or expand the intended use of an LDT?

Answer 10. Modifications to an FDA approved test are generally done to expand the intended use of the test to include needed new sample types or tumor types, and would require the lab to collect extensive additional data to demonstrate the performance of the assay for these purposes. This essentially converts the FDA test to an LDT, and is regulated by guidelines stipulated by CLIA. The same validation process and data collection would be done to extend the use of an assay that was originally classified as an LDT.

SENATOR ISAKSON

Question. Knowing your background in infectious diseases and emerging threats, how do we ensure that innovation is not stifled at academic labs like Emory and at CDC who are both developing rapid responses to emergency situations like Zika and Ebola?

Answer. Labs have historically developed many tests and procedures to provide diagnosis of emerging infections. Our lab successfully utilized an in house influenza assay during the 2009 H1N1 (swine pandemic), and again when certain commercially available assays were found to miss some cases of the virus as it underwent its usual seasonal DNA evolution. More recently a lab-developed assay for Zika virus was launched to provide much needed diagnosis in the Houston area. In many locations, patients are waiting weeks for test results, an unacceptable situation, especially for pregnant patients. Hospital laboratories are on the front lines of these epidemics and emerging infections, and need to be able to provide correct and timely diagnoses for patients, and also to limit the spread of infections. Better coordination with the public health system labs would be beneficial. Labs need access to tests early in an outbreak, either via access to the CDC test assays (because the public health labs capacity to test samples is rapidly overrun) or by a mechanism to utilize acceptable in-house-developed tests that meet quality and performance standards; The FDA emergency use approval program is too slow to be effective in making test reagents available in outbreak situations.

SENATOR CASEY

Question 1a. Under the current system, it's possible for both an FDA-approved diagnostic and one or more LDTs to be available to patients and providers at the same time. I have several questions about what happens in these situations. How does a health care provider or a patient know if the test being ordered is FDA-approved or if it's an LDT?

Answer 1a. Truly, if the goal is the best patient care possible, it would not matter if an FDA-approved test or lab-developed test is used. They are both maintained in the lab using the same standards for quality, which includes ongoing proficiency testing and review of data by external lab inspectors, regardless of which test is used. The initial approval process may differ, but it would be helpful for performance standards to be defined for all tests to meet prior to being placed into clinical service.

Question 1b. Does the existence of an FDA-approved test raise questions about the validity or accuracy of other LDTs testing the same thing?

Answer 1b. Currently, there are many examples of FDA-approved tests that do not satisfy needs of physicians and patients, and are not compliant with treatment guidelines. Many of the FDA-approved gene mutation tests in cancer are approved for one tumor but not another that needs that particular gene tested. Many FDA-approved tests don't cover the needed spectrum of gene mutations to be compliant with current consensus treatment guidelines.

Question 1c. If you were a patient and were given the choice of either an FDA-approved test or a laboratory-developed test, with no difference in cost, which would you choose?

Answer 1c. I have been a patient, and so have my family members. If I knew that both test types satisfied identical quality standards, and cost the same, I would not have a preference between an FDA approved test and an LDT. I would want the most complete and accurate test possible, and the reality is that in many cases, this will be an LDT. And in nearly every instance, the LDT will be the less costly alternative. In the end, quality, safety, and getting the information needed for the patient is most important.

[Whereupon, at 11:49 a.m., the hearing was adjourned.]

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