Senate Committee on Health, Education, Labor and Pensions Hearing on
"Laboratory Testing in the Era of Precision Medicine"

Testimony of

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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 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 US.

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 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 in 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 several-fold 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 '60s, and the genes affected by the translocation were identified in the '80s. 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, studu 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 towards 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 on site 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. 20 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 (98). 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 appropriated. 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 on site 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!

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