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

Testimony of

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September 20, 2016

My name is David Klimstra, MD, 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 100s 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 3rd, 2014. At MSKCC, our LDTs allow the rapid translation of impactful research findings to the clinic ("from bench to beside"), 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 database. 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 five 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/clep/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 text 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 preformed 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 decision-making). 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.