Statement from the Infectious Diseases Society of America (IDSA)
Senate Health, Education, Labor and Pensions Committee

"Laboratory Testing in the Era of Precision Medicine"
Tuesday, September 20, 2016

The Infectious Diseases Society of America (IDSA) thanks the Senate Health, Education, Labor and Pensions (HELP) Committee for holding today's hearing on laboratory developed tests (LDTs) and appreciates this opportunity to share IDSA's perspective about the important role of infectious disease (ID) LDTs in clinical care and public health, and the potential impact the proposed new regulations may have on innovation and patient access to testing. This is a complex set of issues, and we appreciate the Committee convening experts to review these issues in a thoughtful manner and consider appropriate paths forward.

Over the past several years, IDSA has stressed the importance of innovative diagnostic devices that support the care of patients suffering from infectious diseases, most notably in our 2015 report, Better Tests, Better Care: The Promise of Next Generation Diagnostics. ID physicians rely upon diagnostics, both LDTs and commercial tests, to identify the pathogen infecting a patient and its antimicrobial susceptibility. Diagnostics help guide appropriate treatment, increasing the likelihood of a positive patient outcome and decreasing the overuse or misuse of antibiotics that drives the development of resistance. Notably, high quality ID diagnostics have a unique ability to protect the broader public health and serve as a critical tool for triggering and implementing protocols to contain outbreaks and prevent the transmission of infectious agents. With new infectious diseases threats constantly emerging and evolving, it is important to maintain and strengthen patient access to high quality testing (both commercial tests and LDTs), and to promote innovation in both of these areas.

LDTs are often developed to test for pathogens for which there are no commercial tests on the market. LDTs often represent the most rapid testing option available, especially if the only alternative is sending specimens to an external reference laboratory for testing. In the area of infectious diseases, delays in testing of even a few hours can have devastating impacts on patients and public health. LDTs have been used to diagnose and manage a variety of infectious diseases since the mid-1990s, and ID physicians have acquired a great deal of experience with these tests. They are well designed and validated for reliable use in patient care. In many instances, they have become the diagnostic standard of care. IDSA recognizes that there are valid concerns about the risks associated with LDTs, particularly in areas such as oncology or genetic testing. However these risks are not equal across all areas of medicine, and there is little evidence that ID LDTs have provided unreliable results that lead to harmful patient care decisions. IDSA believes the risks raised by the use of ID LDTs are dwarfed by their advances and benefits to patient care.

I would like to provide the committee with four examples of how LDTs are currently used in patient care: 1) management of patients who have received organ transplants and are therefore at risk of developing opportunistic infections due to the action of immunosuppressive drugs needed to reduce the risk of rejection; 2) screening for the sexually transmitted infection gonorrhea,

which is growing increasingly difficult to treat with antibiotics due to antimicrobial resistance; 3) testing of newborns for a rare but deadly infectious disease caused by herpes simplex virus (HSV); and 4) testing for emerging infectious agents causing outbreaks, such as Zika virus, Ebola virus, pandemic influenza and Enterovirus D68.

- **Transplant patients:** Viruses such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), BK virus and others are commonly encountered in patients receiving solid organ and bone marrow transplants. Historically, physicians have relied upon viral cultures of blood todiagnose CMV infections; unfortunately, using this method, more than 50% of cases were missed in the past, leading to serious infections involving the brain, colon, esophagus, liver and eye. BK virus and Epstein Barr virus cannot be cultured in the clinical laboratory, so rapid reliable method to detect these viruses in blood have previously been unavailable. More than 20 years of research has clearly demonstrated that molecular LDTs have become the standard of care for the diagnosis and monitoring of these infections. These tests are rapid, highly sensitive, and able to quantitate the amount of virus in the blood (known as viral load). For many years, US transplant centers have been using these LDTs to significantly improve patient care evidenced by well documented data and peer reviewed literature demonstrating their clinical utility. These LDTs have greatly improved our ability to diagnose infections and monitor response to treatment, leading to far better outcomes for transplant patients. Without LDTs, these advances would be impossible. At this time there is no Food and Drug Administration (FDA) approved or cleared BK viral load test, and there are only two CMV tests, which were only approved within the last two years.

- **Gonorrhea screening:** *Neisseria gonorrhoeae,* the pathogen that causes the sexually transmitted infection gonorrhea, is one of the most frequently reported communicable diseases in the U.S., and has become increasingly difficult to treat due to the development and spread of antimicrobial resistant strains. Rapid identification and treatment will improve patient outcomes and decrease the spread of infection to others. The 2015 Centers for Disease Control and Prevention (CDC) sexually transmitted disease (STD) guidelines state that rectal and pharyngeal screening for gonorrhea should be performed by nucleic acid amplification testing (NAAT). Urogenital specimens are the only sources cleared for use with the currently available FDA-cleared NAAT diagnostics, forcing clinical laboratories to modify these tests for analysis of rectal or throat specimens. The FDA's draft LDT guidance stipulates thata commercial test used on a specimen other than for what it was originally approved would be considered an LDT subject to oversight. The requirement to submit a 510(k) to the FDA for this purpose would likely be cost prohibitive for most academic clinical laboratories, thus reducing access to rapid results for these important infections.

- **Newborns:** Herpes simplex virus (HSV) infection in newborns is a life threatening disease, associated with high morbidity and mortality. Rapid diagnosis and treatment is critical in halting disease progression. Many clinical laboratories have developed and comprehensively validated LDTs to test cerebrospinal fluid (CSF) and blood of these newborns for swift and locally performed testing. Such tests have been found to be just as accurate as brain biopsies and far less invasive. While a rare infection, the annual

number of tests performed in the US exceeds the FDA draft LDT guidance's 4000 tests nationwide threshold for the rare disease testing exemption. Two FDA cleared commercial tests for HSV CSF analysis became available in the last two years, but each testing method requires purchase of an instrument specifically designed for this test. Hospital laboratories are unlikely to commit limited resources to purchase the instrument, due to the infrequent need to test for the disease. Moreover, one of the available FDA cleared tests is a highly multiplexed panel test and clinicians may not need to test for all of the pathogens in the panel, as many of the pathogens included in the panel are not relevant for newborns. There are currently no FDA cleared assays to test blood, so again the use of this specimen would require submitting a 510(k) to FDA, which many academic clinical laboratories lack the resources to do. As a result, academic laboratories would be forced to send the samples for testing to external laboratories,prolonging the turnaround time for results and potentially delaying the treatment of this serious infection.

- **Public Health Responses:** In addition to individual patient care, LDTs remain invaluable for diagnosing emerging pathogens during outbreaks, such as Zika virus, Ebola virus, pandemic influenza and Enterovirus D68 infections. During outbreaks, it is critical that testing be made available as quickly as possible to identify infected persons for treatment, contain the spread of infection, and minimize panic among the public. LDTs can often be developed and deployed more rapidly than commercial tests. LDTs developed by the CDC or other public health laboratories have played vital roles in providing testing for Zika and Ebola virus, as well as other emerging pathogens during outbreaks. During the 2009 H1N1 influenza virus outbreak, many local hospitals relied on LDTs to diagnose and guide treatment of patients.

IDSA appreciates the federal government's responsibility to ensure that all diagnostic tests used to evaluate patients are safe and reliable. We believe that the government can improve the regulation of LDTs in a manner that does not impede patient access to high quality testing or innovation. We are happy to provide some recommendations for the Committee to consider, as well as some points of caution. We look forward to continuing to work with the Committee, the FDA, and other government and non-government stakeholders to assess the complex issues regarding LDT regulation and help craft appropriate policies in the best interest of patients. Earlier this year, IDSA also joined with the American Society for Microbiology and the Pan American Society for Clinical Virology to publish this position paper on LDTs, which we hope will be of interest to the Committee.

Modernizing CLIA

As the Committee may know, last year the Association of Molecular Pathologists (AMP) released a proposal to enhance LDT regulation by modernizing CLIA oversight of labs to include clinical validity of LDTs in addition to its current regulation of analytical validity. As academic clinical laboratories are already familiar with CLIA, this approach will likely be far less disruptive to patient access to testing than subjecting all LDTs to FDA regulation. The AMP proposal includes a risk classification that IDSA believes appropriately categorizes ID tests. It also expands the types of evidence accepted to demonstrate clinical validity, including the use of

peer reviewed data and clinical guidelines, which reduces the financial and administrative burdens for individual laboratories. The proposal appropriately addresses test modifications to ensure that minor changes are only subject to analytical validity during regular inspections, while major changes are reviewed before use in patient care. Finally, the proposal provides regulatory exemptions to ensure that testing for public health emergencies is unimpeded. IDSA believes this proposal enables appropriate regulatory oversight of LDTs while also minimizing the disruption of patient access to novel ID testing. While the AMP proposal has some outstanding issues (including the need to refine the public health exemption, clarify the quantity of data needed to establish clinical validity, and the elimination of uncertainty in the deadline review process), IDSA is confident that CLIA modernization represents the more feasible and appropriate mechanism for enhancing LDT regulation while preserving patient access to high quality testing and fostering innovation of new tests.

FDA Guidance

IDSA also provided comments on FDA's draft guidance, "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)." We appreciate the FDA's commitment to protecting patients, but we have expressed concern that the guidance as drafted could force many clinical laboratories at major academic medical centers to significantly reduce or even stop their development and use of LDTs. This loss of existing testing options and innovation would very likely impede patient access to existing high quality or state- of-the-art tests. We continue to remain in a productive dialogue with FDA, and are pleased to report that FDA is seriously considering at least one of our recommendations—the reclassification of tests for detecting transplant related viruses.

As you know, the draft FDA guidance proposes a risk based classification in which high risk tests would be the first to fall under FDA oversight, followed by moderate risk tests. Such an approach may make sense, but it is very important that tests be appropriately classified. IDSA has provided FDA with a body of evidence that we believe demonstrates that tests for transplant related viruses should be classified as moderate risk. These tests have been in use for many years by clinical laboratories, with well-documented data demonstrating clinical validity and peer reviewed literature evidence supporting their use. The standardization of assays and clinical care for patients with transplant-related virus infections has allowed for the establishment of strong expert guidelines for testing and managing these patients. In many instances, these LDTs have become the standard of care, and management of patients with transplant-related virus infections has become routine. We are pleased that the FDA intends to convene a meeting of the Microbiology Devices Panel of the Medical Devices Advisory Committee Meeting to further discuss this issue.

IDSA also appreciated that the FDA draft guidance provided several categories of LDTs that would be exempt from additional regulatory oversight, including rare diseases, LDTs for unmet medical needs, and LDTs used within a healthcare system. However, we are concerned that each of these definitions as written have been made inappropriately narrow, for example:

- **Rare diseases:** The draft guidance defined rare diseases as those that are tested for no more than 4000 times each year nation-wide. However, patients afflicted with several

rare infections, such as encephalitis caused by herpes simplex virus (HSV) and varicella zoster virus (VZV), or invasive aspergillosis may have symptoms that are also encountered more commonly occurring infections. Hence, in order for these rare infections to be ruled out, they must be tested for at rates that exceed the limit established for rare diseases. IDSA has recommended that the FDA use the Orphan Drug statute classification of rare diseases , defined as diseases that affect fewer than 200,000 people in the U.S.

- **Unmet needs:** The draft guidance exempts LDTs for unmet needs from additional regulatory oversight until one commercial test for that unmet need has been approved or cleared by the FDA. At such a time, clinical laboratories have a 12 month period to either get their LDT approved by the FDA or switch to the commercial option. IDSA has recommended that the unmet need status remain until at least two commercial options have become available in order to give clinical laboratories some flexibility and lessen the need to purchase multiple testing platforms (which would be infeasible for many laboratories and ultimately result in a loss of patient access to testing). Further, we recommended that laboratories be given at least a two-year transition period to better accommodate typical capital upgrade cycles.

- **Tests within a health system:** IDSA appreciates that LDTs used only within the healthcare system in which they are developed would be exempt from additional regulatory oversight. However, this provision fails to cover common arrangements in which a large institution's clinical microbiology laboratory serves as a regional reference laboratory to hospitals outside of its system. In such cases, the out-of-system hospital would utilize the system's LDTs, and the system's laboratory provides a quick turnaround time for tests and valuable consultations to discuss laboratory results and ensure appropriate clinical care decisions are made. This valuable resource would be lost with the definition outlined in the draft guidance.

IDSA is continuing to engage with the FDA to encourage the adoption of policies that provide appropriate oversight for diagnostic tests, foster needed innovation, and maintain patient access to high quality testing options. We greatly appreciate this Committee's engagement in this issue and hope you will conduct robust oversight of FDA's activities in this area and their potential unintended impact on patient care and public health.

House Energy and Commerce Committee/Diagnostic Tests Working Group

As you may know, the House Energy and Commerce Committee has worked with the Diagnostic Tests Working Group on a discussion draft of legislation on the issue of diagnostics regulation that seeks to address some of the concerns expressed by various stakeholders in response to the FDA draft guidance on LDTs. Unfortunately, IDSA remains concerned that the discussion draft would still place new regulatory requirements for premarket review of LDTs that would likely still be prohibitive for clinical laboratories in the hospital setting, thus severely limiting innovation of novel LDTs for emerging and evolving infectious diseases and curtailing patient access to testing. While IDSA appreciates the proposal's inclusion of a grandfather clause that

minimizes disruption to tests currently in use, we are concerned that new test developments that are needed to keep pace with rapidly changing ID threats will be hindered.

Furthermore, IDSA maintains that it would be inappropriate to regulate large scale commercial entities in the same manner as academic clinical laboratories in how they design, validate, and use diagnostic tests. A large manufacturer may develop a commercial test that will be used in widely dispersed geographic areas, where local factors can drive variability in test performance. The high standards of validation necessary for such a commercial test scenario typically would not apply to small academic laboratories that use their own LDTs only for their local hospital system or related community hospitals, and would place an undue burden on their ability to develop new, innovative tests.

IDSA is also concerned that the most recent discussion draft made public by the Committee did not include any exemption for tests utilized during public health emergencies. Given the need to respond swiftly to outbreaks caused by Zika virus, pandemic influenza virus, and others, IDSA continues to recommend that LDTs that have been developed and used by public health laboratories be exempted from additional regulatory oversight.

Options for Rapid Testing Are Essential

IDSA strongly cautions the federal government against adopting policies that will severely limit the ability of clinical laboratories in academic medical centers from developing and using LDTs. Under such a scenario, health systems would either move to available commercial diagnostic tests or send testing to outside reference laboratories, both of which can pose considerable disadvantages. For example, commercial assays are not yet available for the entire range of testing currently covered by LDTs. Those tests that are available may require investment in new instruments from multiple companies, as no one company has the entire menu of tests that are currently covered by LDTs. Such investment will not be feasible for many hospital laboratories.

Most importantly, sending clinical specimens to reference laboratories for testing will significantly increase the turnaround time required to get the results to physicians. Rapid diagnostics that facilitate early initiation of life-saving treatment are critical in infectious diseases patient care, where even a few hours delay can significantly impact patient outcomes. Public health responses also require rapid identification of an emerging health risk, and any delay in activation of important public health protocol allows dangerous infections to spread. Delays incurred by sending specimens to reference laboratories with inflexible testing schedules may significantly impact timely detection of outbreaks of infectious diseases.

Once again, IDSA greatly appreciates the Committee's ongoing commitment to patient care and public health and your willingness to engage on this complex issue. We look forward to continuing to provide our perspective and expertise to the Committee and working with you to craft appropriate policies to spur innovation and protect patient access to high quality diagnostic testing.