JANUARY 2015

IDSA
Infectious Diseases Society of America

Better Tests, Better Care

THE PROMISE OF NEXT GENERATION DIAGNOSTICS

About IDSA

The Infectious Diseases Society of America (IDSA) represents more than 10,000 physicians, scientists, and other health professionals who specialize in infectious diseases in the United States and internationally. IDSA's purpose is to improve the health of individuals, communities, and society by promoting excellence in patient care, education, research, public health, and prevention relating to infectious diseases.

Acknowledgments

IDSA is grateful to the many individuals who provided expert advice and assistance in the development of both this paper and its preceding manuscript. In particular, we would like to thank the IDSA Task Force on Diagnostics. Without their enormous contribution, this report would not have been possible. We are also grateful to the many government and industry officials and others who met with and advised IDSA leaders on the many aspects of diagnostic research and development. We encourage any who are interested in learning more about infectious diseases diagnostics to read the in-depth companion to this report, *"Better Tests, Better Care: Improved Diagnostics for Infectious Diseases."* [1]

IDSA Staff Contacts

For Policy Makers and Advocacy Groups:
Gregory Frank, PhD, Program Officer for Science & Research Policy
703-299-1216
gfrank@idsociety.org

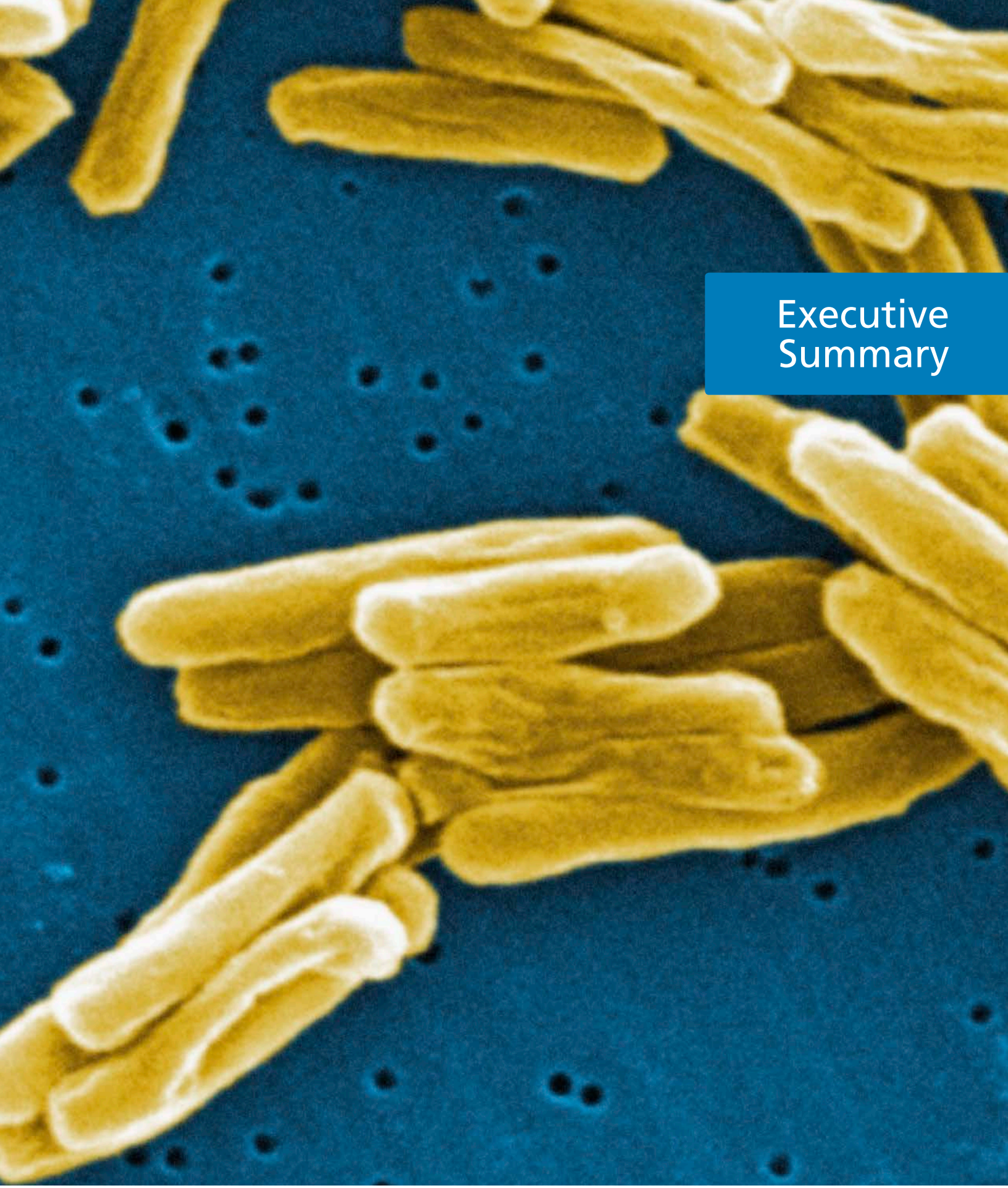
Amanda Jezek, Vice President of Public Policy & Governmental Relations
703-740-4790
ajezek@idsociety.org

For Congressional Staff:
Jonathan Nurse, Director of Governmental Relations
703-299-0202
jnurse@idsociety.org

For Media:
Jennifer Morales, Communications & Public Affairs Officer
703-299-0412
jmorales@idsociety.org

[1] http://cid/oxfordjournals.org/content/57/suppl_3/S139.long

Table of Contents



Executive Summary

A 45-year-old male who has received chemotherapy for Hodgkin's lymphoma is admitted to the hospital with high fever and low blood pressure. Due to his chemotherapy, the patient's immune system is very weak, and his doctors fear invasion of the bloodstream by bacteria, or sepsis. They order a potent intravenous antibiotic and send his blood sample out to the laboratory to test for bacterial infection.

The next day, the patient's condition grows so severe he requires treatment in the intensive care unit where his doctors treat with medications to increase his blood pressure. The laboratory reports the presence of bacteria in his blood (confirming the diagnosis of sepsis) and continues to work to identify the type of bacteria present. Within 18 hours, the culture tests identify the bacteria as *Pseudomonas aeruginosa*. The antibiotic with which the patient is being treated is predictably effective against most strains of *P. aeruginosa*.

Unfortunately, the patient's condition rapidly deteriorates and he dies, despite his doctors attempting several other antibiotics. Several hours after his death, the laboratory's testing discovers that the strain of *P. aeruginosa* that infected the patient is resistant to the antibiotics prescribed by his doctors. The bacteria were susceptible to only one antibiotic, which unfortunately had not been administered. A rapid diagnostic test providing this information several hours earlier could have allowed for appropriate treatment to be administered and may have saved this patient's life.

Laboratory tests that detect infectious agents are fundamental to high quality, life-saving care. Despite dramatic advances in laboratory technology, many patients continue to receive inaccurate, incomplete, or delayed diagnoses, resulting in suboptimal treatment and outcomes. In 2010, 140,000 Americans died from infections. The direct medical costs for care of patients suffering from infection are in excess of $50 billion annually. In some of these cases, a rapid, accurate diagnosis could have saved lives and reduced health care costs.

The Centers for Disease Control and Prevention (CDC) estimates 140,000 Americans died from infection in 2010.

Advances in biomedical research technologies have created new opportunities to develop and deploy novel, cost-effective, and life-saving laboratory tests. Now is the time for policymakers to partner with physicians, scientists, technology companies and regulatory agencies to invest in cutting edge scientific diagnostics that hold the potential to revolutionize the treatment of patients with an infectious disease.

The potential for improved patient care is enormous. Armed with next generation diagnostic tests, physicians can make better treatment determinations, removing much of the uncertainty inherent in current diagnostic practices. These tests hold the potential to identify disease-causing organisms in hours rather than days, allowing for rapid, effective clinical decision making. Because they can provide accurate information to guide the appropriate use of antimicrobial drugs, improved diagnostics are critical to any national or global strategy to combat the overuse of antimicrobial agents that fuels the current antimicrobial resistance crisis. These tests will also improve surveillance of existing and emerging diseases, allow public health workers to respond to outbreaks rapidly as they occur, and better guide infection control practices.

Despite their tremendous potential, next generation diagnostics face a number of challenges. Small, innovative diagnostics developers are hampered by reduced federal funding and also face challenges in obtaining clinical samples to assess the validity of their new tests. In addition, diagnostics developers face regulatory barriers such as institutional conflict of interest policies that can bar relevant experts from independently verifying tests or providing critical input. Finally, next generation diagnostic tests are difficult to integrate into clinical care due to barriers such as a lack of physician education regarding their appropriate use and insufficient reimbursement levels to cover the cost of testing.

These barriers, while significant, are surmountable. The federal government has begun to address these challenges, but additional steps are needed. In this paper, IDSA describes the need for diagnostics, the barriers to their development and appropriate use, and recent relevant federal activities. Finally, IDSA provides a comprehensive set of policy recommendations that build on the federal government's response to address key challenges. Now is the time for policymakers to work with both the scientific and health care communities to implement these recommendations.

The Dilemma of Diagnosis

Infectious Disease Diagnostics

Diagnostics are laboratory tests physicians use to identify microorganisms that cause illness. They look for unique physical characteristics of the microorganisms for identification, such as surface proteins or distinct genetic sequences.

Some tests identify single microbes, while "multiplex tests" can detect and distinguish among multiple microorganisms simultaneously. Other types can identify whether microbes are resistant to antimicrobial drugs. Broadly, these tests are influenced by three factors:

Reliability: Tests that are reliable are highly sensitive (i.e., they minimize false negative results) and highly specific (i.e., they minimize false positive results).

Speed: Speed is crucial. Tests yielding rapid results to speed administration of optimal treatment and infection control practices are ideal.

Complexity: Diagnostic tests can vary widely in complexity, both in the levels of training needed for proper use and the equipment required. Simple tests are well suited for point-of-care situations, such as a doctor's office. More complex tests requiring trained personnel and expensive equipment may be limited to the clinical microbiology laboratory in large hospitals.

A 35-year-old physically fit male visits his physician with a sudden fever, cough, and muscle pain. His doctor finds his blood oxygen level is low and admits him for hospital treatment. Initial diagnosis based on chest X-ray is pneumonia. Samples from the patient's respiratory tract are collected to identify the infecting microbe by growing it in culture. While awaiting test results to identify the infection, doctors prescribe standard antibiotic treatment for the most common bacteria that cause pneumonia.

Unfortunately, the patient's pneumonia worsens despite antibiotics. After 36 hours, the culture test finds the patient's pneumonia is caused by the bacteria *Staphylococcus aureus*, and further testing indicates it is resistant to the first antibiotic. Despite switching to an antibiotic that can kill the bacteria, the patient dies of overwhelming pneumonia 48 hours after admission to the hospital. Would quicker detection of the microbe and its resistance have led to a timelier initiation of effective treatment, and saved this patient's life?

When physicians are caring for patients suffering from infection, they must often decide on the best course of treatment before standard laboratory tests can provide data regarding the specific cause of infection. The microbes that are causing the infection could be bacteria, yeasts, fungi, viruses, or even parasites, such as organisms that cause malaria.

Unfortunately, different microorganisms may cause similar symptoms, creating a challenge for physicians determining the best treatment option. For example, the symptoms of an upper respiratory infection caused by a virus or bacteria can be virtually indistinguishable, but the drugs used to treat a bacterial infection cannot cure a patient suffering from a virus or vice versa.

Physicians rely on diagnostic laboratory tests to identify the types of microorganisms infecting their patients. Unfortunately, these diagnostic tools are often limited in what types of microbes they can detect, and the gold standard, growing them in culture, can take several days to a week. While diagnostic tests that can provide results more rapidly are becoming available, concerns about reliability, complexity, and cost hamper their widespread use.

In addition to uncertainty about what microbe is responsible for the infection, some microorganisms have developed resistance to standard antimicrobial treatments. Even if tests can identify the organism, many of them are unable to identify in a timely fashion whether that organism is drug-resistant. These results often come too late to optimally impact the patient's outcome. Physicians must order treatment using their best educated guess based on their patients'

symptoms, often using broad spectrum antibiotics where targeted therapy would be more appropriate and safer if the pathogen were known. In many cases, the physician chooses an appropriate and effective treatment, but sometimes the standard treatment is ineffective at stopping the infection. As illustrated by our case study, the patient's condition may deteriorate significantly before effective treatment can be administered.

Ineffective, unnecessary treatment with antimicrobial drugs also drives the development of antimicrobial resistance and can cause additional problems for patients. For example, the toxin producing bacteria *Clostridium difficile (C. difficile)* is far more likely to infect patients already treated with antibiotics. In 2009, 330,000 patients suffered from *C. difficile* infection, and 30,000 died.

The difficulty physicians face in rapidly and reliably identifying the cause of infection contributes to escalating health care costs due to longer hospital stays, unnecessary treatments and, most importantly, poor patient outcomes. Patients and the health care community are in dire need of faster, more sophisticated, and reliable diagnostics that are:

- Easy to use: Simple and easy-to-use tests allow adoption by a larger number of users, in hospital and reference laboratories, physician office labs, and point-of-care settings. They can also be incorporated in resource-constrained settings in rural areas.
- Rapid and Reliable: New tests must provide reliable results faster than the current diagnostic tests, ideally in less than 2 hours.
- Capable of identifying antimicrobial resistance: Tests that can reliably identify microorganisms and indicate those strains that are resistant to specific antibiotics can ensure that patients receive optimal, targeted therapy and enjoy the best chance of a favorable outcome.

Inappropriate Treatment and Antimicrobial Resistance

Antimicrobial agents have saved millions of lives since their discovery. Unfortunately, microbes, especially bacteria, are developing resistance to these drugs, rendering the once life-saving miracle drugs ineffective. One of several factors driving this resistance is inappropriate use of antimicrobials. This is largely a side effect of a lack of rapid diagnostic tests that can reliably identify the disease-causing microorganism and help inform timely treatment decisions.

Physicians treat patients with antimicrobial agents while waiting for results from these tests, as a delay in treatment can sometimes mean the difference between life and death. However, inappropriate treatment does not help the patient, can contribute to adverse events, and drives the development of antimicrobial drug resistance.

Efforts to guide appropriate use of antimicrobial drugs are referred to as "antimicrobial stewardship." Better diagnostic tests are critical in establishing better stewardship of our precious antimicrobial drugs.

Case Study

A 33-year-old male visits his doctor's office complaining of cough and nasal discharge and tells his physician he needs an antibiotic. The patient has an important work presentation in a few days and cannot afford to be sick.

The overwhelming likelihood is that the patient is suffering from a viral infection, but there is no rapid, point-of-care diagnostic test to confirm this diagnosis. With pressure from the patient and inability to rule out bacterial infection, the physician prescribes an antibiotic.

THE COST OF INFECTION

Spotlight on Sepsis

Rapid identification of the source of sepsis is critical, and a delay in appropriate treatment of the patient can have dire consequences.

1 in 23 hospitalized patients developed sepsis, or infection of the blood

36k people lost their lives to sepsis

$$$ Direct medical costs reach **$10 billion**

40% of all ICU expenses at hospitals are used for treating septic patients

*

*Data refer to annual costs

1. "Antibiotic resistant threats in the United States, 2013." Centers for Disease Control and Prevention
2. Melamed A, et al., "The burden of sepsis-associated mortality in the United States from 1999-2005: an analysis of multiple-cause-of-death data." *Critical Care* 2009, 13:R28
3. Elixhauser A, et al., "Septicemia in U.S. Hospitals, 2009." *HCUP Statistical Brief #122*, Agency for Healthcare Research and Quality

Next Generation Diagnostics

Tremendous advances in biomedical research in the past few decades are leading to the development of the Next Generation of Diagnostics. Combining simplicity, speed, and reliability, they hold enormous potential for improving patient care. Below are examples of the potential benefits in selected patient populations that can be realized if policymakers work with health care and scientific communities to reduce barriers to the development and clinical integration of next generation diagnostics:

- **Community-Acquired Pneumonia:** Respiratory tract infections, including pneumonia, are the most common indication for antibiotic use in the U.S. Yet, current standard diagnostics identify the specific cause in only 20 percent of patients. Because many cases of community-acquired pneumonia are caused by viruses, the lack of diagnostic test results leads to significant overuse of antibiotics. Tests using new diagnostic technologies indicate that physicians could identify the primary cause of pneumonia in 75 percent of patients, significantly reducing the unnecessary use of antibiotics and ancillary testing costs. In addition, next generation diagnostics could improve the use of targeted, effective therapy and patient outcomes.

- **Patients with Impaired Immune Systems:** Patients receiving organ transplants or cancer treatment, patients with HIV/AIDS, genetic immunodeficiencies, or autoimmune diseases such as lupus or rheumatoid arthritis, preterm infants and others have an impaired ability to fight infections, leaving them open to infections caused by microbes that are not normally harmful. Since these patients can be infected by such a large range of microbes, physicians need to "treat for everything" while hoping tests can guide more focused therapy in a few days. Next generation diagnostics can enable clear and rapid identification of the cause of infections enabling successful, targeted treatment.

Matrix assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS)

MALDI-TOF MS works by using a laser to ionize microbial proteins into a gas and accelerating this cloud of proteins with an electric charge. Different types of proteins move at different speeds, and their "time of flight" can be used to identify the types of proteins present. For diagnostics, MALDI-TOF MS provides a very rapid, sensitive, and highly accurate method of identifying unique protein patterns that can be used to identify microorganisms.

Highly multiplexed polymerase chain reaction (PCR) tests

PCR is a simple, rapid technique that detects and amplifies specific nucleic acid sequences that are unique to a given microorganism enabling rapid detection directly in clinical samples without culture, saving significant time.

Detection of a dozen or more different organisms can be undertaken in a single test using this amplification method, a process called multiplexing.

Multiplexed PCR diagnostic tests can screen up to two dozen microbes in a matter of hours, greatly increasing the ability of physicians to identify the cause of infections.

Next Generation Sequencing

Genetic information can be an excellent method to identify pathogens, but conventional PCR detection requires a known target DNA sequence to work effectively.

Next generation sequencing works on the principle of looking at all the genetic material simultaneously, whether it is blood, a tissue sample, or stool. All the genetic fragments can be catalogued and those belonging to a pathogen can be assembled and identified. This approach can be leveraged for rapid, highly sensitive diagnostic tests, especially in situations where it is unclear what pathogen is causing infection.

- **Sepsis:** Bacterial invasion of a patient's blood stream is a life-threatening infection, where patient survival depends on receiving effective antibiotics rapidly. Standard methods of microorganism identification can take days, thus 20-30 percent of patients receive ineffective initial therapy. Next generation diagnostics can identify microbes in minutes to a few hours, greatly improving patient outcomes.

- **Public Health Responses:** During a disease outbreak, such as infection caused by ingestion of tainted food or an emerging infection like avian influenza, Ebola, or Chikungunya, time is the enemy. It is critical to quickly pinpoint sources of the outbreak to contain further spread. The detection, assessment, and control of outbreaks are traditionally constrained by the lack of rapid and specific diagnostic tests. Current methods can take days to identify the microbial agent. Next generation diagnostics have the capability to identify these microbes in hours, resulting in a swift, effective public health response that saves additional lives.

- **Antimicrobial Drug Development:** Clinical trials to test the safety and effectiveness of new antimicrobial drugs are currently very expensive and challenging, partially due to the difficulty in identifying candidate patients infected with the target microorganism. For example, if a specific microbe is only detected in 25 percent of patients, trial designers must evaluate four patients to find one candidate appropriate to enroll in the study. Next generation diagnostics can enable researchers to more easily identify and recruit these patients, significantly reducing clinical trial costs and the time needed to develop lifesaving antimicrobial drugs.

- **Hard-to-identify Microbial Infections:** The gold standard of diagnostic testing, microbial culture, is only effective if the pathogen can be grown in culture. Unfortunately culturing can only identify a pathogen in a fraction of infected patients, and cannot easily identify most viral infections. For many cases, it is exceedingly difficult or impossible for the laboratory to identify the microbe causing infection in time to effectively guide treatment. Next generation diagnostics would be able to identify these microorganisms rapidly, allowing effective care to be administered to the patient quickly.

Diagnostic tests are being developed that leverage these new technologies and others (see text boxes), and rapid, accurate diagnostics are starting to reach health care workers and patients. Unfortunately, these diagnostic tests face major challenges in development, regulatory approval, and integration into health care that hamper their widespread utilization.

Case Study

A 19-year-old college student reports to the student health service with a sore throat. She has a fever and the throat is inflamed. Within minutes, a rapid point-of-care test excludes the possibilities of a "strep" throat. The patient avoids needless treatment for this infection.

The diagnosis is a viral infection. No antibiotic therapy is medically indicated. The patient is reassured and symptomatic treatments are prescribed.

Unfortunately, this scenario is still too uncommon. For many common infections, rapid point-of-care diagnostics are not available. And even when they are, barriers such as cost, physical space, and provider education often curtail their use.

Challenges to Bringing New Diagnostics to Patients

While new diagnostic technologies hold great potential, there are multiple challenges in the development and implementation of a next generation diagnostic product.

Research and Development (R&D) Obstacles

A new diagnostic laboratory test goes through several phases of research and development, a process that is subject to several challenges.

- **Financing R&D:** Often the best ideas come from small, innovative companies with limited resources. These firms often rely on financing from government sources, such as the National Institutes of Health Small Business Innovative Research (SBIR) grants, or through partnerships with other companies or academic research institutions. Current federal budget austerity has created significant challenges in securing funding to cover the high expense of developing innovative diagnostics.

- **Clinical Specimens:** Developing a clinically useful diagnostic test to detect infectious microbes requires patient specimens that are known to harbor such organisms. Even when such samples are available, the costs and regulations surrounding their access, such as proposed rules to require informed consent for de-identified samples, can be prohibitive. Validated clinical sample banks (biorepositories) and other innovative approaches that simplify the process of obtaining anonymous clinical specimens could save money and time in test development.

Regulatory Barriers

Newly developed diagnostic tests must be validated for safety and effectiveness for Food and Drug Administration (FDA) approval. Test developers are also subject to other regulatory requirements that hamper the development process.

- **Conflict of Interest[2]:** Often expert input and/or independent validation of a potential test is needed during development. Unfortunately institutional conflict of interest (COI) policies often bar those best suited for these activities, sometimes even if they are willing to work for free on their own time. Even when an institution does not explicitly ban such activities, policies are sometimes misinterpreted, resulting

Case Study

A 55-year-old female has smoked heavily since age 14. In the past year, she has been coughing up copious "phlegm" and has experienced chronic shortness of breath. She calls her primary care physician for yet another prescription for an antibiotic. This is the third such prescription in nine months.

Her physician suspects an exacerbation of chronic bronchitis due to the history of smoking. Only a third of these cases are due to bacterial infection, but lacking an easy test to rule out infection, the physician agrees to another likely ineffective prescription.

Institutional Conflict of Interest (COI)

Research collaboration between industry and non-industry partners has been critical to many successful medical advancements. Institutional COI policies are important to identify financial ties between industry partners and physicians/researchers and manage them in order to maintain objective and unbiased research and patient care.

The National Institutes of Health (NIH) has issued a regulatory framework on COI[2] for all institutions that receive NIH funding, providing national guidance on how institutions identify and report COI of their members. Institutions often build in additional policies in response to local priorities and tolerance for COI-related risks. This has resulted in wide variability in institutional COI policies that creates confusion for both researchers and industry partners on what types of activities are permitted.

Unfortunately, COI policies designed to appropriately manage important industry-institution relationships often have the unintended and damaging consequence of stifling interactions. For example, the COI policies at the most risk-adverse institutions can prohibit many research collaboration relationships from even taking place. In addition, misinterpretation of COI policies by institutions or individual researchers can further restrict important dialogue between academic researchers and industry.

510(k) and Premarket Approval (PMA) Pathways

The FDA Center for Radiological Devices and Health (CDRH) has two regulatory pathways for diagnostic device approval, based on the device's risk and whether it is comparable in scope to another already approved, also known as predicate, device.

The 510(k) pathway is for diagnostics that are substantially equivalent to a predicate, and do not pose a high risk to patients. The FDA also has a special process, the de novo 510(k) for novel tests with no predicate that also do not pose a high risk.

The premarket approval (PMA) pathway is for high-risk devices where an erroneous result, would significantly impact patient care. For example, false negative for a test to detect cytomegalovirus (CMV) in transplant patients could have dire consequences on the patient's outcome. A PMA requires that the applicant provides reasonable assurance of the device's safety and effectiveness, and due to its more stringent requirements, is a much more time consuming and expensive approval process.

Current Procedural Terminology (CPT)

The Center for Medicaid and Medicare Services (CMS) administers Medicare reimbursement of laboratory tests. Private insurers frequently follow Medicare's lead in setting reimbursement rates. It relies on the CPT code system to identify the medical service provided for patients and its insurance coverage.

Updating CPT codes for new services is a complex, lengthy process that takes years. Many new tests are "cross-walked," a process where older similar CPT codes are used for reimbursement. This process does not ensure that new reimbursements will cover the full costs of the new tests.

in a stifling of collaboration between academic researchers and industry. This forces developers to forgo expert input or use laboratories lacking expertise for independent testing. This loss of expert input and the resources diverted to train and supervise testing at labs lacking expertise can add considerable time and cost to diagnostic development. In addition, the FDA is subject to its own strict COI policy[3] designed to avoid bias in review that often creates difficulties in convening expert panels to provide input on device submissions. Even small COI disclosures, unrelated to the matter at hand, can bar subject matter experts from panels, possibly delaying the FDA review process for developers.

- **Regulatory Pathway Costs:** Novel diagnostics for certain high risk infections, even when adapted from previously approved tests, may be subject to the expensive FDA premarket approval (PMA) pathway (see text box). The costs to develop a candidate diagnostic can be too high for companies to move forward with clinical trials. In some cases, the less costly route, called the 510(k) pathway, may be sufficient to ensure device safety and effectiveness for novel test types. However the 510(k) pathway's costs can still be difficult for small companies to manage.

- **Reference Methods:** A new diagnostic test must be compared to a "gold standard" to assess its accuracy and reliability. This standard can be older, well established tests or a composite of several different methods. As the sensitivity of innovative diagnostics may far exceed that of the current test procedures, discrepancies that arise must be resolved on a case-by-case basis — a process that is complex, time-consuming and extremely costly.

[2] http://www.gpo.gov/fdsys/pkg/ FR-2011-08-25/pdf/2011-21633.pdf
[3] http://www.fda.gov/oc/advisory/conflictofinterest/policies.html

Challenges to Integration into Clinical Care

Even if a diagnostic test successfully navigates development, validation, and approval, it faces one final series of challenges: acceptance and appropriate use by the health care community.

- **Expense:** Many health care institutions only consider direct laboratory costs without factoring cost savings in shorter hospital stays, benefits in patient care outcomes, and antimicrobial stewardship. New, superior tests are often considered too expensive, therefore hampering adoption. In addition to the cost of running an individual new test, a health care facility must also consider the cost of new equipment needed to process new tests. Such equipment can be expensive and bulky, taking up space that a hospital laboratory or physician's office may not have available. Well-designed clinical and financial outcomes studies are needed to demonstrate to health care facilities and providers the value of new diagnostic tests. New electronic health records (EHR) systems can improve access to information on how the use of diagnostic tests impacts treatment and patient outcomes. However, many EHR systems have not integrated diagnostics usage and results effectively, impeding outcomes research.

- **Medicare Reimbursement:** New diagnostic tests are often more expensive at face value than older counterparts, and the Current Procedural Terminology (CPT) code system used by Medicare to set reimbursement levels is often unable to cover the costs of new tests until new codes are created. Even when new codes are introduced, the full costs of tests still may not be covered. Reimbursement decisions are often made at the local level without national guidance, resulting in wide regional variability of reimbursement levels that also restricts widespread utilization of improved tests.

- **Education:** Many physicians and other health care providers may be hesitant to use new diagnostic tests, in part because they are often uncertain of how best to integrate them in their practice and how to interpret results to impact individual patients' care and outcomes. Physicians often look to educational tools, such as clinical guidelines developed by their professional societies, such as IDSA, and government bodies, such as the Agency for Healthcare Research and Quality (AHRQ), to suggest the best methods to diagnose and treat an infection. Aside from guidance[4] on specimen collection and transport, little guidance currently exists to help physicians identify what tests should be used if a patient has a particular set of symptoms or how to appropriately integrate new tests into patient care. The ability to develop these new guidelines is hindered by the lack of clearly designed outcomes studies demonstrating patient benefit when tests are used as part of clinical decision making.

[4] http://cid.oxfordjournals.org/content/early/2013/06/24/cid.cit278.full.pdf+html

Challenge in Clinical Integration: The Emergency Department (ED)

ED physicians work in a fast-paced acute care setting where there are multiple competing demands on the clinician's time and where providers must balance the risks of providing less than optimal antimicrobial use versus the need to expedite the discharge of patients in order to make space for new patients. The ED illustrates the challenges in clinical integration seen in many health care settings, including primary care physicians' offices and other inpatient settings:

Education: ED physicians see a wide range of diseases when caring for their patients, creating a major challenge when trying to keep up-to-date on advances in care. They often do not have the time to learn adequately the advantages and shortcomings of new diagnostics as well as their appropriate use and impact on patient care. If educational tools are not made available to demonstrate to physicians how a new test can provide a clear benefit to patient care, ED physicians often will not use a diagnostic test, even if it is beneficial.

Integration into workflow: New rapid diagnostic tests have the potential to provide physicians information in hours as opposed to days. However, due to resource limitations, rapid tests that are run by supporting clinical microbiology laboratories are often run in batches once enough samples for the same test reach the lab, as opposed to testing samples as they arrive. In these cases, the advantages of a rapid test are not realized. These test results may take too long to help ED physicians, where very rapid turnaround times for tests are required to inform their patient care decisions.

The Federal Government's Response

Since the publication of IDSA's "Better Tests, Better Care" Report in 2013, the White House, NIH, CDC, FDA, and Congress have begun taking action to address the challenges in bringing next generation diagnostics to patients. These first steps are a promising foundation for additional efforts.

White House National Strategy for Combating Antibiotic-Resistant Bacteria

In fall 2014, the White House released an executive order[5] with provisions to implement an accompanying National Strategy[6] for Combating Antibiotic Resistant Bacteria (CARB). The CARB national strategy, based on the recommendations[7] of the President's Council of Advisors on Science and Technology (PCAST), lists the development of innovative diagnostics as one of its five goals to address antibiotic resistance. In particular, the CARB strategy recommends federal investment towards developing rapid, point-of-care diagnostic tests that can distinguish between viral and bacterial infection and identify resistance as well as those that will guide treatment of resistant infections and public health responses. This strategy also advocates for a streamlined approval process for certain types of infectious disease (ID) diagnostics. The CARB strategy also recommends that improvements be made to diagnostic reimbursement to encourage the routine use of innovative diagnostic technologies as well as new regulatory processes to enable expedited approval for diagnostics for unmet clinical needs. As a first step, the NIH and the Biomedical Advanced Research Development Authority (BARDA) will co-sponsor a $20 million prize for the development of rapid, point-of-care diagnostic tests that can identify highly resistant bacterial infections.

The National Institutes of Health Diagnostics Investments

In early 2014, the National Institute of Allergy and Infectious Diseases (NIAID) published a report[8] on its antibacterial resistance research program and its future directions. Investment in ID diagnostics has been one strategic focus and several diagnostics-centric initiatives have been announced, including investments shown in:

NIAID Diagnostic Funding

Diagnostics to quickly detect bacteria responsible for antibacterial resistant infections in hospital settings, **$12 million, fiscal year (FY) 2015**	New diagnostic tests to identify reservoirs of latent HIV infection, **$1.3 million, FY 2015**
Diagnostic tests that minimize the amount of clinical sample needed, **$5.5 million, FY 2015**	Advanced development of multiplexed diagnostic platforms for the detection of infectious diseases, **$6 million, FY 2015**

[5] http://www.whitehouse.gov/the-press-office/2014/09/18/executive-order- combating-antibiotic-resistant-bacteria
[6] http://www.whitehouse.gov/sites/default/files/docs/carb_national_strategy.pdf
[7] http://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast_carb_ report_sept2014.pdf
[8] http://www.niaid.nih.gov/topics/antimicrobialresistance/documents/arstrategicplan2014.pdf

The NIAID-supported Antibacterial Resistance Leadership Group (ARLG) has also supported early clinical research on diagnostics that identify resistant bacterial infection. The ARLG is also preparing a "virtual biorepository" of clinically well-characterized bacterial isolates for use in diagnostic research, which is often hampered by lack of clinical samples for testing. The repository samples will remain at their respective institutions, while the ARLG virtual biorepository will provide a central point of contact.

The Centers for Disease Control and Prevention (CDC) Advanced Molecular Detection Initiative

The CDC Advanced Molecular Detection Initiative[9] focuses on new diagnostic technologies for infectious diseases. This investment enables public health responses to identify reservoirs of disease, new outbreaks, and tainted food supply sources more rapidly. Congress provided $30 million to launch this initiative in FY 2014. The CDC recently announced its "No Petri Dish" Diagnostics challenge[10] that aims to spur development of innovative tests that can characterize pathogenic organisms from clinical samples without the need to culture them.

FDA Guidance on Diagnostic Device Regulations

The FDA has taken several promising steps to simplify diagnostic regulatory approval through two draft guidance documents released in 2014. The first draft guidance, "Expedited Access for Premarket Approval Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibility Debilitating Diseases or Conditions,"[11] streamlines the premarket approval (PMA) pathway for high risk diagnostics that address unmet needs by allowing alternative study designs.

The second guidance document, "Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval,"[12] allows smaller clinical studies for approval of diagnostics that address unmet medical needs, with the admission that smaller trials may leave more uncertainty about the risks or benefits of these tests. However, that uncertainty is preferable to a complete lack of diagnostics for certain infections where there is unmet medical need. Additional data can then be collected post-approval to provide additional information about the diagnostic's efficacy and appropriate utilization in real world settings.

The Protecting Access to Medicare Act of 2014 (P.L. 113-93) In spring 2014, Congress enacted the Protecting Access to Medicare Act of 2014 (PAMA). This law included several provisions designed[13] to improve diagnostic test reimbursement that provide an excellent foundation on which to build future diagnostic reimbursement reform:

- Requires the Secretary of Health and Human Services (HHS) to form an expert panel for input on issues surrounding diagnostic tests.
- Instructs the panel to provide input on reimbursement levels, temporary CPT code assignment for new diagnostic tests, and help develop policies to facilitate the appropriate use of diagnostic tests.
- Provides payment adjustments to the reimbursement system based on the weighted median reported costs. This approach should reduce regional variability in reimbursement levels.
- Enumerates provisions to implement a new reimbursement category for new advanced diagnostics that have yet to receive a CPT code. The goal is to ensure the full costs of new tests are reimbursed when they first reach patients.

Centers for Medicare and Medicaid Services (CMS)

In its 2014 proposed Clinical Laboratory Fee Schedule (CLFS), CMS announced its intention to review codes and associated payment levels to better set payment levels in light of many advances in clinical laboratory testing. However, the passage of PAMA has created provisions on diagnostic testing that supersede the CMS 2014 proposed revisions. In light of this, CMS has announced in its proposed 2015 CLFS rule its intention to begin implementation of PAMA's new reimbursement system (see above).

---

[9] http://www.cdc.gov/amd/
[10] http://www.cdc.gov/amd/cidtchallenge/index.html
[11] http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm393879.htm
[12] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm393882.htm
[13] http://www.idsociety.org/uploadedFiles/IDSA/Policy_and_Advocacy/Current_Topics_and_Issues/Diagnostics/Background/Diagnostic%20Reimbursement%20Improvements.pdf

IDSA Policy Recommendations

The aforementioned barriers, while significant, are not insurmountable. Below, IDSA provides a range of policy recommendations that build on the federal government's response to address these challenges.

Recommendations for Diagnostics Research and Development (R&D)

Congress

Increase funding to stimulate R&D of emerging diagnostic technologies by government agencies and private companies, including:

- NIH -- the major funder of early to mid-stage diagnostics research.
- BARDA -- undertakes advanced clinical development of innovative infectious diseases diagnostics and treatments.
- CDC -- administers the Advanced Molecular Detection (AMD) initiative to enhance diagnostics that support public health responses, and the proposed "Detect and Protect" antimicrobial resistance initiative that includes an isolate biorepository bank that could be used for diagnostics R&D.

Incentivize and support further diagnostic research

- Enact legislation to support a tax credit to cover 50% of clinical research costs for next generation diagnostics that address defined unmet medical needs.
- Consider additional prizes that spur diagnostic innovation like the CARB NIH/BARDA sponsored rapid diagnostic prize.
- Enact the 21st Century Global Health Technology Act (H.R. 1515/S. 2407 in the 113th Congress), which will strengthen health R&D programs at the United States Agency for International Development (USAID) and does not require new funding.
- Provide incentives and support for institutions to save de-identified specimens for biorepositories when possible for the purposes of new test development as well as FDA clinical trials for diagnostic test validation.

HHS

Promote innovative funding mechanisms and clinical research infrastructure

- Coordinate various agency efforts to ensure that there is a strategic, organized national effort to spur the development and appropriate use of infectious disease diagnostics.
- Explore opportunities to establish large scale public private partnerships (PPP) similar to European efforts such as the Rapid Point-of-Care Test Platforms for Infectious Diseases[14] (RAPP-ID) program.

NIH and NIAID, working with other stakeholders

Prioritize funding and support of innovative diagnostic research

- Increase Small Business Innovative Research (SBIR) grant programs, U01 grants, and other similar funding mechanisms that support and provide incentives for innovative research.
- Ensure that the peer review process for diagnostics grant submissions includes study sections with appropriate expertise to evaluate feasibility and clinical applicability, as well as scientific merit.
- Promote the development of biorepositories or other clinical infrastructure elements to facilitate the procurement of clinical specimens, such as the Antibacterial Resistance Leadership Group's (ARLG) virtual biorepository initiative.
- Expand NIAID support for early clinical trials of diagnostic devices.

CDC

- Implement the AMD initiative and ensure open access to its isolate bank for diagnostics R&D.
- Continue to develop diagnostics R&D incentives similar to the "No Petri Dish" Diagnostics Test Challenge.

[14] http://www.imi.europa.eu/content/rapp-id

Solutions for Addressing Regulatory Barriers for Diagnostics

Congress

Work with Federal Agencies to address regulatory barriers

- Include report language with relevant authorizing or appropriations legislation to clarify NIH-funded institutions should implement COI policies that appropriately enable, not prohibit, transparent industry/institutional research collaborations.
- Work with the HHS and FDA to clarify and revise the FDA COI policy to enable more effective recruitment of subject matter experts while retaining objective regulatory review.
- Provide direction and oversight as appropriate to facilitate agency adoption of additional recommendations.

HHS

Ensure informed consent rules for clinical samples do not create unnecessary barriers

- Withdraw and amend the draft proposal to institute a new informed consent requirement for research with de-identified residual clinical samples, outlined in the 2011 Advanced Notice of Proposed Rulemaking for human subjects research protections (i.e., the Common Rule), as it would severely limit the conduct of diagnostics research.

FDA/CDRH

- Build on recent draft guidance documents (Docket No. FDA-2014-D-0363 and FDA-2014-D-0090) and continue efforts to expedite the regulatory process for diagnostics subject to PMA for unmet medical needs.
- Clarify the classification of organisms and patient populations whose diagnostic tests require PMA compared to the less burdensome 510(k) process.
- Identify ways to eliminate the need to re-demonstrate the clinical validity of a novel diagnostic product after multiple studies already have been conducted for similar products.
- Assist other agencies, such as the NIAID-supported ARLG and the CDC's resistance isolate bank, in developing strategies to standardize the collection and preservation of de-identified clinical specimens for biorepositories or for public health surveillance purposes.

Solutions for Health Care Integration: Encourage Adoption of New Tests

- Harmonize recommendations to provide laboratories with greater clarity of the processes for clinical validation or verification for new assays.
- Collaboratively develop guidelines on how to establish reference methods for new technologies that are more sensitive and specific than the existing "gold standard."

Solutions for Health Care Integration: Reimbursement for Diagnostics Testing

Congress

- Oversee implementation of diagnostic testing reimbursement provisions contained in the Protecting Access to Medicare Act of 2014 and take action if needed.

HHS

Ensure appropriate implementation and composition of HHS PAMA(P.L. 113-93) expert panel

- Ensure that infectious diseases specialists (physicians and clinical microbiologists) are appointed to the PAMA-required expert panel to provide input on the development, validation, performance, and application of clinical laboratory tests.

CMS

Implement the diagnostic reimbursement provisions from PAMA (P.L. 113-93) and the CARB National Strategy

- Ensure that reimbursement, at a minimum, covers the cost of testing.
- Eliminate the wide regional variations in reimbursement for diagnostic testing.
- Simplify, expedite, and increase the transparency of the process of assigning new CPT codes.

Solutions for Health Care Integration: Educate Health Care Providers on New Diagnostic Tests

Congress

Work with Federal Agencies to address regulatory barriers

- Fund the development of information technology solutions for rapid communication of laboratory data to doctors that so they can quickly and effectively use this information to guide patient treatment.

HHS

Ensure informed consent rules for clinical samples do not create unnecessary barriers

- Promote outcomes research to demonstrate whether the costs associated with testing and rapid diagnosis translates into improved patient care.
- Investigate pay-for-performance standards that focus on the proper use of new diagnostic tests.
- Through the Office of the National Coordinator for Health Technology (ONC) promote integration of improved electronic medical record systems that include transmission of diagnostic test results for reportable diseases to local, state, and federal health departments.

CDC

- Expand the "Get Smart" program on antimicrobial stewardship to include education on infectious disease diagnostic testing and the role it plays in combating antimicrobial overuse and misuse.

CMS, health care institutions, diagnostics companies, and other stakeholders

- Encourage the development of cost-effectiveness models that assess the impact of diagnostics on all facets of patient care, e.g., mortality, length of stay, use of antimicrobial agents, and isolation procedures.
- CMS should seek opportunities to incentivize the integration of new diagnostics into laboratory workflow practices to help ensure that rapid test results are quickly provided to physicians in order to impact patient care.

AHRQ and HRSA

Work with professional societies and health care institutions to educate health care providers on the appropriate use of new diagnostics

- Fund and encourage strong educational programs to disseminate the results of research on diagnostic test utilization to inform physicians about the utility of new diagnostics.
- Professional societies, educational institutions and other stakeholders involved in the education of physicians should ensure that education includes detailed training on the appropriate use and limitations of next generation diagnostic tests, and other relevant information, to maximize their effective use.
- Professional societies and other stakeholders, with the inclusion of appropriate experts in diagnostics, should develop clinical practice guidelines that include recommendations on the use of diagnostic tests and their proper integration into care.
- Test, validate, and integrate diagnostic test "bundles" for common infectious disease clinical syndromes.

Conclusion

Diagnostics have had a tremendous impact on the treatment of patients with infectious diseases and are essential in providing routine patient care, combating pandemics and outbreaks, and ensuring public health. Next generation diagnostics can streamline the complex diagnosis process, allow more timely and effective treatment, ease clinical trials, and allow rapid mobilization of public health responses. New diagnostics have the potential to save the lives of thousands, if not millions of patients with infectious illness, and allow physicians to use antimicrobial drugs more appropriately, thereby limiting the development of antimicrobial drug resistance.

However, new diagnostic development and clinical integration face major barriers that cannot be overcome without federal government action. Now is the time for policymakers to implement these recommendations and help bring these diagnostics to patients. The consequences of inaction are dire. The scientific and health care communities, along with the federal government, must redouble their efforts to ensure the safety and wellbeing of patients. Without federal action, we risk impairing or even halting the development and adoption of lifesaving new tests.

1300 Wilson Boulevard, Suite 300
Arlington, VA 22209
703.299.0200
www.idsociety.org

The Infectious Diseases Society of America is an organization of physicians, scientists, and other health care professionals dedicated to promoting human health through excellence in infectious diseases research education, prevention, and patient care.

The Society, which has nearly 10,000 members was founded in 1963 and is headquartered in Arlington, Virginia.

For more information, visit **www.idsociety.org**