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IDSA
Infectious Diseases Society of America

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Robert W. Eisinger, PhD
Division of Program Coordination, Planning, and Strategic Initiatives
Office of the Director
National Institutes of Health
5601 Fishers Lane, Room 2F42
Rockville, MD, 20853

Re: "Announcement for Request for Comment for 'Antimicrobial Resistance Rapid, Point-of-Care Diagnostic Test Challenge'"

Dear Dr. Eisinger:

The Infectious Diseases Society of America (IDSA) welcomes the opportunity to comment on the Antimicrobial Resistance Rapid Point-of-Care Diagnostic Test Challenge. IDSA has worked tirelessly to address the public health crisis of antimicrobial resistance for more than a decade, beginning with our 2004 Bad Bugs, No Drugs report. The Society is encouraged by the release of the National Action Plan to Combat Antibiotic Resistant Bacteria (CARB), and its commitment to implementing a multipronged policy solution that protects patients and public health from the dangers of antibiotic resistant infections, including the development of novel infectious disease (ID) diagnostics.

IDSA has stressed the importance of innovative diagnostics in combating antimicrobial resistance, most recently in our 2013 policy report "Better Tests, Better Care: Improved Diagnostics for Infectious Diseases." Traditional ID diagnostics are often too slow to inform physicians' early treatment decisions of seriously ill patients, forcing them to empirically treat with broad spectrum antimicrobial drugs while awaiting test results. Empiric treatment not only subjects patients to serious adverse events, such as deadly *Clostridium difficile* infections, but also contributes to the rise of antimicrobial resistance. Emerging rapid diagnostic technologies allow swift determination as to the presence, or absence, of a pathogen. This enables physicians to safely decide whether to use, or not to use, an antibiotic, and what antibiotic will be most effective. The result is improved patient care, and parsimonious use of our limited antimicrobial arsenal.

IDSA strongly supports the National Institutes of Health (NIH) and Biomedical Advanced Research Development Authority (BARDA) sponsored competition for rapid, point-of-care diagnostics that can identify antimicrobial resistance. IDSA is pleased to respond to key criteria topics for the challenge below:

1. Purpose: There are different types of tests that could be considered to meet the goal of combating antimicrobial resistance. The first are rapid screening tests that rule out bacterial infection, therefore enabling physicians to feel secure in the knowledge that it is unlikely that a bacterial pathogen is present. Better yet, such tests could detect an etiologic viral pathogen. The result is avoidance of antibiotics for infections that are often viral: sinusitis, pneumonia, acute bronchitis, and middle ear infections.

In addition to detecting pathogens themselves, there are other ways to rapidly determine if an infection is viral or bacterial. Procalcitonin is an innate immune inflammatory biomarker; its concentration in serum increases rapidly with an invasive bacterial infection, but does not following an active viral infection. While procalcitonin level testing is currently used for inpatients and Emergency Department (ED) patients, second generation assays have the potential for office, clinic, or even home use. Other biomarkers may be better. Invasion by microbes stimulates a large number of genes that constitute the host immune system. Emerging data suggest that the pattern of patient genes that are "turned" on or off can be used to rapidly differentiate host invasion by a virus versus a bacterium. In short, current science and technology is ripe for empowering patients and their physicians with tests that can quickly rule out bacterial infection, or a lack of infection. These types of tests would likely be point-of-care diagnostics in predominately outpatient settings, and must be rapid enough to prevent the initiation of inappropriate antimicrobial treatment.

Diagnostics that identify specific bacterial pathogens and their susceptibility patterns are more likely to be used in inpatient hospital settings, including critical care units. Current methods to determine susceptibility take a day or more after the culture turns positive, and testing for antibiotic resistance gene activity is hard to interpret due to the many mechanisms of resistance. Innovation in rapid antibiotic susceptibility testing would enable swift, targeted antimicrobial treatment for critically ill patients, improved infection control in hospitals, and would support hospital-based antimicrobial stewardship programs. These tests will require significantly higher standards of specificity and sensitivity to prevent misidentification of a pathogen or its susceptibility. These tests will likely be more complex and have longer turnaround times than screening tests that rule out infection. Throughout our comments, IDSA stresses that these broad types of tests will have very different considerations should they be pursued as objectives of the competition.

2. Characterizing drug susceptibility: The genetics of antimicrobial drug susceptibility is complex, difficult to interpret, and may miss novel mutations that have as yet unknown impacts on susceptibility. In the short run, IDSA recommends that the prize focus on diagnostics that identify phenotypic markers of resistance and susceptibility, as they are clinically relevant end products of many genetic pathways. An approach that phenotypically identifies and characterizes drug susceptibility would also have broader applications to new antimicrobial drugs where the genetics of resistance are not yet well understood. As the tools of genetics evolve, it may be possible for genetic methods to be revisited. For example, it may be plausible that exposure to an effective antibiotic would result in a unique expression pattern of bacterial genes that can be observed to establish susceptibility.

3. Sample matrix: In outpatient settings, a significant portion of inappropriate antimicrobial prescriptions are used for upper respiratory tract infections. For tests designed for these settings, IDSA recommends that the challenge focus on non-invasive respiratory specimens such as nasal swabs. Other non-invasive samples, including urine and blood obtained by finger or heel pricks, will also be effective in both inpatient and outpatient settings for identifying pathogens and antimicrobial susceptibility, especially in pediatric cases where invasive sample collection can be traumatic for patients.

Diagnostics that can successfully test a variety of sample types have a clear value in screening as well as pathogen identification and resistance detection. While IDSA understands the prize's objective is to develop diagnostics to directly test clinical samples, rapid processing of positive cultures, such as the use of mass spectroscopy, is a clear improvement in combating resistance. IDSA recommends the prize considers the impact of tests validated to work with a variety of clinical specimen types as well as on isolates recovered from positive cultures, if applicable.

Diagnostics, especially non-quantitative molecular methods, have difficulty identifying and distinguishing pathogens from colonizers. IDSA advises that prize criteria account for isolates from normally sterile body site specimens whose presence may have greater importance than isolates from sites that have potentially colonizing or contaminating microbiota.

4. Speed: In almost every clinical setting, the longer a result takes, the less likely it will be acted on by a physician. However the ideal, achievable turnaround time of a diagnostic will be dependent on both its setting and intended use. For example, a diagnostic used in a physician's office or the ED to rule out a bacterial infection or identify the presence of a virus must be extremely rapid to influence patient management. IDSA recommends these tests should have an ideal turnaround time of 10-15 minutes and no longer than 30 minutes. The ease of use of these diagnostics must be considered to achieve these required speeds. Sending specimens to a central laboratory is time prohibitive, so these types of diagnostics must be simple, allowing non-laboratory trained personnel to use the tests and interpret their results at the point-of-care.

Diagnostics that identify a pathogen and its resistance profile will likely require longer testing times. IDSA believes a goal of less than 2-4 hours will significantly improve clinical care over existing methods. These types of diagnostics will likely have higher requirements of expertise, which may require the inclusion of central laboratories.

5. Setting: Clearly, rapid point-of-care testing would be of value in all clinical settings. However to effectively combat resistance, new diagnostic tests are needed in a variety of inpatient and outpatient settings to facilitate antibiotic stewardship across the continuum of care. IDSA recommends that the prize focus on diagnostics for use in the offices of primary care physicians, the ED, urgent care clinics, outpatient clinics, and inpatient units, especially critical care units. As stated above, the types of tests most needed to combat resistance will depend on the setting. In outpatient settings as well as the ED, tests that can prevent inappropriate antibiotic prescription by ruling out bacterial infection would have the greatest impact. However, in inpatient settings, including critical care units, tests that can identify the organism and its resistance profile, to better direct appropriate antimicrobial use, would be most beneficial.

6. Ease-of-use: IDSA recommends the competition make ease-of-use a major focus, especially for diagnostics used in outpatient settings. Ideally, any reagents needed to perform a diagnostic test should be stored at room temperature with an extended shelf life of at least a year. While testing equipment may be intricate, we recommend the test itself be very easy to use, with internal performance controls to ensure not only appropriate use but also that quality is maintained. Complex answers will need to be distilled effectively to provide straightforward results to a variety of personnel. For example, a diagnostic that can identify resistance may focus not on a particular resistance mutation, but instead provide the physician with a recommendation on whether particular antimicrobial drugs will be effective.

7. Diagnostic performance: A diagnostic test's performance needs will depend on its intended use and setting. For diagnostics that rule out bacterial infection in outpatient settings or the ED, when the patient is not seriously ill, IDSA believes a sensitivity of 90-95%, a specificity of ~98%, and a negative predictive value of ~95% is reasonable. However, for inpatient settings, including critical care units, where tests are likely designed to improve the efficacy or lower the risk of antibiotic treatment, the bar must be higher to improve patient care. With seriously ill patients, an incorrect result cannot be tolerated. For example, if a physician cannot trust the accuracy of a negative test result, he or she is likely to decide to continue antibiotic treatment for a very ill patient. As another example, a test that misidentifies a resistant organism as susceptible to a particular antimicrobial drug may lead to inappropriate treatment and devastating results. We recommend these tests have a sensitivity of 95-98%, nearly 100% specificity, and a negative predictive value of 99%.

8. Tradeoffs: In general, a test's performance, including ease-of-use, speed, and reliability (sensitivity/specificity), often comes at the expense of cost. Again, the setting and intended use of a test will instruct which trade-offs are acceptable for the competition. In outpatient settings, IDSA recommends that cost be a major driving factor to consider; if tests are effective but are costly to use, they will not be adopted widely enough to impact antimicrobial resistance. For inpatient tests used to identify pathogens and susceptibility, IDSA believes a higher cost should be tolerated in order to encourage and maintain a higher reliability. The prize may also consider trading off ease-of-use to achieve other goals in inpatient settings, as they often have access to personnel with diagnostic expertise in central or rapid response laboratories.

9. Cost: The acceptable cost of a test is related to its setting, intended use, and the potential cost savings based on a patient's health and outcome. For tests to screen and rule out bacterial infection in outpatient settings, we recommend that tests focus on minimizing costs to encourage wider adoption, with a goal of $10-20 per test. Another consideration is situations in which multiple tests are needed to rule out bacterial infection in a patient. To keep total patient care costs down, the prize should emphasize diagnostics that multiplex major pathogen targets or focus on host biomarkers to distinguish viral or bacterial infection. In these cases, a slightly higher test cost should be considered in the context of lower overall costs to patient care.

The complexities of diagnostics that identify an infectious agent and its susceptibility will likely require a higher test premium as compared to those in the outpatient settings. IDSA recommends that the competition for these types of diagnostics aim for costs of $50-150 per test. As above, the impact of these tests on overall patient care should be considered, as a higher cost test may

result in significantly improved patient outcomes and lowered healthcare cost. Lastly, IDSA urges NIH and BARDA to work with the Centers for Medicare and Medicaid Services (CMS) to help ensure that these tests are reimbursed at an appropriate level to facilitate access.

11. Key technologies: In order to achieve a realistic timeline to licensure, IDSA believes developers should strive to have a candidate diagnostic test approved within 3-4 years, with a development time of no more than 2 years and 1-2 years devoted to trials and regulatory approval. However, less complex tests that use more established technologies would likely be developed and licensed more rapidly than those using more investigational methods. IDSA recommends that the competition consider a tiered approach to its timeline, to provide opportunities for less developed novel diagnostics that may hold great potential to combat antimicrobial resistance.

12. Interest: Developers will likely consider a number of factors, including the resources needed to bring the test to market, access to specimens, the regulatory barriers to approval, and whether the tests will be appropriately reimbursed and properly used by clinicians. We discuss several of these issues in the "barriers section" below. IDSA recommends that developers who pursue this competition be encouraged to collaborate closely with physicians, laboratorians, and industry stakeholders to ensure that the diagnostic assay is feasible in the laboratory, provides useful clinical information, and has industry backing to navigate the development and licensure process.

13. Use: In ED and outpatient settings such as doctor's offices, low-complexity screening tests will likely be used by non-laboratory trained personnel. Pathogen and resistance identification assays will predominately be used in hospital settings, including sicker patients in the ED and inpatient units. These tests will likely be of moderate to high complexity, and will probably be used by laboratory trained personnel. IDSA recommends the test developers describe their plans on how they will interact with stakeholders in the settings above who will use the test, to identify how the tests will integrate most effectively into patient care.

14. Barriers: While IDSA firmly believes the prize provides an excellent incentive to develop rapid diagnostics to combat resistance, several challenges should be considered. First, regulatory obstacles posed by novel diagnostics may dissuade developers from pursing the prize. Biomarker-based ID diagnostics that may interpret multiple signals to predict whether a patient has a viral or bacterial infection are not yet prevalent, and present challenges to both the Food and Drug Administration (FDA) and developers in their appropriate validation. Another regulatory concern is a test that uses multiple sample types and/or targets a rare pathogen. In Clinical Laboratory Improvement Amendment (CLIA)-waived sites, such as physician offices, clinics, and urgent care settings, the regulatory approval for all sample types will be critical for wide-spread adoption. However, the requirements to validate across multiple sample types can make the expense of clinical trials prohibitive, especially if the diagnostics can detect multiple pathogens, some of which may not be very prevalent. A final example is how clinical trials will evaluate outpatient diagnostics that aim to rule out bacterial infection. Traditional trials that rely on clinical outcomes may be prohibitively expensive to developers, but could be more easily evaluated by focusing on whether antimicrobial prescription is reduced. However, these types of trials are difficult to undertake without close coordination with the FDA.

The Society is encouraged to see that the FDA will contribute its technical and regulatory expertise to the award evaluation process. IDSA urges the FDA to engage competition developers early and identify flexible regulatory strategies to surmount the regulatory barriers discussed above. We are also unsure whether the prize would be awarded before or after FDA licensure, and recommend that NIH and BARDA clarify this point as the agencies finalize the prize criteria.

A major challenge in clinical trials for new diagnostics is access to clinical samples, particularly those containing rare pathogens. Many clinical laboratories no longer freeze specimens containing novel or unusual organisms for further use. Even when such critical samples are available, the cost of accessing them has, in many cases, become prohibitive. The Antibacterial Resistance Leadership Group (ARLG), a strategic research team funded by NIAID, established a Virtual Biorepository (VB) Catalogue, a web-based system that provides researchers with unique access to clinically well-characterized bacteria for the development of diagnostic tests and other research. IDSA recommends that NIH and BARDA ensure that prize developers have access to the virtual biorepository, and that NIAID support its expansion to include additional samples.

Another key barrier is the appropriate reimbursement of tests. New diagnostics, especially those in inpatient settings that identify pathogens and their susceptibility, may be more expensive than older counterparts. These new diagnostics often use the older tests' Current Procedural Terminology (CPT) codes until they are assigned their own, and reimbursement levels for these older codes may not cover the cost of running the test, creating uncertainty for developers. IDSA recommends that NIH and BARDA engage with CMS to identify expedited solutions for the appropriate reimbursement of prize-winning diagnostics.

A final challenge is that of education so that there is appropriate use of new diagnostic tests. Rapid, point-of-care diagnostics will not reach their objective potential in combating antimicrobial resistance without additional training of healthcare personnel in the indications, test methodology, results, interpretation, and other use details of such tests. IDSA recommends that an education plan be part of this diagnostic challenge to ensure patient care workers understand the availability of these tests and their appropriate use. In addition, IDSA recommends that NIH and BARDA, perhaps in collaboration with the Agency for Healthcare Quality and Research (AHRQ) or other appropriate body, consider opportunities for outcomes studies on the prize-winning tests. Outcomes research on diagnostics tests is crucial to demonstrate to clinicians how a particular diagnostic can impact their treatment decisions and patient outcomes and therefore is vital to widespread adoption of new tests.

IDSA appreciates the opportunity to provide comments on criteria to consider for the diagnostics challenge. Novel, rapid ID diagnostics will play a crucial role in battling antimicrobial resistance and optimizing patient care, and IDSA appreciates incentives such as the diagnostics challenge that support their development. Should you have any questions or concerns about these comments, please feel free to contact Greg Frank, PhD, IDSA Program Officer for Science and Research Policy, at gfrank@idsociety.org or 703-299-1216.

Sincerely,

Stephen B. Calderwood, MD, FIDSA
IDSA President

About IDSA

IDSA represents over 10,000 infectious diseases physicians and scientists devoted to patient care, disease prevention, public health, education, and research in the area of infectious diseases. Our members care for patients of all ages with serious infections, including meningitis, pneumonia, tuberculosis, HIV/AIDS, antibiotic-resistant bacterial infections such as those caused by methicillin-resistant *Staphylococcus aureus* (MRSA) vancomycin-resistant enterococci (VRE), and Gram-negative bacterial infections such as *Acinetobacter baumannii, Klebsiella pneumoni*ae, and *Pseudomonas aeruginosa*, and, finally, emerging infectious syndromes such as Ebola virus fever, enterovirus D68 infection, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and infections caused by bacteria containing the New Delhi metallo-beta-lactamase (NDM) enzyme that makes them resistant to a broad range of antibacterial drugs.