

**United States Department of Health and Human Services
National Institutes of Health (NIH)
and
Biomedical Advanced Research and Development Authority (BARDA)**

**Public Consultation on Antimicrobial Resistance Rapid, Point-of-Care
Diagnostic Test Challenge**

**Marriott Marquis San Diego Marina Hotel
San Diego, California
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Meeting Summary

WELCOME AND MEETING OVERVIEW

Robert W. Eisinger, Ph.D., NIH

Dr. Robert Eisinger welcomed the participants. He stated that the goal of the workshop is to obtain stakeholder input regarding the technical criteria, objectives, and performance characteristics of the Antimicrobial Resistance (AMR) Rapid, Point-of-Care Diagnostic Test Challenge Prize of \$20 million (M), sponsored by the NIH and BARDA. Dr. Eisinger noted that the workshop agenda includes several presentations on the need for rapid diagnostics and the considerations for the development of such assays, two open public discussions, and a panel discussion on the focus and criteria for the Prize.

Dr. Eisinger provided the background for the workshop. In September 2014, President Obama issued Executive Order 13676 on Combating Antibiotic-Resistant Bacteria. Simultaneously, the National Strategy for Combating Antibiotic-Resistant Bacteria was released with specific goals for addressing the increasing public health threat of antibiotic-resistant microorganisms. An accompanying White House Fact Sheet called for a \$20M prize to facilitate the development of a rapid, point-of-care diagnostic test(s) for health care providers to identify highly resistant bacterial infections and to facilitate antibiotic stewardship. The Fact Sheet noted that the U.S. Department of Health and Human Services would host a public forum to obtain stakeholder input to ensure that the competition focuses on the type of diagnostic most needed by the medical and public health communities. In March 2015, the White House issued the National Action Plan for Combating Antibiotic-Resistant Bacteria with specific milestones and timeframes. Dr. Eisinger explained that the competition will be designed by NIH and BARDA, with technical and regulatory expertise from the Centers for Disease Control and Prevention (CDC) and Food and Drug Administration (FDA). A Request for Information seeking public stakeholder input for this Challenge competition was issued in June 2015.

Dr. Eisinger encouraged the participants to provide comments during the open discussion portions of the Public Consultation, as stakeholder input will be used when designing the technical criteria and performance evaluation characteristics of the diagnostic(s). He noted that the Challenge will be announced formally in early 2016, submissions will be due in the summer of 2016, and the award(s) will be announced in the summer of 2019.

RELATED EFFORTS TO SPUR DIAGNOSTICS DEVELOPMENT

Overview of the U.K. Longitude Prize and Horizon Antimicrobial Resistance Diagnostic Prize

Robert W. Eisinger, Ph.D., NIH

Dr. Eisinger highlighted two ongoing assay competitions: the U.K. Longitude Prize and the Horizon Prize. The Longitude Prize is being launched under the United Kingdom Technology Strategy Board and is being coordinated by Nesta, the United Kingdom's innovation foundation. The Longitude Prize is a challenge with a £10M prize for a diagnostic to detect antibiotic-resistant bacteria. The organizational structure includes a Longitude Prize Committee, chaired by Lord Martin Rees, and a Scientific Advisory Board. The goal of this Prize is to develop approaches to prevent the rise of resistance to antibiotics. Dr. Eisinger stated that the Longitude Prize will reward a competitor who can develop a transformative point-of-care diagnostic test that will conserve antibiotics for future generations and revolutionize the delivery of global health care. The test itself must be available to anyone, anywhere in the world, and it will serve to help health care providers determine when antibiotics should or should not be administered. The winning test must be needed, accurate, affordable, rapid, easy to use, scalable, and safe, and a prototype is required to be submitted. The selection process encompasses a 5-year timeframe, and a winner can be declared at any time before the end of 2019. Entries will be assessed every 4 months starting from the end of May 2015, which was the deadline for the first round of submissions. The first competitor who meets the criteria for the award will receive £8M, and £2M will go to the Longitude Discovery Award to stimulate early-stage innovations. Dr. Eisinger reminded the audience that the next submission end date will be in January 2016. Entries can be submitted through the participant portal from the Prize website: www.longitudeprize.org.

The Horizon Prize is being sponsored by the European Commission. The challenge is open to any single person, legal entity, or group in the European Union member states or countries associated with Horizon 2020, and the prize amount is 1M Euros (€1M). The goal is to develop a rapid test that will allow health care providers to distinguish, at the point of care, between patients with upper respiratory tract infections that require antibiotics and those that can be treated safely without them. In this context, upper respiratory tract infections include pharyngitis, sinusitis, otitis, and bronchitis. The objectives of the Prize are (1) to reduce the unnecessary use of antibiotics in upper respiratory tract infections, (2) to reduce costs and side effects associated with the use of antibiotics, (3) to delay the emergence of antibiotic-resistant organisms, (4) to enable health care providers to make early decisions in the management of upper respiratory tract infections, and (5) to tackle the widespread and significant health care issue of respiratory infections. The deadline for submissions is slated for mid-August 2016, and the winners will be announced during the last quarter of 2016. Entries can be submitted through the participant portal on the Prize website: <http://ec.europa.eu/research/horizonprize>.

Diagnostic Strategies for Addressing Antimicrobial Resistance: Emerging Insight from the Wellcome Trust

Nicholas Gertler, J.D., Galen/Atlantica

Mr. Nicholas Gertler presented diagnostic strategies for addressing antimicrobial resistance (AMR) with emerging insight from the Wellcome Trust. The Wellcome Trust, located in the United Kingdom, is a global charitable foundation dedicated to improving public health. He mentioned that discussions about ways of integrating the use and development of antibiotics and diagnostics have been the topic of a workshop organized by the NIH in 2014 and other workshops that brought together leaders in the field, including representatives from the Wellcome Trust. Mr. Gertler stressed that diagnostics are extremely helpful if they lead to a better use of therapeutics and that it would make sense to integrate diagnostics and therapeutics. His company, Galen/Atlantica, partnered with the Wellcome Trust to strategically

develop ideas and integrative thinking along these lines. The starting point in the integrative thinking process was identifying what needs to be accomplished in the infectious diseases area, in particular with respect to bacterial infections. Optimal treatment objectives are to treat the infection, minimize collateral harm to the patient, and minimize harm to society. The ultimate goal of treating an infection is to use the exact medication needed to treat a specific pathogen. This will require full integration of therapeutics and diagnostics. Mr. Gertler stated that a problem unique to bacterial infections is that the gold standard for diagnosis, the culture method, can take up to 3 days or longer for results. At present, the empirical treatment relies on physician judgment, so a patient may be treated prior to knowing the cause and susceptibility. Additionally, there appears to be a bias toward broad-spectrum coverage, which could lead to unnecessary treatment and contribute to antibiotic resistance.

Mr. Gertler further stated that methods of detection and diagnosis are needed that will more rapidly distinguish bacterial from viral upper respiratory infections. The ideal outcome is to have a system in which the source knowledge identifies the problem and drives a more accurate form of treatment. The vision and hope is to develop precision medicine for treating infections, and a transition to these efforts is necessary. The Wellcome Trust hypothesizes that: (1) there is not a single diagnostic, but several; (2) focus should be on the patient, not the technology; (3) there is a need to integrate drugs and diagnostics; and (4) this is an interdisciplinary problem. The Wellcome Trust recently sponsored a multidisciplinary workshop and brought together 50 participants, including drug developers, diagnostic developers, health system leaders, clinicians, patient advocates, and think tanks. The focus of the workshop was to aid the transition to a patient-centered approach to the integrated use and development of diagnostics and therapeutics for treating infection. Several patient presentations—which represented various aspects of the problem ranging in severity, urgency, required accuracy, and consequences of error—were reviewed to assess the role a diagnostic would play. Multiple dimensions of the patient treatment journey would influence the diagnostic profile, such as patient presentation, care setting, decision needed, key decision makers, diagnostic information needed, and the minimum diagnostic performance profile. It was concluded that the diagnostics need to be considered in the context of clinical factors, human factors, and the health system. Within the clinical context, four considerations (diagnostic typologies) emerged: avoiding unnecessary treatment (decision to not treat); optimizing patient treatment and antibiotic use (diagnostic to select antibiotic); identifying high-risk patients (diagnostic to predict host response); and improving drug development (diagnostic to support clinical trial). In closing, Mr. Gertler stated that the technological problem of developing a device is secondary to the treatment of the patient, and this should result in a more realistic and focused performance criteria. No single universal diagnostic exists, so various diagnostic strategies are needed. Stewardship, health system investment, reimbursement, and a patient-centered approach are all important for the integration of diagnostics and therapeutics.

QUESTIONS

Ms. Carole Moss, Nile's Project, shared the story of her son, Nile, who died of sepsis in 2006 within 48 hours of contracting methicillin-resistant *Staphylococcus aureus* (MRSA) at a hospital in Orange County, California. She recommended that consumers be educated about health care-associated infections, sepsis, and related events and asked whether patients in all hospitals could be screened using a rapid, affordable test, as she said is done at Veterans Affairs (VA) hospitals. Dr. Eisinger that the NIH and BARDA have supported and continue to support a number of innovative research and strategies for the development of diagnostic assay systems independent of the \$20M challenge.

Dr. Robert Sambursky, Rapid Pathogen Screening, expressed the need for a proper definition of a “clinically relevant infection” and proposed using “the presence of an antigen culture or molecular component in association with an immune response,” which he believes can categorize patients into those

who do and do not need antibiotic treatment. He also recommended shifting the focus of the prize and antimicrobial stewardship to the outpatient setting, noting that physicians need a tool that demonstrates to patients that they do not have a bacterial infection. Dr. Eisinger commented that both the National Strategy and National Action Plan for Combatting Antibiotic Resistance emphasize the need to improve the stewardship of antibiotic use and to ensure that antibiotics are being used only when necessary.

Frederic Sweeney, Ph.D., T2 Biosystems, commented that the development of a rapid test for sepsis—with a turnaround time of minutes to hours—is complicated by the need to use a blood culture, which requires 2 to 5 days for processing. Only one sepsis test, approved in September 2015, can deliver results in approximately 3 hours.

THE NEED FOR RAPID DIAGNOSTICS TO ADDRESS ANTIMICROBIAL RESISTANCE

The Importance of Antibiotic Stewardship

Robert Bonomo, M.D., Cleveland Veterans Affairs Medical Center

Dr. Robert Bonomo discussed the importance of antibiotic stewardship. The timely and accurate identification of pathogens is critical to choosing appropriate therapy and informing stewardship efforts. The discovery of unsuspected pathogens can improve decisions for therapy and illuminate disease processes. He stated that bacterial cultures are too often unrevealing. Sometimes there are useful data and treatment is started, but when there are no data, treatment options are often the same. This is the dilemma clinicians are faced with today. It is not clear how to control antibiotic use in these settings. The Infectious Diseases Society of America (IDSA) published an article in 2013 addressing this problem. Some of their recommendations were to stimulate diagnostics research and development and to expedite integration of improved diagnostics tests into patient care. Dr. Bonomo discussed the case of an elderly patient who presented with multiple problems. The patient was treated with broad-spectrum antibiotics, and the outcome was not favorable. The stewardship issues to consider with this case are that it was a high-risk patient with fever, morbidities, and a previous use of antibiotics within less than 90 days. A suspected infection was treated, but an avoidable infection developed. An ounce of prevention can truly save a life.

Dr. Bonomo emphasized that guidelines are important and, according to the IDSA, the primary goal of antimicrobial stewardship is to optimize clinical outcomes while minimizing unintended consequences. Clinicians seek effective antimicrobial stewardship, an expanded infection control program, and the ability to link point-of-care diagnostics to antibiotic stewardship. The technologies and methods that clinicians currently can use include nucleic acid amplification technology (NAAT), microarrays, and T2 magnetic resonance technology. The objective is to determine whether these methods will help with an antimicrobial stewardship program. Dr. Bonomo stated that it is time to look beyond cultures to other methods. NAAT may offer a unique advantage with hard-to-grow pathogens, provides an opportunity to target antimicrobial therapy, and could potentially change the understanding of the disease processes. It may achieve microbiological diagnoses where conventional methods cannot. Several methods for pathogen identification are available in NAAT, such as multiplex polymerase chain reaction (PCR), broad-range PCR of the 16S ribosomal RNA, and PCR coupled with electrospray ionization mass spectrometry (PCR/ESI-MS). The PCR/ESI-MS method has been shown to be efficient in detecting specific pathogens. For example, an otherwise healthy patient presented with a 1-month history of fevers, cough, and headaches, and appeared ill. Although a series of tests that included appropriate cultures were all negative, the PCR/ESI-MS detected *Fusobacterium nucleatum*. These results were verified by three modalities. This platform has been evaluated in a clinical trial setting and the sensitivity was 81 percent, the specificity was 69 percent, and the negative predictive value was 97 percent at 6 hours from sample acquisition. This is strong evidence that PCR/ESI-MS technology could potentially alter treatment and

outcomes. It also has been effective in ruling out the possibility of infection within 6 hours. PCR/ESI-MS is culture-independent, the clinician does not have to decide what to test for *a priori*, and the turnaround time is 6–8 hours.

To address the direction and future process of identification as the patient enters the hospital setting, the human and bacterial genes most relevant for therapy must first be identified. Next, correct management requires looking for host biomarkers, identifying the pathogen, and selecting the right antibiotics. Finally, genes that predict less favorable outcomes and markers that define the illness in the context of the ecology of the hospital must be identified. After a patient is admitted to the hospital, multiple complicated steps occur as the patient travels through the system. Using a screening platform also can address what pathogens the patient may be bringing into the hospital. In summary, Dr. Bonomo stressed that the best technology or platform is still the clinician's mind and the ability to integrate all the information with consideration of the entire clinical context.

Clinical Laboratory Perspectives

Robin Patel, M.D., Mayo Clinic

Dr. Robin Patel presented a clinical laboratory microbiologist's perspective. Using a systems-based approach, the ideal new microbiology test should be more affordable, more accurate, or faster than current tests. It should fit the workflow of the laboratory and should have the capability to be connected to the Laboratory Information System (LIS), as well as to the emergency room. Ultimately, the results need to be available to the people who need them. As with any test, cost is a factor. The cost could be greater in the laboratory while saving money elsewhere in the system. New technology may be better than its predecessors at identifying species of bacteria, but sometimes it may not be clinically significant. If the test is faster, it can be equally accurate but more expensive, and an assessment of the benefit would be necessary. An improved test could potentially save lives and decrease the need for hospitalization. Over the long-term, it could decrease AMR if it leads to definitive narrow-spectrum treatment. A softer endpoint to consider is reducing the spread of antibiotic resistant organisms. The key is in finding the antibiotic resistant organisms and getting patients into isolation faster. The ultimate benefit will be in preventing the spread of highly antibiotic resistant microorganisms in the broader health care system.

One newer technology is the Matrix-Assisted Laser Desorption Ionization Time-of-Flight Mass Spectrometer (MALDI TOF MS), which is more accurate, faster, and less expensive than other methods. This technology for bacterial identification is rapidly being adopted in clinical laboratories across the world. Rapid multiplex PCR test systems that can be used on a positive blood culture bottle is another example of an accurate, fast, but more expensive diagnostic method. Results can be obtained within 1 hour of identifying a positive culture. In a clinical trial designed to weigh the benefits of positive blood cultures in rapid multiplex PCR, patients were randomly assigned to either the control group, which used only the rapid test, or a group that used the rapid test with stewardship. Clinical outcomes showed no difference between the groups, but differences were observed in antibiotic utilization. Overall, the rapid test led to more judicious antibiotic use without worsening clinical outcomes. This clinical trial and study design helped the antibiotic stewardship team understand how best to use this diagnostic in routine practices. Following the clinical trial, the rapid test has been adopted into routine clinical practice at the Mayo Clinic as an add-on assay.

Dr. Patel stated that antibiotic resistance is complicated, and one diagnostic will not be adequate to solve this problem. A laboratory intending to address antibiotic resistance must consider the syndrome, the specimen type, the microorganism, and the analyte. The diagnostic test should be able to cover all of these areas. Targeted diagnostics, not a "one size fits all" model, are necessary. A spectrum of sites of care exists, including assisted living facilities, clinics, hospitals, and laboratories, but the primary site of care is the home. People are able to test themselves using various kits for some health conditions and are

accustomed to doing this in their everyday lives. In some contexts, patients may be able to test themselves to determine if they have an infection. In the case of influenza, ways to self-test are forthcoming, and treatment decisions could be reached outside of a traditional medical setting. Another important area of focus is the category of assisted living facilities and nursing homes, which are frequent sites of antibacterial resistance. Alongside the spectrum of sites of care is the spectrum of care provided. Laboratories have highly trained professional operators, but non-traditional operators also must be able to use the diagnostic properly. In summary, the ideal test has to be affordable, accurate, and fast, and it must improve outcomes. The existence of many syndromes, specimen types, microorganisms, and analytes makes the ideal of a single new diagnostic challenging to attain. Development of a diagnostic also must factor in many test performance locations and regulations issues, as well as the fact that performance may vary depending on local epidemiology.

OPEN PUBLIC DISCUSSION OF THE OBJECTIVES AND POTENTIAL CRITERIA FOR THE NIH/BARDA ANTIMICROBIAL RESISTANCE DIAGNOSTIC CHALLENGE

Moderators: *Ann Eakin, Ph.D., NIH; Rosemary Humes, M.S., MT(ASCP) SM, BARDA*

Dr. Fred Tenover, Cepheid, asked whether institutions are likely to consider a difference in antibiotic usage to be enough to justify the implementation and use of a rapid test. Dr. Robin Patel replied that it is up to individual institutions to value the differences in antibiotic use in addition to patient outcomes. Mayo's infectious diseases clinical practice committee had sufficient buy-in to justify use of the test, although there were some caveats, such as rationing PCR testing of positive blood cultures.

Dr. Barry Eisenstein, Merck, asked about the steps being taken to determine the true value of antibiotic stewardship from a public health epidemiology standpoint, in terms of decreasing the emergence of AMR in the community and nationally. Dr. Robin Patel responded that preventing breeding and spreading resistance in a hospital or health care system involves a number of players, including the laboratory; an infection, prevention, and control team; and a stewardship team. Dr. Jean Patel, CDC, said that CDC would consider a decrease in antibiotic use as a positive step toward decreasing AMR, although she acknowledged that it will take several such steps to reduce the number of infections caused by antibiotic resistant microorganisms. She noted that Dr. Eisenstein pointed out that infection control diagnostics are important for decreasing AMR and preventing transmission.

Dr. Bonomo stressed the importance of outcomes from the patient's perspective. He stated that it is not enough for technologies to help health care providers identify infections that previously could not be identified; they also must change clinical practice. Dr. Robin Patel agreed and stated that such factors as ordering, running, and reporting results of the test are important as new diagnostics are introduced. She describes this as stewardship of laboratory tests, or "test utilization."

Dr. Linda Miller, GlaxoSmithKline, requested additional information about the de-escalation of antibiotics in Dr. Robin Patel's study. Dr. Patel stated that potential clinician concerns may have included a lack of trust in the result, the possibility that the patient has a pathogen that has not yet been detected, or the psychological component of potentially harming the patient by de-escalating treatment to a more targeted antibiotic. Dr. Bonomo added that the use of host biomarkers could be helpful and that integrating multiple types of data could help clinicians make a better decision.

Dr. Miller posed a question about whether the AMR Diagnostic Challenge should incorporate appropriate utilization, that is, an evaluation of how the diagnostic will fit into the health care system. Dr. Robin Patel said that the diagnostic that wins the Prize ideally would be rapid, accurate, and actionable. Dr. Bonomo emphasized the importance of finding the pathogen and understanding its clinical relevance, e.g., differentiate colonization from infection.

Ms. Moss asked Dr. Bonomo whether patients at VA hospitals are screened before they are admitted and, if so, which rapid test is used. Dr. Bonomo stated that the VA uses the Becton Dickinson platform to screen for MRSA in high-risk populations. Ms. Moss commented on the importance of educating the public about MRSA and the availability of rapid testing.

Dr. Randall Kincaid, NIH, inquired about the significance of variability in positive predictive value (test performance relative to disease prevalence) when considering the potential utility of a new diagnostic. Dr. Robin Patel recommended that each hospital or clinic examine its own population to see which patients may be at higher risk and need to undergo a given test. She also noted the importance of the context—that is, assessing whether the purpose of the screening is to know whether the patient has a pathogen or whether the pathogen exists in the health care setting. Dr. Bonomo pointed out that many areas have unique needs, e.g., community needs, population needs, special interests needs.

Dr. Steve Gitterman, FDA, asked whether any decision analysis mathematical models exist that could help the AMR Diagnostic Challenge Working Group compare the effect of diagnostic tests. Dr. Robin Patel replied that the cost-effectiveness factors that were evaluated in the study she conducted included the cost to the laboratory, the overall cost of care per patient during that hospitalization, and a comparison of the overall cost of care for patients in each of the three groups. She added that a consideration of the payers also is germane to the issue. Dr. Gitterman noted that if multiple prizes were being considered for the AMR Diagnostic Challenge Competition, one possibility could be having one test with superior sensitivity and the other with superior specificity.

Dr. Miller proposed that the AMR Diagnostic Challenge Working Group identify, as a first step, a small number of potential target clinical scenarios on which to have the largest impact. Dr. Bonomo noted the importance of this idea, but commented that a prize for outpatient antibiotics would run into issues of comparison and metrics. He proposed a platform with the versatility to benefit both community- and hospital-based health care settings, although he noted the difficulty in defining and identifying the pathogen in such illnesses as pneumonia. Dr. Jean Patel recommended that the Prize's specific impact be the reduction of overall antibiotic use. Dr. David Ecker, Ibis Biosciences, suggested that AMR Diagnostic Challenge prize applicants be required to make the business case for their diagnostic. Another meeting participant seconded the idea that a diagnostic test be shown to be commercially viable and adoptable. Mr. Gertler noted that the skillset required to develop the business case for a diagnostic differs from the skillset required to develop the diagnostic and having such a requirement may unduly burden entrants in this Challenge competition.

Dr. Andrew Tomaras, BacterioScan, stated that there is a need for an effective diagnostic to be more prescriptive about the course of action. In the context of the Prize, a 30-minute timeframe brings certain restrictions in terms of phenotypic versus genotypic information. Dr. Robin Patel said that the Prize should not specify which type of diagnostic to use (e.g., molecular technologies, DNA, RNA, proteins, antibodies), but the test has to produce an actionable result that leads to a beneficial and desired outcome. Dr. Bonomo added that clinicians must accept that even current phenotypic susceptibility testing has limitations.

Ms. Moss asked if other countries have diagnostic tests that come close to meeting the requirements that the AMR Diagnostic Challenge Competition is seeking in early diagnostics. Dr. Jonathan Cabardo responded that some tests in the Philippines can be performed within 15 minutes, in part because of fewer government regulations regarding testing.

Ms. Moss asked whether the AMR Diagnostic Challenge Competition takes into consideration the environment (e.g., hospitals, health care settings, food sources). Dr. Eakin responded that environmental

testing is not a focus of the NIH-BARDA AMR Diagnostic Challenge, but the broader Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (CARB) strategy does include the environment and non-health-specific applications of potential diagnostics. Dr. Bonomo added that it would be helpful to have a platform that also could be used in such applications as veterinary medicine, agriculture, environmental infection control, and daycare settings. Ms. Moss also recommended noninvasive verification along U.S. borders using a rapid test.

Dr. Miller recommended that the AMR Diagnostic Challenge Working Group develop a clear description of the goal that the Challenge will strive to meet. She encouraged the committee to take a holistic view and consider whether the goal will be to develop a platform that can detect pathogens quickly and cheaply or one that can make a difference in a specific clinical scenario. Dr. Robin Patel agreed that many syndromes exist that need improved diagnostic testing. She acknowledged that pneumonia, for example, will be challenging to tackle. Dr. Patel commented that integrating artificial intelligence data with a diagnostic is an interesting possibility.

Ms. Moss recommended implementing a national certification requirement to ensure that health care workers who interact with patients have appropriate knowledge and receive adequate training.

PRAGMATIC CONSIDERATIONS FOR THE DEVELOPMENT OF RAPID DIAGNOSTICS

Diagnostic Developer Perspective

Fred Tenover, Ph.D., Cepheid

Dr. Fred Tenover presented on issues from a diagnostic industry perspective. He compiled his talk by engaging the thoughts and opinions of colleagues in the industry and others outside the industry regarding their views on rapid diagnostics and the AMR Diagnostic Challenge. Some of the companies whose views are represented include Alere, Becton Dickinson (BD), BioMérieux, Cepheid, Roche, and T2 Biosystems. Several initiatives, such as the Prize to recognize the importance of novel diagnostics, the National Action Plan, the President's AMR agenda, the World Health Organization, and the IDSA, all have an emphasis on better diagnostics, yet representatives from the diagnostics industry have had limited representation on critical advisory boards. The diagnostic industry recommends that the funding be geared toward the development of a novel assay platform capable of detecting bacteria, viruses, fungi, parasites, and host response biomarkers indicative of infection in order to differentiate between patients with and without infections. The platform should be required to detect nucleic acids and proteins. A majority of the results should be available in less than 30 minutes, the regulatory path for clearance should be expedited, and the assay should have reimbursement in place at the time of clearance for use in any health care setting.

He noted that many of the established diagnostic companies in the United States have their own 5-year strategic plans already in place, thus the AMR Diagnostic Challenge prize would not be an incentive for them to change their developmental strategies. However, this prize will be a potential incentive to smaller companies that could benefit from a large infusion of capital. It is important to note that the smaller companies typically have neither the infrastructure to carry out clinical trials of sufficient size for FDA approval/clearance nor the ability to scale up for sustainable manufacturing and commercialization. The AMR Diagnostic Challenge competition may lead to new partnerships between smaller diagnostic companies that can be nimble and reorient their direction to meet the goals of this competition and established companies that can provide the infrastructure for clinical trials and commercialization. The pharmaceutical industry has a proven record of forming partnerships between established and smaller companies to bring novel molecules to market, and the diagnostics industry can learn from this example.

Dr. Tenover suggested that the awarding of the AMR Diagnostic Challenge prize be considered in a two-tiered system. First, to ensure a successful return on investment, at least one prize should be reserved for a test that can be readily implemented in U.S. laboratories and requires FDA approval/clearance. A second prize(s) may be for promising novel technologies that are not yet FDA cleared, but for which some clinical and analytical data are available to indicate likely success. Additionally, two types of tests would be valuable to optimize the prescription of antimicrobial agents in both inpatient and outpatient settings. Most antimicrobial agents are prescribed in the outpatient setting. Therefore, rapid tests differentiating among bacterial, fungal, and viral infections, including key antimicrobial resistance genes, and performed directly on clinical samples could improve antimicrobial prescribing. Inclusion of biomarkers indicative of infection would be highly encouraged, and sample type should not be limited. More drug-resistant strains are found in the inpatient setting. To improve outcomes within the inpatient setting, a diagnostic test needs to rapidly detect key pathogens and host response markers to confirm infection directly on blood, respiratory, urine, or pus samples. This may be accomplished by using 200–300 target microarrays or multi-microwell formats, by next-generation sequencing, or by other novel technologies for multianalyte detection. Although some resistance phenotypes, such as those mediated by porin changes and efflux systems, may be missed if using the nucleic acid-based test, it would be a dramatic improvement over the slow phenotypic assays currently in use for guiding therapy for critically ill patients. The presence of a resistance gene has relatively good predictive value, but the absence of it is not predictive.

In the clinical context, the time to result should be less than 90 minutes for inpatient testing and less than 30 minutes for outpatient or emergency department testing, where the patient is waiting for results or may need to be treated quickly. There should be minimal sample processing in outpatient testing in order to keep complexity low and to ensure ease of use. For inpatient testing, it is strongly suggested that the assay design incorporate the capability to be linked to an LIS.

Ease of use is a critical factor for diagnostics. Tests should be Clinical Laboratory Improvement Amendment (CLIA)-waived or moderately complex to allow broad use in multiple settings. Ease of use should require the inclusion of internal or external controls, or a combination of both, to facilitate implementation. Ease of use also should include ease of interpretation—the results should be readily understandable by physicians.

As previously stated, there is no one-size-fits-all answer to the performance characteristics of a rapid diagnostic test. A high negative predictive value is needed for ruling out bacterial infections, and a high positive predictive value is needed for identifying antimicrobial resistance markers. A rapid result with high sensitivity and specificity still would have tremendous impact if the actual values are greater than 95 percent sensitivity or 99 percent specificity, especially in inpatient settings where one could effectively rule out a disease.

The cost will vary dramatically with complexity. A 15-minute CLIA-waived test for respiratory pathogens will be less costly to develop and manufacture than a 200-test microarray that identifies multiple bacteria and resistance genes directly in blood samples. The AMR Diagnostic Challenge competition should be open to all technologies. Placing restrictions on the cost of an assay would not be prudent at this point. For example, a \$100 assay that reduces the length of hospital stay by 5 days, reduces additional diagnostic testing (e.g., MRIs, bronchoscopies), and allows de-escalation of antibiotics may seem expensive by relative standards for a microbiology laboratory, but it has the potential to save \$25,000 in patient care costs. Designating a price range for the end product up front may discourage diagnostic developers that may have very creative ideas for assays.

Dr. Tenover stated that the diagnostic industry suggests that a streamlined regulatory pathway is one of the most important factors to consider when awarding the AMR Diagnostic Challenge prize(s). The FDA,

to its credit, has developed novel and innovative strategies to improve clinical trials for antimicrobial agents, but this is not the case for diagnostics. Streamlined pathways should be developed to facilitate moving novel diagnostics into clinical use more quickly. The FDA could partner with the diagnostics industry to develop updated clinical trial strategies and approval pathways for diagnostics. Additional needs include flexibility in the FDA approval process, streamlining the regulatory pathway, and reimbursement strategies.

In conclusion, Dr. Tenover stressed that the AMR Diagnostic Challenge prize(s) should focus on innovative ways to improve antimicrobial prescribing in both inpatient and outpatient settings. At least one prize should be awarded after FDA clearance/approval to ensure a reasonable return on the government's investment. Using host response markers to differentiate between infectious and non-infectious processes is highly encouraged as a complement to detecting pathogenic microorganisms directly in clinical samples. The FDA should be encouraged to consider novel regulatory pathways to speed these innovations into clinical use. He stated that novel reimbursement strategies should accompany this award to promote rather than prohibit broad adoption of the new assays.

Therapeutic Developer/Clinical Trial Perspectives

Barry Eisenstein, M.D., Merck

Dr. Barry Eisenstein presented the therapeutic industry's perspective on better diagnostics for both developing and using antibiotics for resistant bacteria. Infections are a public health problem and, according to data from the CDC, are the third most common cause of death in the United States. A 2014 global review of AMR by economist Jim O'Neill entitled, "Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations," states that infections are the second most common cause of death in the world. The number of deaths worldwide that will be attributed to AMR is estimated to increase from 700,000 to 10 million by the year 2050, with a cumulative economic impact of \$100 trillion. According to the O'Neill report, the continents most affected by AMR are Asia and Africa, but the impact is not restricted to any particular region. Resistance is on the rise in areas where 70 percent of hospital-acquired infections are caused by bacteria that are resistant to at least 1 percent of antimicrobials. For example, Carbapenem-resistant *Acinetobacter* is well-distributed throughout the United States; it represented approximately 5 percent of infections in 2000 and had increased to 40 percent by the year 2009. This increase is seen globally as well. Using data from three clinical studies, it has been shown that adverse outcomes are associated with antibiotic resistance. The mortality and length of hospital stay increased significantly in patients infected with antibiotic-resistant organisms. Dr. Eisenstein quoted Dr. Margaret Chen, Director General, World Health Organization: "A post-antibiotic era means, in effect, an end to modern medicine as we know it. Things as common as strep throat or a child's scratched knee could once again kill. Some sophisticated interventions, like hip replacements, organ transplants, cancer chemotherapy, and care of preterm infants would become far more difficult or even too dangerous to undertake." He noted that the general press has been reporting on the health concerns of AMR.

For more than 15 years, the FDA has commented that therapeutic options for resistant infections are its highest priority. Tremendous barriers to developing new antibiotics include the costs of bringing a new drug to market, reduced market potential, regulatory uncertainty, and a failure of research to discover new molecules. Additionally, during the past 20 years, several companies have halted or substantially reduced their anti-infective discovery efforts. Antibiotic development has fallen victim to market failure, and such large companies as Pfizer, Merck, and GlaxoSmithKline would rather invest in disease research, which has greater returns on investment than antibiotic research. The number of antibacterial therapeutics being FDA-approved dropped significantly between 1995 and 2015, with an 8-year gap during which there were no approvals. Dr. Eisenstein has been involved in a group effort to work with the FDA to develop a more streamlined approach for the highly antibiotic resistant microorganisms.

Moving to the role of diagnostics in antibiotic development and optimized use, Dr. Eisenstein cited a 2014 National Public Radio “Your Health” segment that suggested that antibiotics are being prescribed in children twice as often as needed. However, because pneumonia is the leading cause of death in children worldwide, caution is needed not to underestimate children’s need for antibiotics. The need for a diagnostic that will be able to distinguish between infected versus non-infected patients and bacterial versus viral infections is still paramount. The U.K. Longitude Prize and Horizon Prize competitions both identify similar criteria for entry evaluation, including the ability to differentiate between bacterial and viral infections, distinguish between bacterial classes, specify the resistance profile and antibiotic susceptibility, and be used at the point of care. This issue is being considered by multiple stakeholders throughout the world. Bacterial infections create unique challenges for integrating diagnostic results into treatment decisions. In sepsis, for example, the risk of death increases rapidly without the appropriate antibiotic treatment, but not all infections require immediate treatment. One would argue that a single diagnostic is not the answer, and that the answer depends on the clinical situation.

The economic interests of various stakeholders need to be united to realize system-level benefits to hospitals and payers. Quick and appropriate antibiotic use leads to lower mortality rates, shorter hospital stays, and decreased costs. Conversely, appropriate antibiotic restriction has profound environmental benefits and reduces the emergence of antimicrobial resistance. Using the right drug at the right time for the right duration is the true meaning of “antibiotic stewardship.” Appropriate antibiotics and related diagnostics should be considered for reimbursement based on the value each offers the system.

Biosensor technology appears to be available for application in many ways. One can envision the ability to connect the sensor to a smartphone and upload the diagnostic results to obtain treatment options. The real problem will be integrating the technology into an efficient system. With this in mind, a company like Merck could consider how best to develop antibiotics with the appropriate diagnostic using a new proposed model. A multi-pronged strategy would include targeted agents, value captured by innovators, high access to innovation, treatment decisions primarily driven by patient outcomes, high alignment of stewardship goals with a novel product pricing paradigm, and a reliance on precision medicine.

In closing, Dr. Eisenstein commented that this problem is not a chronic condition linked to a specific area of the body. It is a worldwide problem, and infections can happen to anyone, anywhere, at any time.

OPEN PUBLIC DISCUSSION ON APPROPRIATE TRANSLATIONAL REQUIREMENTS FOR THE NIH/BARDA ANTIMICROBIAL RESISTANCE DIAGNOSTIC CHALLENGE

Moderators: *Rosemary Humes, M.S., MT(ASCP) SM, BARDA; Randall Kincaid, Ph.D., NIH*

Dr. Gitterman voiced concern about the possibility of structuring the AMR Diagnostic Challenge to offer multiple prizes for different outcomes. He questioned whether this would offer applicants enough incentive. Dr. Eisenstein agreed that prioritizing what is needed on the diagnostic side is important. Dr. Tenover said that if FDA clearance or approval is not the ultimate goal for the AMR Diagnostic Challenge prize, then it will be a challenge to ensure that the technology being funded will be implementable in U.S. laboratories so that it can make a difference. One way to ensure that the government’s investment will yield a return is to divide the prize into a few smaller awards. Although Dr. Gitterman commented that this will reduce the dollar amount of the incentive to accomplish the goal, Dr. Tenover responded that even \$10M still is a significant investment and sufficient incentive for smaller companies to reorient.

Dr. Ecker asked how to convince senior management to invest in research and development simply because of the possibility of winning \$20M in 2019. He added that if the overall impact on humanity, costs, and mortality is as high as is being estimated, then business barriers to investment must be

alleviated. Dr. Tenover agreed, stressing the need to hasten both the ability to generate a result and the ability to put it in the hands of people who can use it.

Dr. Sung Lin, Specific Technologies, offered the perspective of a startup company and recommended that the prize not impose limitations (e.g., a 30-minute turnaround time) and be open to all technologies that can benefit society.

Dr. Bonomo wondered whether the FDA should allow the fast-tracking of variation detection, because many genes and biomarkers have biological variation that is constantly evolving and affecting clinical syndromes. Dr. Tenover acknowledged that this has been an issue for MRSA and Carbapenem-resistance and recommended building in redundancy to try to stay ahead of the drift in the genetic sequences.

Dr. Sambursky recommended breaking the AMR Diagnostic Challenge prize into two \$10M awards, one targeting inpatient settings and the other targeting outpatient settings. Inpatient settings require a more selective and robust platform focusing on pathogen identification, whereas outpatient settings need an inexpensive triaging platform. Dr. Sambursky said that separating the Prize into these categories would have the most appropriate benefit to both diagnostic companies and patients.

Dr. Sweeney asked about ideas for working more concretely with diagnostic developers, as it is not uncommon for an antimicrobial developer to have 50 to 100 sites globally. Dr. Eisenstein explained that there may be an approach for the development of companion diagnostics, as the FDA has allowed the use of not-yet-approved diagnostics in some clinical trials. Dr. Gitterman corroborated Dr. Eisenstein's statement, though also noting that clinical drug development is slow relative to development in the diagnostics industry.

Dr. Ecker asked about enrichment in clinical trials and how to count patients who have negative cultures, but who show evidence of disease by molecular methods. Dr. Eisenstein said that this test is being used primarily for screening to enrich the sample. Dr. Bonomo explained the term "salvage microbiology," which refers to the detection of DNA evidence of disease in patients with negative cultures. He hypothesized that there is a biological reason that nine out of 10 cultures at most clinical biology laboratories are negative—that it may be driven by the host response.

PANEL DISCUSSION: FOCUS AND CRITERIA FOR THE ANTIMICROBIAL RESISTANCE DIAGNOSTIC CHALLENGE PRIZE

Moderator: *Randall Kincaid, Ph.D., NIH*

Panelists: *Sara Cosgrove, M.D., M.S., Johns Hopkins University; Arjun Srinivasan, M.D., CDC; Linda Miller, Ph.D., GlaxoSmithKline; Theoklis Zaoutis, M.D., MSCE, Children's Hospital of Philadelphia; and Frederic Sweeney, Ph.D., T2 Biosystems*

Dr. Kincaid invited the panelists to share their priorities and perspectives on the preferred intended use for a rapid diagnostic and specifically to address the most significant impact that such a diagnostic may make.

Dr. Sara Cosgrove described two areas in the outpatient setting with active struggles. The first is the diagnosis and treatment of gonorrhea since Ciprofloxacin was removed as a treatment option from guidelines because a small portion of people are resistant. Dr. Cosgrove recommended the development of a rapid test that could provide phenotypic results for quinolone susceptibility. The second area is acute pyelonephritis, with which many women arrive at the emergency department. Many emergency departments have removed Bactrim and quinolones from treatment guidelines; a rapid phenotypic test would help with more timely, targeted treatment of these patients.

Dr. Cosgrove commented that the Johns Hopkins Hospital has experience with its own rapid test for gram-positive bacteria in blood. Despite the simplicity of the test, the antibiotic stewardship program has had to make a “cheat sheet” for health care workers to understand the microbiology of each pathogen and which therapeutics can be used to treat it. Dr. Cosgrove believes that a rapid test for gram-negative bacteria would be of high value. She noted that the priority for a “rapid” diagnostic is the 6–12 hours after an initial antibiotic dose in a hospital setting, rather than a 30-minute turnaround time.

Dr. Arjun Srinivasan expressed support for new diagnostic tests that are not necessarily rapid, point-of-care tests, but that have their primary application in the infection control arena. Diagnostic tests that are not being used primarily for patient care decisions, such as MRSA nasal swabs, have had very significant effects on infection control. Dr. Srinivasan also recommended being open to the development and use of more complex diagnostics, such as sequence-based tests, the results of which may not be clear-cut but could be useful when properly interpreted by stewardship committees. He also emphasized the need for education about diagnostic stewardship.

Dr. Miller stressed the need to distinguish between diagnostics for inpatients and those for outpatients and noted that pneumonia and urinary tract infections are particularly challenging areas. She reiterated the point that new diagnostics and advances in precision medicine will result in some tradeoffs and mistakes, and the need to address diagnostics for patients requiring complex management decisions (antibiotics, immunomodulators, comorbidities, and microbiome disruption). Overall, better diagnostics will improve health care. Dr. Miller also pointed out that new biomarkers—completely different analytes—are needed; the host is critical. From the perspective of a pharmaceutical company, Dr. Miller said that it is challenging to put a diagnostic into use as part of a clinical trial, which is why companies like to know as early as possible which diagnostic test is needed for clinical trials and for a drug to be used. For new antibiotics, new business models are needed. It must make sense for diagnostics companies to produce these tests.

Dr. Theoklis Zaoutis identified considerations regarding diagnostic tests as they relate to children. One unique issue pertaining to children is the volume of specimens, which clearly may be different in children than adults, especially in blood-based assays. In addition, based on previous biomarker tests that have been used in children, it is known that the test characteristics and performance may differ. Dr. Zaoutis said that outpatient pediatrics accounts for a significant amount of the antibiotic prescriptions nationally, and the majority of those are for upper respiratory tract infections for which antibiotics are not indicated. He commented on the threshold of performance that would change the decision-making process, tipping a pediatrician from prescribing antibiotics to not prescribing them. He wondered whether more qualitative research is needed or whether this question needs to be part of the design of such an assay to engage the end user in the decision. He also indicated that the socio-cultural factors that play a role in prescribing antibiotics may be underestimated.

Dr. Fred Sweeney shared his perspective as a diagnostics developer. He stated that combating AMR is a major problem for a modest AMR Diagnostic Challenge prize. He noted that this prize competition is a significant step forward, but the industry as a whole could benefit from many more such prizes. He suggested breaking the antimicrobial resistance issue into multiple smaller problems (e.g., how to solve sepsis or pneumonia in the context of AMR), adding that the answers to these smaller questions probably are very different from one another. He posed a question about the costs and benefits of shifting a diagnostic development team’s focus and strategic planning to such a large degree. Dr. Sweeney added that understanding the workflow is important. One challenge facing all diagnostics developers is how to fit the diagnostic into the workflow and be cost-effective on the back end.

Dr. Tenover commented on the importance of genotyping. He stated that clinicians using old Clinical Laboratory Standards Institute break points for Carbapenems probably are grossly undertreating many people. Dr. Tenover pointed out that there never has been a controlled trial of genotype versus phenotype. He said that the predictive value of a resistant phenotypic test is pretty high, whereas the predictive value of a susceptible phenotypic test is dubious at best, depending on host factors. In developing the AMR Diagnostic Challenge competition, Dr. Tenover recommends performing a phenotypic versus genotypic outcomes study. He has learned from speaking with clinicians for 30 years that clinicians consider a phenotype to be 100 percent sensitive and specific, and it is rarely doubted. He suggests that it is time to conduct a controlled study. Dr. Bonomo added that there are at least 500 cases in literature in which scientists have studied the presence of the *Klebsiella pneumoniae* carbapenemase (KPC) gene and the minimum inhibitory concentration (MIC). He recommends integrating these data to make logical deductions based on high MIC genotype levels. Dr. Cosgrove said that it is challenging for health care providers to understand genotype results for gram-negative bacteria. From a hospital epidemiology and public health standpoint, genotypic and phenotypic data are incredibly important.

Dr. Shaun Yang, University of California, Los Angeles, commented that the microbe population is highly heterogeneous. The phenotypic test provides results for only 99 percent of the population; it is important for the molecular test to take this into consideration. Dr. Srinivasan acknowledged that there is always a role for both genotypic and phenotypic tests and that no single test will replace all of the tests that are already in existence. A meeting participant added that because of some silent mutations in genotypes, that genotypes, phenotypes, and cultures are all important. Dr. Cosgrove noted that genotype testing alone helps with escalation, whereas she also would like to be able to de-escalate early, so it helps to know as much as possible about susceptibility to narrower agents.

Dr. Kincaid described the developer's crosscutting dilemma of finding the proper value proposition, which is linked to the ability of the physician community to adopt a practice and the ability and willingness of hospital administrators to implement processes recommended by physicians and advisory groups. He invited the panelists to identify relevant drivers and recommend how the AMR Diagnostic Challenge Working Group could align the criteria of this solicitation to attract diagnostics that could meet those expectations.

Dr. Cosgrove reflected on how the clinical microbiology field has moved forward to this point and wondered how to persuade others that the ideas being discussed are the future of the field. She added that rapid diagnostics for more than just bacteremia are needed. Dr. Miller emphasized the importance of generating data that demonstrate that a given diagnostic has clinical impact on patients or hospitals. Dr. Zaoutis remarked that inherent in the idea of value proposition, which is the equation of quality over cost, is that both quality and cost are drivers. For quality specifically, metrics and outcomes are needed.

Dr. Sweeney commented on the mismatch around expectations versus stage of development and explained that diagnostic developers place a large amount of value in early adopters who believe in the technology. He said that selling to a stewardship committee is more difficult because each member has his or her own requirements, so it becomes a difficult value proposition. Sometimes a technical approach is effective, but most of the time it is a value-based proposition. Dr. Miller recommended that the AMR Diagnostic Challenge Working Group consider the inpatient and outpatient settings separately. For example, in inpatient therapies and serious infections where there are issues around escalation and de-escalation, the cost of diagnostics and characteristics will be very different. She added that host response detection is critical. Dr. Sweeney agreed that inpatient and outpatient settings are very different, with different requirements, turnaround times, and levels of ease of use, among other differences.

Dr. Kincaid stated that the technology exists to develop many of the types of tests that have been discussed, but that the challenge lies in crafting a package of opportunities that both inspire innovators

and reward them for their efforts. He acknowledged that it is not a small task to ask anyone to work at risk. Dr. Kincaid felt that there was a general consensus that the AMR Diagnostic Challenge Working Group needs to distinguish between the diagnostic needs of inpatient and outpatient communities and that the additional value that can be harvested through capturing both host and pathogen data could be remarkably important and drive the adoption of new diagnostics that reflect disease conditions.

Ms. Rosemary Humes commented that the topic of host biomarkers arose repeatedly throughout the day. She wondered whether a new test that focused only on host biomarkers and that could be used in conjunction with existing bacterial susceptibility testing or genetic marker testing would be of interest. Dr. Cosgrove responded positively, highlighting the example of stark differences in procalcitonin use, which depends on how much effort an individual is willing to put into its stewardship. Dr. Srinivasan added that any additional piece of information that helps overcome diagnostic uncertainty is useful. Dr. Miller stated it would be transformational to have all of these in a single test.

Dr. Miller pointed out that the U.K. Longitude Prize began offering small seed grants to promising technologies, having recognized that some companies do not have sufficient funding to get started. She recommended that the AMR Diagnostic Challenge Working Group also consider this idea.

SUMMARY AND NEXT STEPS

Robert W. Eisinger, Ph.D., NIH

Dr. Eisinger expressed his appreciation to all of the attendees for their participation and informative comments at this public consultation, which he noted is an important part of obtaining stakeholder input for developing the design parameters for this AMR Diagnostic Challenge competition. In designing the competition, the AMR Diagnostic Challenge Working Group will take into account the input from this meeting and the responses to the Request for Information issued in June and the recent Request for Comments issued in September. Dr. Eisinger reiterated that the AMR Diagnostic Challenge competition will be announced in early 2016 with notices in the *Federal Register*, *NIH Guide for Grants and Contracts*, and on the challenge.gov website. Submissions for this challenge competition will be due in the summer of 2016; and the award(s) will be announced in the summer of 2019.

Dr. Eisinger thanked the presenters and panelists; his colleagues from BARDA, NIH, FDA, and CDC; and all of the meeting participants. The meeting was then adjourned at 3:30pm PDT.

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
BIOMEDICAL ADVANCED RESEARCH AND DEVELOPMENT AUTHORITY**

**PUBLIC CONSULTATION ON ANTIMICROBIAL RESISTANCE
RAPID, POINT-OF-CARE DIAGNOSTIC TEST CHALLENGE**

*October 7, 2015
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