Precision Medicine in Infectious Diseases: *Changing the treatment paradigm for bacterial infections to end the Antimicrobial Resistance Crisis.*

by Linda Federici Miller Ph.D and Marielena Mata Ph.D

Precision medicine is often associated with oncology where the ability to screen and select patients based on a particular mutation is critical for use and efficacy of many new cancer drugs. Technologies and innovations in diagnostic devices have advanced to the stage where the methodology, accuracy, and clinical relevance of the test results make them feasible for use in a clinical setting in oncology. Yet the definition of Precision Medicine – the right medicine at the right dose for the right patient at the right time – encompasses so much more than just finding the somatic mutation target of a new cancer drug. With the increase in antibacterial agent resistance and a decreasing antibacterial pipeline, there is a need for coordinated efforts to promote appropriate use of antibacterial agents. Such "antibacterial agent stewardship" measures encourage the appropriate use of antimicrobials by promoting the selection of the optimal drug regimen. Clearly, this sounds an awful lot like the Precision Medicine 'right drug at the right dose for the right patient at the right time'. Precision Medicine can help solve the crisis of antimicrobial resistance (AMR) by changing the way antibacterial agents are developed and prescribed.

Why Precision Medicine is Needed in Infectious Disease Therapy

One of the greatest medical advances of the last century was the discovery and development of antibacterial agents – beginning with sulfa drugs and penicillin, to treat bacterial infections. Antibacterial agents have saved lives, decreased mortality and allowed advances in modern medicine such as transplants, heart surgery and chemotherapy. While it was recognized, even as early as the time of Alexander Fleming, that bacteria would evolve resistance to antibacterial agents, and Fleming himself warned of resistance development, (1) the benefits to individual patients were seen as outweighing concerns over "potential" problems with resistance in the future. Indeed, as time passed and new antibacterial agents were developed, there was a belief that even if resistance did develop, there would always be a new antibacterial agent developed to solve the problem. The result of these beliefs has led to a "tragedy of the commons" where the benefits to individuals outweighed the benefits to present and future societies and resulted in a severe drain of our "limited" antibacterial agent resource. (See Figure 1)

The belief in a never ending pipeline of new antimicrobial agents was ill-conceived. For multiple reasons, the antibacterial agent pipeline has slowed to a trickle, and while new global efforts to solve the problem have started to spur development, the world is on the verge of a potential crisis and faces a major medical challenge that may prove insurmountable. Multiple global health organizations and governments have been sounding the alarm for years. In a comprehensive report, the CDC identified "urgent", "serious" and "concerning" threats in order to help set objectives for solutions (2) (See Figure 2). The key to preventing the crisis are rapid, inexpensive, accurate, simple, Point of Care diagnostics for bacterial infections.

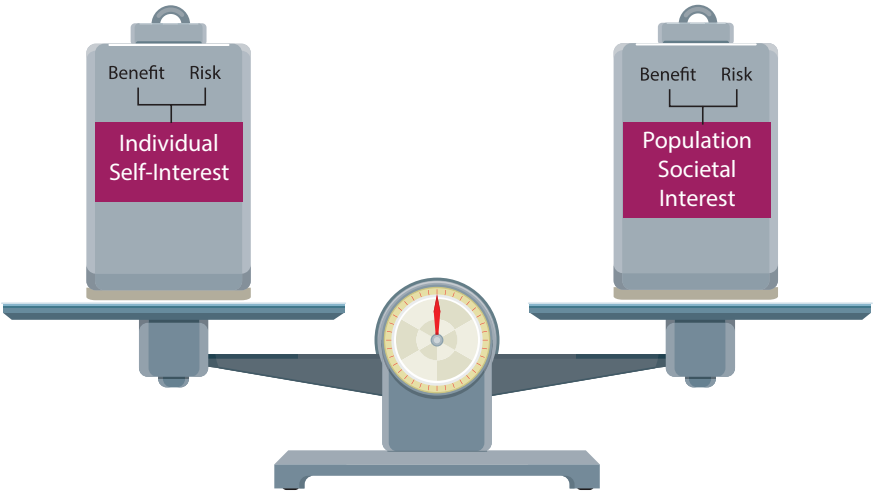

FIGURE 1. Appropriate Antibacterial Prescribing is a Balance.

Unlike oncology or even some infectious diseases, serious bacterial infections need to be treated rapidly to maximize patient chance of survival. In some infections, such as ventilator associated pneumonia and sepsis, and in certain critical situations, even minutes matter. In the absence of rapid diagnostics, empiric therapy, based on an "educated guess" as to the causative agent of the infection, has become the standard of care. While empiric therapy paradigms have saved many lives, decreased mortality and enabled advances in modern medicine such as transplants, heart surgery, and chemotherapy, there are trade-offs (i.e. both benefits and costs) – both to patients and society of empiric therapy. Alternatively, while a Precision Medicine approach to treating bacterial infections is appealing, it will likely result in less antibacterial agent use and help extend

HAZARD LEVEL: **URGENT**

Carbapenem-resistant Enterobacteriaceae
Drug-resistant *Neisseria gonorrhoeae*
Clostridium difficile

HAZARD LEVEL: **SERIOUS**

Multidrug-resistant *Acinetobacter* species; Multidrug-resistant Enterobacteriaceae; Multidrug-resistant *P. aeruginosa*; Drug-resistant *Salmonella* & *Shigella*; MRSA; Drug-resistant S. *pneumoniae*; Drug-resistant TB; Drug-resistant *Campylobacter*; Vancomycin-resistant *Enterococcus* (VRE)

HAZARD LEVEL: **CONCERNING**

Vancomycin-resistant S.*aureus*; Erythromycin-resistant Group A *Streptococcus*; Clindamycin-resistant Group B *Streptococcus*

From the Center for Disease Control and Prevention.
Antibiotic Resistance Threats in the United States. 2013.
http://www.cdc.gov/drugresistance/threat-report-2013/

FIGURE 2. Antimicrobial Resistance Threats Identified by the CDC

the life of these drugs. There are trade-offs to a Precision Medicine approach as well, such as delays in diagnosis and therapy and/or false positive/negative results, etc. (See Figures 3a and 3b)

While the trade-offs to a Precision Medicine paradigm of prescribing must be addressed, primarily by improving the quality and feasibility of diagnostics to be used, the evidence of costs of continued empiric therapy and "business as usual" in the treatment of bacterial infections is substantial (2, 3, 4, 5). An additional benefit of Precision Medicine for bacterial infection is that improved diagnostics will help drive new drug development by facilitating clinical trials for new antimicrobials, particularly agents to be reserved for resistant pathogens or agents that are intended for use only against a limited range of pathogens. Without the benefit of rapid, point of care diagnostics, clinical trials for bacterial infections generally enroll patients with relevant clinical symptoms, but only a percentage of those enrolled patients are infected with the target pathogen (e.g. a particular species or multi-drug resistant pathogens).

The exodus of the pharmaceutical sector from antibacterial R&D is thought to be caused by several factors including scientific, commercial and regulatory challenges (4, 5). Scientifically, the" low hanging fruit" have already been picked and the science supporting novel modes of action is more challenging and requires greater investment in R&D. From a commercial perspective, due to multiple reasons (including the high cost of clinical trials), antibacterial agents have a low return on investment (ROI). The last challenge, though one where progress has been made, is the continued differences in US vs. EU regulatory requirements, such as different clinical endpoints required for clinical trials. An effective Precision Medicine approach can advance solutions to each of these challenges and support a continuing robust antibacterial-pipeline. Diagnostics can support development of narrow spectrum agents that previously were considered impractical for use in clinical settings. Targeted therapy will support new business models for antibacterial agents, focusing treatments for the right patients at the right time. For some clinical trials, rapid diagnostics can decrease the cost of a clinical trial– which in turn helps industry maintain R&D for new agents. Precision Medicine could also enable harmonization of regulatory guidelines by increasing the comparability of patient populations. The evidence is clear; Precision Medicine must become the guiding principle for the future.

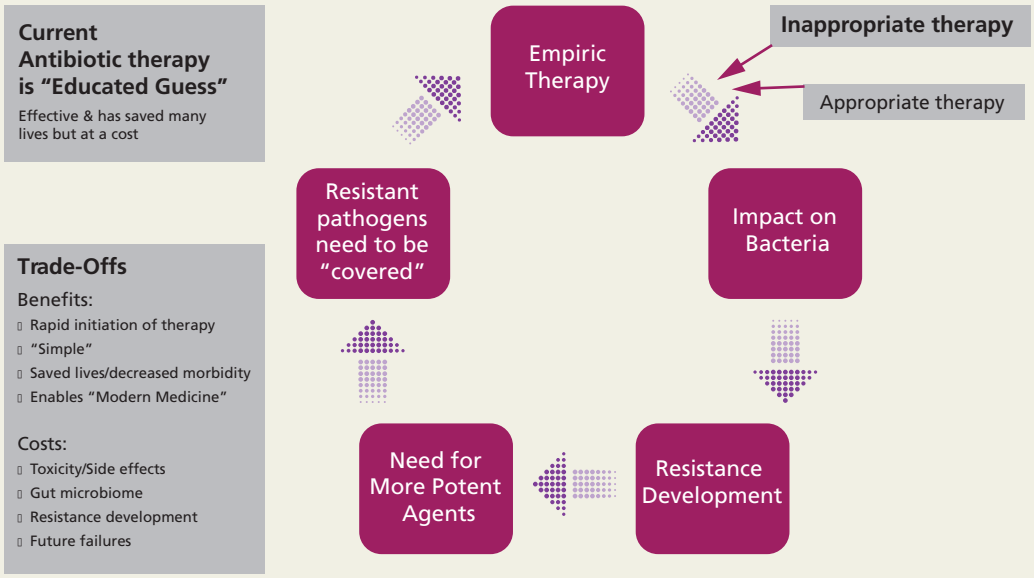

FIGURE 3A. Trade-offs with Current Prescribing Paradigm for Antibacterials

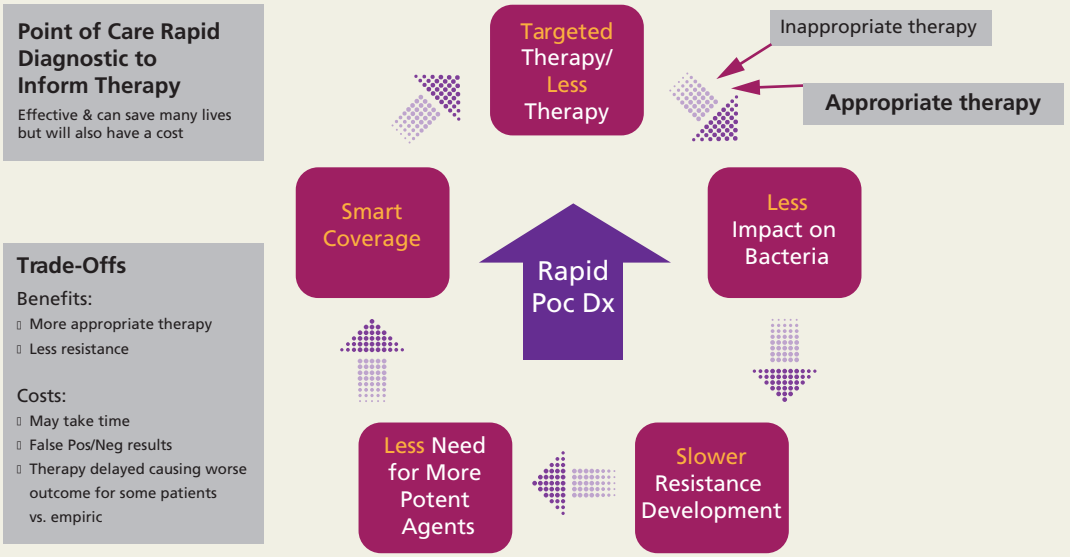

FIGURE 3B. Trade-offs with Precision Medicine Approach

The Challenges to a Precision Medicine Approach for Bacterial Infections

In recent years, medical, scientific and technological breakthroughs have converged to create a tsunami of change in clinical microbiology laboratories and Precision Medicine, at the point of care, is poised to impact the field of infection therapy. Diagnostics for some infections, such as group a streptococcal pharyngitis and bacteremia are available and used widely. Rapid diagnostics for the major respiratory viruses are also now available.

There are also multiple devices to detect MRSA (methicillin-resistant Staphylococcus aureus) directly from patient blood or skin specimens in about an hour, using small bench top devices. While the progress has been tremendous, truly transformational tests are still lacking and the empiric therapy paradigm remains largely in place for the vast majority of bacterial infection. Similar to the hurdles to the development of new antibacterial agents, there are clinical/scientific reimbursement and regulatory hurdles that have impeded the diagnostics field for bacterial infections (4). These hurdles will need to be overcome to ensure the development of transformational diagnostics and biomarkers that can easily be used to diagnose infections directly from clinically relevant specimens.

For the purpose of this paper, truly tranformational direct from specimen diagnostics can be defined as those that are:

- Inexpensive (for out-patient/developing world use),
- Simple (like a pregnancy test) with minimal or no instrumentation,
- Rapid (30 minutes)
- Have a high degree of accuracy, and
- Utilize targets and/or specimens that can be used to distinguish both bacterial and viral etiologies as well as colonizing organisms from infecting pathogens.

A high level assessment of the current and/or currently emerging status of transformational direct from specimen diagnostics (as described above) for select bacterial infections is listed in Table 1.

To achieve the objective of transformational diagnostics for key infections, the specific challenges must be identified and overcome. There are many challenges along the Diagnostic Test Process.

The Target Challenge

The first step in the Diagnostic test process is to determine the target or analyte to be measured. For bacterial infections, there is often a need to detect multiple pathogens, as an infection that presents as pneumonia, for example, can be caused by a wide range of different bacteria. More challenging is that other non-bacterial microbes, and even non-infectious processes, could also be causing the patient's symptoms. Tests may need to be quantitative to determine the bacterial load since, for some infections, the presence of a bacterial species alone does not suffice to identify those bacteria as a pathogen. For example, normal bacterial flora in the respiratory tract, intestinal tract and on the skin are the same bacteria that, under certain circumstances, may cause infection. Importantly, in this era of bacterial resistance to current agents, it is crucial that we determine how to identify key resistance mechanisms to guide the use of novel agents – and preserve them for use only when needed.

Most of the diagnostics tests available or in development have targeted the pathogen or the resistance genes as the analyte. While these tests are needed, other biomarkers could be used in place of or to supplement such pathogen focused tests. As noted above, the presence of bacteria in a sample from a patient does not necessarily mean that the infection is caused by the bacteria identified. Additionally, since resistance emerges so quickly, tests that a *priori* are designed to detect specific resistance genes will quickly become inadequate as new resistance develops. Even worse, for many instances, the presence of a resistance gene does not always correlate with clinical resistance in a patient.

Other exciting areas to consider for new targets for tests that diagnose infection are the patient microbiome (particularly the "gut" microbiome) as well as the host genome. Instead of thinking of the bacteria as the enemy and the single reason for the infection, diagnostic tests that could assess the complex interplay and balance of host, microbiome and bacteria would change how infections are understood and allow more intricate use of multiple host defense and bacterial targeting therapies. For these reasons and others, there is an urgent need for more research and development into a new set of host and pathogen biomarkers that can fill these gaps.

The Specimen Challenge

The traditional approach to diagnosis in a Clinical Microbiology laboratory has been to identify the presence of a pathogen in a biological sample (specimen) from the patient. While this new idea at the dawn of Microbiology was in itself transformative, there have always been limits related to the specimen. First of all, a high quality specimen, that reflects the disease process, is not always easy to obtain from a patient or reflective of the clinical syndrome. For example, urine samples are easy to obtain, but if not collected properly will be contaminated with normal flora. Patients can try to "cough up" a sputum sample, but often what is sent to the lab is merely a saliva sample and not reflective of what is happening deep in the lung. Key to transformational diagnostics and a Precision Medicine approach are strategies to 1) improve collection techniques and 2) supplement these specimens with tests that detect novel host and pathogen biomarkers to determine if the bacterial species identified is actually causing the infection. Significant progress has been made in host and pathogen biomarkers and research funding should continue to support these critical advances.

Together, the target and specimen challenges are the most formidable hurdles to a widespread Precision Medicine approach for bacterial infections. Even the most sophisticated "magic box" that detects bacteria will generate results that are difficult to interpret if the target detected and the specimen analyzed are not necessarily clinically relevant. Efforts to solve these challenges should be given highest priority.

The Test Platform Challenge

While there are challenges at each step in a test platform – the sample preparation; the assay itself; the detection system; and the reporting process, in some ways, these technological hurdles should be among the easiest to solve. Techniques developed for other therapy areas, such as oncology, have applications in infectious disease. Advances in molecular diagnostics have been dramatic in

TABLE 1. Standard Practice & Progress toward Transformational Direct From Specimen Diagnostics

Infection	Current and/or Emerging Standard Practice	Transformational Direct From Specimen Diagnostics Needed	Prediction: Likelihood of Commercial Availability < 5 yrs**
uRTI	• Group A Strep Antigen (pharyngitis)	• Viral vs. bacterial • Colonizers vs. pathogens • Need for antimicrobial therapy vs. supportive • Breath tests • PoC/Rapid/Simple/Accurate*	++
CAP	• Culture & Gram Stain • Rapid Legionella Antigen • Pneumococcal Antigen • Respiratory Virus Detection • Atypical Bacteria Detection	• Colonizers vs. pathogens • Viral vs. bacterial • Need for antimicrobial vs. supportive therapy • Presence of known resistance markers • Phenotypic resistance • Breath tests • PoC/Rapid/Simple/Accurate	+
VABP	• Culture & Gram Stain	• Colonizers vs. pathogens • Viral vs. bacterial • Need for antimicrobial vs. supportive therapy • Presence of known resistance markers • Phenotypic Resistance • PoC/Rapid/Simple/Accurate	++
Bacteremia	• Automated Blood Culture Systems + Molecular Detection after incubation period (approx. 1-4 hours)	• PoC/Rapid/Simple/Accurate	+++
ABSSSI	• Culture & Gram Stain • Molecular Detection of MRSA/MSSA	• PoC/Rapid/Simple/Accurate	+++
UTI	• Culture & Gram Stain • Rapid growth detection systems	• PoC/Rapid/Simple/Accurate • Presence of *E. coli* and/or known resistance markers	+++
GC	• NAAT • Culture & Gram Stain	• PoC/Rapid/Simple/Accurate • Presence of known resistance markers	+++

• Key: uRTI: Upper Respiratory Tract Infection; CAP: Community Acquired Pneumonia; VABP: Ventilator-Associated Bacterial Pneumonia; ABSSSI: Acute Bacterial Skin and Skin Structure Infections; UTI: Urinary Tract Infections; MRSA/MSSA: Methicillin-Resistant *Staphylococcus aureus* and Methicillin-Susceptible *S. aureus*; GC: Gonococcal Infections; NAAT: Nucleic Acid Amplification Test

• * PoC/Rapid/Simple/Accurate defined as: Point of Care; Rapid (< 30 minutes); Simple: both inexpensive (for out-patient/developing world use) and easy to use (like a pregnancy test) with minimal or no instrumentation; and accurate: meets needed degree of accuracy.

• ** Key: (+++) High; (++) Moderate; (+) Low

the last decade. assays have become faster, and systems smaller, including a number of cell phone applications. Genomic, proteomic, metabolomic technologies as well, which should facilitate the need to detect both host biomarkers as well as pathogen biomarkers.

The Clinical Relevance Challenge

For certain infections, simply the presence of a pathogen can indicate the need for treatment or determine a therapeutic option. For example, a test that detects Legionella antigen in a urine sample highly correlates with a *Legionella pneumophila* pneumonia with bacteremia infection. However, as stated previously, target and specimen challenges have a direct impact on the clinical utility of a test result. Information is often a valuable piece in the puzzle used by a clinician to assess a patient, but may not in itself be "diagnostic". Other important factors in assessing clinical relevance are questions such as:

- Is the test result actionable?
- Was the test completed and reported in time to impact therapy?
- Did the clinician read the test result and understand what to do about it?
- Should the physician act upon the test result?
- What is the risk of acting on a false positive or false negative to the patient?
- What are the trade-offs for the patient of determining therapy based on the test result?

The answers to these questions must be addressed as part of the clinical development of the diagnostic test.

Companion vs. Complementary Diagnostics

In oncology, "companion" diagnostics are often part of the standard of care for targeted therapies but more recently, a new category of diagnostics has emerged, complementary diagnostics. However, the terms companion and complementary diagnostics are often misunderstood, particularly in therapy areas outside of oncology. The definition of companion diagnostic is well established in the regulatory sense by FDA guidance as "an *in vitro* diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product. The use of an IVD companion diagnostic device with a therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product…" (6)

Unlike "companion" diagnostics, "complementary" diagnostics tests may not be required but may be a recommended helpful piece of information for the physician. As such, clear regulatory guidance is not yet available and the definition of complementary diagnostics remains more elusive and frequently associated more broadly with classes of drugs rather than with a specific drug.

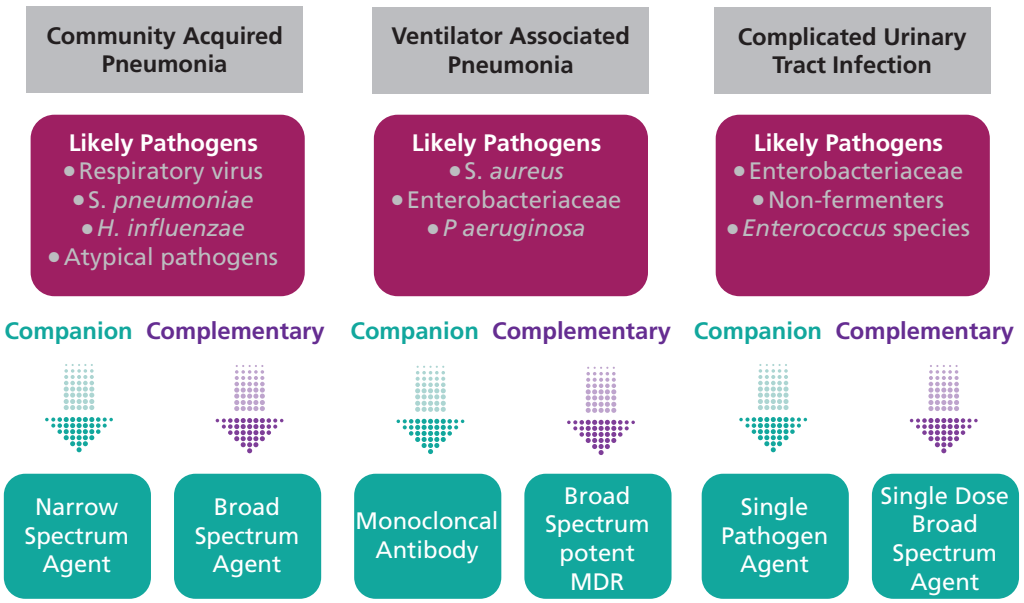

FIGURE 4. "Companion" vs. "Complementary" Diagnostics Scenarios

In Infectious Diseases, particularly for most bacterial infections, it may not be feasible or in the best interest of patients to require that diagnostic tests be used strictly as "Companion" Diagnostics. Until the specimen and target challenges are overcome and until diagnostics can be truly rapid, inexpensive, accurate, easy to perform and highly clinical relevant, "Complementary" diagnostics may provide the most feasible approach while still allowing access to drugs in a global setting.

Figure 4 provides some examples of when a 'companion" vs. "complementary" diagnostic may be more appropriate for a certain clinical scenario.

Solutions

Investment and incentives are needed to drive the transformational diagnostics that will support a Precision Medicine approach for bacterial infections. Fortunately, the need for better diagnostics in ID is supported by both the technological revolution in molecular diagnostics as well as public policy efforts to drive Precision Medicine across therapeutic areas. In 2015, President Barack Obama announced the investment on a Precision Medicine Initiative to create a large cohort of patients to understand disease mechanisms and link with electronic health records (EHR).

There is an opportunity to leverage these efforts, including the EHRs to develop a better understanding of prescription patterns of antibacterial agents. Diagnostic tests and data-based insights could then be used to understand a patient's bacterial infection more

precisely and so select treatments with more predictable, safer, cost-effective outcomes.

Additionally, consistent with President Obama's Precision Medicine Initiative, global plans to address the antimicrobial resistance crisis from the CDC, the WHO and the EU, include a focus, investment and incentives to improve diagnostic tests and drive appropriate use of antibacterial agents. In March of 2015, the White House released The National Action Plan for Combating Antibacterial agent-Resistance Bacteria. The National Action Plan focuses on 5-year federal activities and investment to enhance domestic and international capacity to prevent and contain outbreaks of antibacterial agent-resistant infections, maintain the efficacy of current and new antibacterial agents, and develop and deploy next-generation diagnostics, antibacterial agents, vaccines and other therapeutics.(7)

The National Action Plan also included plans for the U.S. Department of Health and Human Services (HHS) to hold a prize competition where up to approximately $20 million could be made available (subject to the availability of funds), for the delivery of one or more successful rapid point-of-care diagnostics that can be used to identify bacterial infections. Similar prizes have also been launched in the EU: 1) The Longitude Antibacterial Agents Prize 2014 and 2) The Horizon 2020 Antibacterial Agents Inducement Prize. See Figure 5.

GSK's commitment to the antibacterial agent development area and appropriate use of antibacterial agents through a Precision Medicine approach is exemplified by a number of investments into diagnostics for bacterial infections. In 2010, GSK joined the Innovative Medicines Initiative RAPP-ID project (Rapid Point-of-Care Test Platforms for Infectious Diseases) to contribute to the development of diagnostics. In 2014, GSK joined with several other pharmaceutical companies to fund additional studies needed to support development of the Cepheid Xpert® Carba-R test for use with urinary tract and respiratory tract specimens. GSK continues to engage with and support groups focused on development of transformational diagnostics as these tests are seen as crucial to the scientific community's antibacterial R&D efforts and to resolving the AMR crisis.

	Longitude Prize 2015	Horizon 2020 Antibiotics Inducement Prize	AMR Rapid, Point-of-Care Diagnostic Test Challenge
Prize Fund	£10M	1M Euros	Up to $20M
Opens for Submissions	Fall 2014	2015	To be detemined
Award Date	2020	Late 2016	To be determined
Prize Statement	"...to better target... treatment, and helps ensure that right antibiotic is used at the right time."	"...prove a sustained reduction in the number of unnecessary courses of antibiotics prescribed for an upper respiratory tract infection.."	"...of significant clinical and public health utility to combat the development and spread of antibiotic resistant bacteria."

www.nesta.org.uk/sites/default/files/kcfinder/files/H2020 Longitude AMR Comparison.pdf
https://www.federalregister.gov/articles/2015/06/02/2015-13113/announcement-for-request-for-comment-for-antimicrobial-resistance-rapid-point-of-care-diagnostic

FIGURE 5. Three Precision Medicine & Diagnostics Prizes

Conclusion

The time has come for a revolution in how to think about and treat bacterial infections. Going beyond the detection of the pathogen is crucial to transforming the diagnosis of bacterial infections. Consideration of the evolutionary and ecological principles between the host and their microbiome might provide "new strategies for restoring and maintaining human health."(8) Innovative diagnostics that can identify host, microbiome, environmental and pathogen biomarkers are crucial to a Precision Medicine approach. That data can then be used to design optimal therapeutic strategies for patients that can restore them to health by coordinating agents that can target the pathogen, the host and the microbiome thereby intervening appropriately in the ecological balance in the patient. Such novel approaches can not only improve patient care, but preserve antibacterial agents for the future.

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Marielena Mata., Ph.D. As the Head of the Precision Medicine team across R&D Dr. Mata is in charge of delivering on the vision of equipping GSK to be a leader in precision medicine through excellence in scientific discovery, clinical translation and companion diagnostic development driving value by treating the right patient with the right medicine.

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