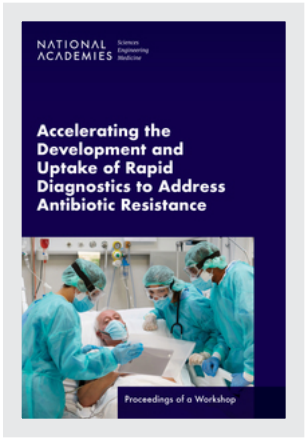

Accelerating the Development and Uptake of Rapid Diagnostics to Address Antibiotic Resistance: Proceedings of a Workshop (2023)

DETAILS

150 pages | 6 x 9 | PAPERBACK

ISBN 978-0-309-70240-9 | DOI 10.17226/27008

CONTRIBUTORS

Erin Hammers Forstag and Carolyn Shore, Rapporteurs; Forum on Drug Discovery, Development, and Translation; Forum on Medical and Public Health Preparedness for Disasters and Emergencies; Forum on Microbial Threats; Board on Global Health; Board on Health Sciences Policy; Health and Medicine Division; National Academies of Sciences, Engineering, and Medicine

SUGGESTED CITATION

National Research Council. 2023. *Accelerating the Development and Uptake of Rapid Diagnostics to Address Antibiotic Resistance: Proceedings of a Workshop*. Washington, DC: The National Academies Press. https://doi.org/10.17226/27008.

NATIONAL ACADEMIES *Sciences Engineering Medicine*

NATIONAL ACADEMIES PRESS
Washington, DC

Accelerating the Development and Uptake of Rapid Diagnostics to Address Antibiotic Resistance

Erin Hammers Forstag and
Carolyn Shore, *Rapporteurs*

Forum on Drug Discovery,
Development, and Translation

Forum on Medical and
Public Health Preparedness for
Disasters and Emergencies

Forum on Microbial Threats

Board on Global Health

Board on Health Sciences Policy

Health and Medicine Division

PREPUBLICATION COPY—Uncorrected Proofs

Proceedings of a Workshop

NATIONAL ACADEMIES PRESS 500 Fifth Street, NW Washington, DC 20001

This activity was supported by contracts between the National Academy of Sciences and Administration for Children and Families (Contract No. HHSP233201400020B; Task Order No. 75P00120F37103); American Burn Association; American College of Emergency Physicians; American College of Surgeons-Committee on Trauma; American Hospital Association; American Red Cross; American Society of Tropical Medicine and Hygiene; Amgen Inc.; Association of American Medical Colleges; Association of Public Health Laboratories; Association of State and Territorial Health Officials; AstraZeneca; Biogen; Burroughs Wellcome Fund (Contract No. 1023129, 1022390); Centers for Disease Control and Prevention (Contract No. 75D30121F00095, 75D30121D11240; Task Order No. 75D30121F00001): National Center for Emerging Zoonotic Infectious Diseases; Council of State and Territorial Epidemiologists; Critical Path Institute; East West Protection LLC; EcoHealthAlliance; Eli Lilly and Company; Emergency Nurses Association; ExxonMobil Foundation; FasterCures, Milken Institute; Foundation for the National Institutes of Health; Friends of Cancer Research; Healthcare Ready; Infectious Diseases Society of America; Johnson & Johnson (Contract No. C2022024120); Medable; Merck & Co., Inc. (Contract No. APA-21-151620; Grant No. MEM-22-160471); National Association of Chain Drug Stores; National Association of County and City Health Officials; National Association of Emergency Medical Technicians; National Fire Protection Association; National Highway Traffic Safety Administration (Contract No. 693JJ922P000037); National Institutes of Health (Contract No. HHSN263201800029I; Task Order No. HHSN26300007, HHSN26300011, HHSN26300026): National Cancer Institute, National Center for Advancing Translational Sciences, National Institute of Allergy and Infectious Diseases, National Institute of Environmental Health Sciences, National Institute of Mental Health, National Institute of Neurological Disorders and Stroke, Office of the Director; New England Journal of Medicine; New Venture Fund (Contract No. NVF-NGDF-NAT10-Subgrant-017387-2022-04-01); Office of the Assistant Secretary for Preparedness and Response (Contract No. 75A50121P00089); Sanofi (Contract No. 70602577); Takeda; The MITRE Corporation; The Rockefeller Foundation; Trauma Center Association of America; Uniformed Services University of Health Sciences (Award No. HU00012210001); U.S. Agency for International Development (Grant No. 7200AA18GR00003); U.S. Department of Defense; U.S. Department of Homeland Security (Contract No. HSHQDC-17-A-B0001; Task Order No. 70RWMD21F00000031); U.S. Department of Veterans Affairs (Contract No. 36C25022C0273); U.S. Food and Drug Administration (Contract No. 1R13FD007302-01, 75F40120P00; Award No. 5R13FD006897-03). Any opinions, findings, conclusions, or recommendations expressed in this publication do not necessarily reflect the views of any organization or agency that provided support for the project.

International Standard Book Number-13: 978-0-309-XXXXX-X
International Standard Book Number-10: 0-309-XXXXX-X
Digital Object Identifier: https://doi.org/10.17226/27008

This publication is available from the National Academies Press, 500 Fifth Street, NW, Keck 360, Washington, DC 20001; (800) 624-6242 or (202) 334-3313; http://www.nap.edu.

Printed in the United States of America.

Suggested citation: National Academies of Sciences, Engineering, and Medicine. 2023. *Accelerating development and uptake of rapid diagnostics to address antibiotic resistance.* Washington, DC: The National Academies Press. https://doi.org/10.17226/27008.

The **National Academy of Sciences** was established in 1863 by an Act of Congress, signed by President Lincoln, as a private, nongovernmental institution to advise the nation on issues related to science and technology. Members are elected by their peers for outstanding contributions to research. Dr. Marcia McNutt is president.

The **National Academy of Engineering** was established in 1964 under the charter of the National Academy of Sciences to bring the practices of engineering to advising the nation. Members are elected by their peers for extraordinary contributions to engineering. Dr. John L. Anderson is president.

The **National Academy of Medicine** (formerly the Institute of Medicine) was established in 1970 under the charter of the National Academy of Sciences to advise the nation on medical and health issues. Members are elected by their peers for distinguished contributions to medicine and health. Dr. Victor J. Dzau is president.

The three Academies work together as the **National Academies of Sciences, Engineering, and Medicine** to provide independent, objective analysis and advice to the nation and conduct other activities to solve complex problems and inform public policy decisions. The National Academies also encourage education and research, recognize outstanding contributions to knowledge, and increase public understanding in matters of science, engineering, and medicine.

Learn more about the National Academies of Sciences, Engineering, and Medicine at **www.nationalacademies.org**.

Consensus Study Reports published by the National Academies of Sciences, Engineering, and Medicine document the evidence-based consensus on the study's statement of task by an authoring committee of experts. Reports typically include findings, conclusions, and recommendations based on information gathered by the committee and the committee's deliberations. Each report has been subjected to a rigorous and independent peer-review process and it represents the position of the National Academies on the statement of task.

Proceedings published by the National Academies of Sciences, Engineering, and Medicine chronicle the presentations and discussions at a workshop, symposium, or other event convened by the National Academies. The statements and opinions contained in proceedings are those of the participants and are not endorsed by other participants, the planning committee, or the National Academies.

Rapid Expert Consultations published by the National Academies of Sciences, Engineering, and Medicine are authored by subject-matter experts on narrowly focused topics that can be supported by a body of evidence. The discussions contained in rapid expert consultations are considered those of the authors and do not contain policy recommendations. Rapid expert consultations are reviewed by the institution before release.

For information about other products and activities of the National Academies, please visit www.nationalacademies.org/about/whatwedo.

PLANNING COMMITTEE ON ACCELERATING THE DEVELOPMENT AND UPTAKE OF RAPID DIAGNOSTICS TO ADDRESS ANTIBIOTIC RESISTANCE[1]

KENT E. KESTER (*Co-chair*), Vice President, Translational Medicine, International AIDS Vaccine Initiative
BETSY WONDERLY TRAINOR (*Co-chair)*, Alliance Director, Diagnostics, CARB-X
JOHN BILLINGTON, Head of Commercial Pipeline and Health Security Policy and Advocacy, GSK
CAREY-ANN BURNHAM, Chief Clinical Officer, Pattern Bioscience
PAUL EDER, Senior Scientific Officer, National Institute of Allergy and Infectious Diseases, NIH
DEBORAH HUNG, Associate Professor and Core Faculty Member, Harvard Medical School
AMANDA JEZEK, Senior Vice President of Public Policy and Government Relations, Infectious Diseases Society of America
ROBIN PATEL, Elizabeth P and Robert E Allen Professor of Individualized Medicine, Division of Clinical Microbiology, Mayo Clinic
RIBHI SHAWAR, Assistant Director, Division of Microbiology Devices, Center for Devices and Radiological Health, Food and Drug Administration
SUSAN VAN METER, President, American Clinical Laboratory Association

Health and Medicine Division Staff

JULIE LIAO, Forum Director
CAROLYN K. SHORE, Forum Director
LISA BROWN, Senior Program Officer
SCOTT WOLLEK, Senior Program Officer
BIANCA ESPINOSA, Associate Program Officer (*from July 2022*)
DEANNA GIRALDI, Associate Program Officer (*until September 2022*)
CLAIRE BIFFL, Research Associate
ASHLEY BOLOGNA, Senior Program Assistant (*from July 2022*)
MELVIN JOPPY, Senior Program Assistant
ANDREW M. POPE, Senior Director, Board on Health Sciences Policy (*until June 2022*)

[1] The National Academies of Sciences, Engineering, and Medicine's planning committees are solely responsible for organizing the workshop, identifying topics, and choosing speakers. The responsibility for the published Proceedings of a Workshop rests with the workshop rapporteurs and the institution.

CLARE STROUD, Senior Director, Board on Health Sciences Policy (*from June 2022*)

Consultant

ERIN HAMMERS FORSTAG, Science Writer

FORUM ON DRUG DISCOVERY, DEVELOPMENT, AND TRANSLATION[1]

GREGORY SIMON (*Cochair*), Kaiser Permanente Washington Health Research Institute and University of Washington
ANN TAYLOR (*Cochair*), Retired
CHRISTOPHER P. AUSTIN, Flagship Pioneering
LINDA BRADY, National Institute of Mental Health, NIH
JOHN BUSE, University of North Carolina, Chapel Hill School of Medicine
LUTHER T. CLARK, Merck & Co., Inc.
BARRY S. COLLER, The Rockefeller University
TAMMY R.L. COLLINS, Burroughs Wellcome Fund
THOMAS CURRAN, Children's Mercy, Kansas City
RICHARD DAVEY, National Institute of Allergy and Infectious Diseases, NIH
KATHERINE DAWSON, Biogen
JAMES H. DOROSHOW, National Cancer Institute, NIH
JEFFREY M. DRAZEN, *New England Journal of Medicine*
STEVEN K. GALSON, Retired
CARLOS O. GARNER, Eli Lilly and Company
DEBORAH HUNG, Harvard Medical School
LYRIC JORGENSON, Office of Science Policy, NIH
ESTHER KROFAH, FasterCures, Milken Institute
LISA M. LaVANGE, University of North Carolina
ARAN MAREE, Johnson & Johnson
CRISTIAN MASSACESI, AstraZeneca
ROSS McKINNEY JR., Association of American Medical Colleges
JOSEPH P. MENETSKI, Foundation for the National Institutes of Health
ANAEZE C. OFFODILE II, University of Texas MD Anderson Cancer Center
SALLY OKUN, Clinical Trials Transformation Initiative
ARTI RAI, Duke University School of Law
MARK ROGGE, University of Florida
KLAUS ROMERO, Critical Path Institute
JONI RUTTER, National Center for Advancing Translational Sciences, NIH
SUSAN SCHAEFFER, Patients' Academy for Research Advocacy
JOSEPH SCHEEREN, Retired
ANANTHA SHEKHAR, University of Pittsburgh

[1] The National Academies of Sciences, Engineering, and Medicine's forums and roundtables do not issue, review, or approve individual documents. The responsibility for the published Proceedings of a Workshop rests with the workshop rapporteurs and the institution.

JAY SIEGEL, Retired
ELLEN V. SIGAL, Friends of Cancer Research
MARK TAISEY, Amgen Inc.
AMIR TAMIZ, National Institute of Neurological Disorders and Stroke, NIH
PAMELA TENAERTS, Medable
MAJID VAKILYNEJAD, Takeda
JONATHAN WATANABE, University of California Irvine School of Pharmacy and Pharmaceutical Sciences
ALASTAIR WOOD, Vanderbilt University
CRIS WOOLSTON, Sanofi

Forum Staff

CAROLYN K. SHORE, Forum Director
BIANCA ESPINOSA, Associate Program Officer (*from July 2022*)
DEANNA GIRALDI, Associate Program Officer (*until September 2022*)
ANDREW MARCH, Associate Program Officer
ASHLEY BOLOGNA, Senior Program Assistant (*from July 2022*)
MELVIN JOPPY, Senior Program Assistant
ANDREW M. POPE, Senior Director, Board on Health Sciences Policy (*until June 2022*)
CLARE STROUD, Senior Director, Board on Health Sciences Policy (*from June 2022*)

FORUM ON MEDICAL AND PUBLIC HEALTH PREPAREDNESS FOR DISASTERS AND EMERGENCIES[1]

SUZET MCKINNEY (*Co-Chair*), Sterling Bay
CRAIG VANDERWAGEN (*Co-Chair*), East West Protection, LLC
JOANNE ANDREADIS, Centers for Disease Control and Prevention
TOM COTTER, Healthcare Ready
BROOKE COURTNEY, U.S. Food and Drug Administration
CINNAMON DIXON, National Institute of Environmental Health Sciences
DAVID EISENMAN, University of California, Los Angeles
CARINA ELSENBOSS, National Association of County and City Health Officials
BRUCE EVANS, National Association of Emergency Medical Technicians
DAVID FERRARO, Society for Critical Care Medicine
PRITESH GANDHI, U.S. Department of Homeland Security
ASHA GEORGE, Bipartisan Commission on Biodefense
NATALIE GRANT, Administration for Children and Families
JANET HAMILTON, Council of State and Territorial Epidemiologists
DAN HANFLING, In-Q-Tel
DAVID (CHRIS) HASSELL, Administration for Strategic Preparedness and Response
JOHN HICK, Hennepin County Medical Center
THOMAS KIRSCH, Uniformed Services University of the Health Sciences
RICHARD KWOK, National Institute of Environmental Health Sciences
JAMES LAWLER, University of Nebraska Medical Center
NICOLETTE LOUISSAINT, Healthcare Distribution Alliance
FREDA LYON, Emergency Nurses Association
MONIQUE MANSOURA, The MITRE Corporation
BIRGITTE MESSERSCHMIDT, National Fire Protection Association
AUBREY MILLER, National Institute of Environmental Health Sciences
BARBARA MULACH, National Institute of Allergy and Infectious Diseases
IRA NEMETH, American College of Emergency Physicians
JOHN OSBORN, Mayo Clinic College of Medicine
TARA O'TOOLE, In-Q-Tel
ANDREW PAVIA, Infectious Diseases Society of America
LEWIS RADONOVICH, National Institute for Occupational Safety and Health

[1] The National Academies of Sciences, Engineering, and Medicine's forums and roundtables do not issue, review, or approve individual documents. The responsibility for the published Proceedings of a Workshop rests with the workshop rapporteurs and the institution.

TERRY RAUCH, U.S. Department of Defense
SARA ROSZAK, National Association of Chain Drug Stores
COLLEEN RYAN, American Burn Association
ROSLYNE SCHULMAN, American Hospital Association
RICHARD SERINO, Harvard T.H. Chan School of Public Health
SCOTT SHONE, Association of Public Health Laboratories
BRANNON TRAXLER, Association of State and Territorial Health Officials
TENER VEENEMA, Johns Hopkins Bloomberg School of Public Health
JENNIFER WARD, Trauma Center Association of America
GAMUNU WIJETUNGE, Department of Transportation
MATTHEW WYNIA, University of Colorado, Denver
DAVID ZONIES, Committee on Trauma - American College of Surgeons

Forum Staff

LISA BROWN, Senior Program Officer
SCOTT WOLLEK, Senior Program Officer
SHALINI SINGARAVELU, Program Officer
MICHAEL BERRIOS, Research Associate
CLARE STROUD, Senior Director, Board on Health Sciences Policy

FORUM ON MICROBIAL THREATS[1]

PETER DASZAK (*Chair*), EcoHealth Alliance
KENT E. KESTER (*Vice Chair*), International AIDS Vaccine Initiative
EMILY ABRAHAM, Johnson & Johnson
KEVIN ANDERSON, Retired
DANIEL BAUSCH, American Society of Tropical Medicine and Hygiene
CHRISTOPHER BRADEN, Centers for Disease Control and Prevention
CRISTINA CASSETTI, National Institute of Allergy and Infectious Diseases, NIH
ANDREW CLEMENTS, U.S. Agency for International Development
MALICK DIARA, ExxonMobil
SCOTT F. DOWELL, Bill & Melinda Gates Foundation
MARCOS A. ESPINAL, Pan American Health Organization
EVA HARRIS, University of California, Berkeley
JON H. HEINRICHS, Sanofi
ELIZABETH D. HERMSEN, Pfizer Inc.
MARK G. KORTEPETER, Uniformed Services University of the Health Sciences
MICHAEL MAIR, U.S. Food and Drug Administration
JONNA MAZET, University of California, Davis
VICTORIA McGOVERN, Burroughs Wellcome Fund
SALLY A. MILLER, The Ohio State University
SUERIE MOON, The Graduate Institute of International and Development Studies, Geneva
RAFAEL OBREGON, United Nations Children's Fund
KUMANAN RASANATHAN, World Health Organization
GARY A. ROSELLE, U.S. Department of Veterans Affairs
PETER A. SANDS, The Global Fund to Fights AIDS, Tuberculosis, and Malaria
THOMAS W. SCOTT, University of California, Davis
MATTHEW ZAHN, Orange Country Health Care Agency

Forum Staff

JULIE LIAO, Forum Director
LIZ ASHBY, Associate Program Officer
CLAIRE BIFFL, Research Associate
JUSTIN HAMMERBERG, Senior Program Assistant (*until November 2022)*

[1] The National Academies of Sciences, Engineering, and Medicine's forums and roundtables do not issue, review, or approve individual documents. The responsibility for the published Proceedings of a Workshop rests with the workshop rapporteurs and the institution.

Reviewers

This Proceedings of a Workshop was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published proceedings as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the charge. The review comments and draft manuscript remain confidential to protect the integrity of the process.

We thank the following individuals for their review of this proceedings:

CAROLE ANN BEWLEY, National Institute of Diabetes and Digestive Kidney Diseases, NIH
BRIAN RAUX, bioMérieux
ANTHONY SO, Johns Hopkins Bloomberg School of Public Health

Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the content of the proceedings, nor did they see the final draft before its release. The review of this proceedings was overseen by **JIM E. RIVIERE,** North Carolina State University. was responsible for making certain that an independent examination of this proceedings was carried out in accordance with standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the rapporteurs and the National Academies.

Acknowledgments

Support from the sponsors of the Forum on Drug Discovery, Development, and Translation, the Forum on Medical and Public Health Preparedness for Disasters and Emergencies, and the Forum on Microbial Threats is crucial to support this and other work of the National Academies.

The National Academies' staff wish to express their gratitude to the speakers whose presentations helped inform workshop discussions; to the members of the planning committee for their work in developing the workshop agenda and shaping the discussions; and to additional National Academies staff, without whom this workshop and the accounting thereof would not have been possible: Christie Bell, Samantha Chao, Robert Day, Rebekah Hanover Pettit, Benjamin Hubbert, Noah Ontjes, Devona Overton, Marguerite Romatelli, Bettina Seliber, Lauren Shern, Elizabeth Webber, and Taryn Young.

Contents

Boxes, Figures, and Tables

BOXES

FIGURES

TABLES

Acronyms and Abbreviations

ABC	*Acinetobacter calcoaceticus-baumannii* complex
AI	artificial intelligence
AMR	antimicrobial resistance
ASSURED	affordable, sensitive, specific, user-friendly, rapid, equipment-free, and deliverable
AST	antimicrobial susceptibility testing
ATTACK	*Acinetobacter* Treatment Trial Against Colistin
BAA	Broad Agency Announcement
BARDA	Biomedical Advanced Research and Development Authority
BCID	Blood Culture Identification
BEI	Biological Exposure Indices
BIO	Biotechnology Innovation Organization
BPP	BIOFIRE® Pneumonia Panel
CAP	Concept Acceleration Program
CARB-X	Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator
CDC	Centers for Disease Control and Prevention
C. diff	*Clostridioides difficile*
CFUs	colony-forming units
CLFS	Clinical Laboratory Fee Schedule
CLIA	Clinical Laboratory Improvement Amendments
CLSI	Clinical and Laboratory Standards Institute
CMS	Centers for Medicare & Medicaid Services

COVID-19	coronavirus disease 2019
CPT	Current Procedural Terminology
CRE	carbapenem-resistant Enterobacterales
DARPA	Defense Advanced Research Projects Agency
DNA	deoxyribonucleic acid
DRG	Diagnosis Related Group
E. Coli	*Escherichia coli*
ED	emergency department
ESBL	extended spectrum beta-lactamase
EU	European Union
EUA	Emergency Use Authorization
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	U. S. Food and Drug Administration
HHS	Health and Human Services
IDEA	Innovation + Design Enabling Access
IDSA	Infectious Diseases Society of America
IRB	institutional review board
IRS	Internal Revenue Service
ITAP	Independent Test Assessment Program
IV	intravenous
LDTs	laboratory developed tests
LMIC	low- and middle-income countries
MALDI-TOF	MSMatrix Assisted Laser Desorption Ionization Time of Flight Mass Spectrometry
MAAP	Mapping Antimicrobial Resistance and Antimicrobial Use Partnership
MDR	multidrug resistant
MIPS	Merit-Based Incentive Payment System
mNGS	metagenomic next generation sequencing
MRSA	methicillin-resistant *Staphylococcus aureus*
MSF	Médecins Sans Frontières/Doctors Without Borders
MTB	*Mycobacterium tuberculosis*
NG	*Neisseria gonorrhoeae*
NGS	next generation sequencing

NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health (U.S.)
NLA	National Limitation Amounts
NTAP	new technology add-on payment
NWSS	National Wastewater Surveillance System
OECD	Organization for Economic Cooperation and Development
PACCARB	Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria
PCR	polymerase chain reaction
PCS	Pre-Clinical Services
POC	point-of-care
RADx	Rapid Acceleration of Diagnostics
R&D	research and development
RAPIDS GN	Randomized Trial Evaluating Clinical Impact of Rapid Identification and Susceptibility Testing for Gram-negative Bacteremia
RCT	randomized controlled trial
REASSURED	real-time connectivity, ease of specimen, affordable, sensitive, specific, user-friendly, rapid, equipment-free, and deliverable
RIF	rifampin
RSV	respiratory syncytial virus
SALSA	Saving Access to Laboratory Services Act
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
STIs	sexually transmitted infections
SUL-DUR	sulbactam-durlobactam
UTI	urinary tract infection
VA	Department of Veterans Affairs
VRE	Vancomycin-resistant enterococci
WHO	World Health Organization

1

Introduction

The use and misuse of antibiotics contributes to the rise in drug-resistant bacteria—a serious and worsening threat to human health. Addressing the problem of antibiotic resistance requires measures to spur innovation and ensure the prudent use of existing drugs. The development and use of rapid point-of-care diagnostics in the healthcare setting plays an important role in avoiding unnecessary use of antimicrobials by providing clinicians with the right information at the right time to help them make decisions about appropriate drug treatment for patients. Diagnostics also have the capacity to support early detection and diagnosis of drug-resistant bacterial infections, enable disease surveillance, and help prevent disease spread.

On October 13th and 14th of 2022, a workshop entitled Accelerating the Development and Uptake of Rapid Diagnostics to Address Antibiotic Resistance was convened by the National Academies' Forum on Drug Discovery, Development, and Translation;[1] the Forum on Medical and Public Health Preparedness for Disasters and Emergencies;[2] and the Forum on Microbial Threats.[3] The workshop provided a venue for stakeholders to discuss the current landscape of rapid diagnostics and to address antibiotic resistance, consider challenges and opportunities for spurring innovation,

[1] See https://www.nationalacademies.org/our-work/forum-on-drug-discovery-development-and-translation (accessed January 25, 2023).

[2] See https://www.nationalacademies.org/our-work/forum-on-medical-and-public-health-preparedness-for-disasters-and-emergencies (accessed January 25, 2023).

[3] See https://www.nationalacademies.org/our-work/forum-on-microbial-threats (accessed January 25, 2023).

and consider practical next steps for accelerating the development and uptake of new diagnostic tools. Given the breadth and depth of the issues related to diagnostic development and use, the focus of this workshop was on U.S.-based healthcare settings, policies, and incentives. Workshop participants discussed some of the global implications and considerations as well, which merit further time and attention.

Kent E. Kester (Vice President, Translational Medicine, International AIDS Vaccine Initiative) and Betsy Wonderly Trainor (Alliance Director, CARB-X), welcomed workshop participants, some of whom attended in person in Washington, D.C. and some virtually. Trainor began by sharing her thoughts on the issue and emphasized that the use and misuse of antibiotics continues to contribute to the rise in drug-resistant bacteria. Antibiotic resistance—which occurs when bacteria develop the "ability to overcome the effects of drugs designed to kill or disarm them—is one of the greatest public health threats" today. According to the World Health Organization (WHO), over 700,000 annual deaths worldwide can be attributed to drug-resistant bacterial infections, and this number is growing (WHO, 2019).[4] To keep up with antibiotic resistance, researchers need to produce several innovative antibiotics every decade, but it currently takes between 10 and 15 years to produce a single new antibiotic (WHO, 2022a). Addressing the problem of antibiotic resistance requires not only measures to accelerate the discovery and development of new antibiotics but also efforts to ensure that existing antibiotics are properly used and prescribed.

Rapid diagnostics can play a crucial role in reducing the unnecessary use of antibiotics, said Trainor, by providing clinicians with the right information at the right time so they can make better decisions about appropriate treatment for patients. Additionally, early detection and diagnosis of drug resistant bacterial infections can further enable disease surveillance and help prevent disease spread. There are several rapid diagnostics available today, and more are in the pipeline, but few have been adopted by the healthcare system. Trainor suggests several reasons for the lack of uptake, including regulatory hurdles, misaligned economic incentive, and health inequities. Addressing the problem of antibiotic resistance, she said, will require innovative approaches and cross-sector collaborations that bring together the scientific, medical, regulatory, diagnostic, pharmaceutical, payer, and patient advocacy communities.

The workshop was planned according to a Statement of Task (Box 1-1) and builds upon previous works of the National Academies, including past

[4] To view the WHO report, see https://www.who.int/news/item/29-04-2019-new-report-calls-for-urgent-action-to-avert-antimicrobial-resistance-crisis (accessed March 13, 2023). Other estimates suggest deaths associated with AMR are much higher, see https://doi.org/10.1016/S0140-6736(21)02724-0 (accessed March 13, 2023).

BOX 1-1
Statement of Task

An ad hoc planning committee[a] under the auspices of the National Academies of Sciences, Engineering, and Medicine, will organize a two-day public workshop to discuss the current landscape of rapid diagnostics to address antibiotic resistance, consider challenges and opportunities for spurring innovation, and discuss practical next steps for accelerating the development of new diagnostic tools. The public workshop will feature invited presentations and discussions to:

- Examine the current state of rapid diagnostic development, including examples of successes and limitations of current approaches.
- Consider the unique challenges for the development and use/uptake of rapid diagnostics in health care settings (e.g., feasibility of clinical utility studies).
- Consider gaps that rapid diagnostics may be best suited to address (e.g. tools to support targeted treatment decisions in the health care setting, tools to enable real-time surveillance based on routine hospital data).
- Discuss practical short- and long-term opportunities for spurring the development and uptake of new diagnostics that can help address antibiotic resistance.

The planning committee will organize the workshop, develop the agenda, select and invite speakers and discussants, and moderate or identify moderators for the discussions. Proceedings of the presentations and discussions at the workshop will be prepared by a designated rapporteur in accordance with institutional guidelines.

[a]The planning committee's role was limited to planning the workshop, and the Proceedings of a Workshop has been prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants and are not necessarily endorsed or verified by the National Academies of Sciences, Engineering, and Medicine, and they should not be construed as reflecting any group consensus.

workshops on *Antibiotic Resistance: Implications for Global Health and Novel Intervention Strategies* (2010); *Technological Challenges in Antibiotic Discovery and Development* (2014); and *Combating Antimicrobial Resistance: A One Health Approach to a Global Threat* (2017). In addition to these workshops, a recent National Academies consensus report, titled *Combating Antimicrobial Resistance and Protecting the Miracle of Modern Medicine* (2022), offered recommendations for improving the detection of resistant infections, incentivizing the development of drugs and diagnostics, and the role of the United States in coordinating global action to combat

microbial resistance. While much work has been done in this space, Kester emphasized that "more needs to be done."

This workshop proceedings largely follows the organization of the workshop agenda, found in Appendix A. All speaker biographies can be found in Appendix B. Chapter 2 provides an overview of the current state of rapid diagnostics and examines how these tools might fit into the healthcare system. Chapter 3 summarizes discussions about challenges and opportunities for the development and use of rapid diagnostics. Chapter 4 examines incentives and disincentives for the development of new antibiotics and complementary diagnostics, and Chapter 5 considers health equity implications in this area. Chapter 6 explores approaches to facilitate the adoption of rapid diagnostics by health care systems, including integration with antibiotic stewardship programs. Finally, Chapter 7 looks at the path forward, summarizing input from workshop participants on practical and potential opportunities for spurring the development and use of rapid diagnostics in healthcare settings.

2

Exploring the Need for Rapid Diagnostics

Key Points Made by Individual Speakers:

- Antibiotics are becoming rare as a class of therapy, but the diseases they treat are common. (Burnam)
- Providers have an ethical obligation to their patients to provide the right treatment at the right time, with full informed consent. The current system of antibiotic testing and treatment does not meet this obligation. (Cohen)
- Traditional tests for antibiotic resistance or susceptibility are slow, but emerging innovations hold promise for rapid point-of-care testing. (Carroll)
- There are tradeoffs to consider across the different approaches for antibiotic resistance and susceptibility testing. (Whiteford)
- Lengthy and unpredictable pathways for coverage, coding, and payment for rapid diagnostics are barriers to the development and uptake of these products for testing antibiotic resistance and susceptibility. (Van Meter)

Karen C. Carroll (Director, Division Medical Microbiology and Professor of Pathology, Johns Hopkins University School of Medicine) provided an overview of the current state of rapid diagnostic development and gaps that rapid diagnostics might be best suited to address (e.g., to support targeted treatment decisions or to enable real-time surveillance). Workshop speakers

then discussed how rapid diagnostics fit into the healthcare system and how "success" in this area could be defined.

Antimicrobial resistance (AMR) is ranked by the WHO as one of the top ten global public health threats facing humanity (WHO, 2021). By 2050, it is projected that AMR will be responsible for 10 million deaths and a loss of $100 trillion to the global economy due to loss of productivity (O'Neill, 2016). In the United States alone, there are 2.8 million antibiotic-resistant infections each year, resulting in 35,000 deaths. Further, some of the most urgent threats to health, according to Carroll, include multi-drug resistant gram-negative bacteria (e.g., carbapenem-resistant *Acinetobacter*, Enterobacterales), drug-resistant *Neisseria gonorrhoeae* (NG), *Candida auris*, and *Clostridioides difficile* (C. diff) (CDC, 2019a). The coronavirus disease 2019 (COVID-19) pandemic has exacerbated the global AMR crisis, she added.

Patient Perspective

"I was the kid who invented his own cure for a nonhealing wound caused by a relentless, antibiotic-resistant infection," said Bradley Burnam (AMR survivor and Founder, Turn Therapeutics). Burnam contracted an antimicrobial-resistant skin infection while working in hospitals as a device representative, which resulted in months of pain, surgeries, and antibiotic treatment. He ultimately developed his own ointment that put an end to the recurring infections. However, the "romantic tales of garage laboratories" do not tell the full story, said Burnam. The stories did not adequately describe the fear of seeing half of his face purple with a double-in-size cellulitic ear or mention the infectious disease specialist who advised emergency surgery and a powerful course of intravenous (IV) antibiotics. "They don't talk about the sound of the scalpel cutting, scraping" for hours, or "describe the smell of the electrocautery" from burning tissue, he said. The stories do not mention that no anesthesiologist was available to numb his senses, or that it took nearly two hours to affix 50 stiches to piece his face back together. They did not speak to the months of antibiotic treatment and the effects on his gut or the four months he spent with deep abscesses in his face and skull that were packed with gauze and topical antibiotics. These "antiquated tools offered nothing but allergic responses and occasional comfort," said Burnam.

Sadly, he said, the story of his hospital-acquired infection is not uncommon; thousands of patients suffer from drug-resistant infections each year. A future in which the supply of antibiotics no longer keeps pace with the organisms is a real and current scenario: humans did not administer the first dose of a systemic antibiotic until 1941, and it took microbes less than a decade to defeat it (Dhingra et al., 2020).

As a patient, said Burnam, he is angry that in the last 20 years there have been only four new antibiotic class drugs approved. At the current pace of drug approval, resistant mutations could develop before a new antibiotic is approved. According to Burnam, it may be time to take dramatic steps. For example, antibiotic resistance could be declared a national health emergency, opening pathways for Emergency Use Authorization (EUA) of drugs and devices. Legislation could be passed that would incentivize investors to deploy capital and support the economic viability of AMR products. Antibiotics are becoming rare as a class of therapy, said Burnam, but the diseases they treat are common. Burnam suggests that investors and developers "love orphan drugs" because of the lower hurdles to completing clinical trials, high rate of reimbursement, and longer exclusivity periods. In contrast, antibiotics do not benefit from federal incentives such as EUA, expedited review, transferable exclusivity vouchers, orphan drug designations, tax incentives, and reimbursement subsidies.

Bioethics Perspective

Treatment decisions involving antibiotics—including whether to prescribe an antibiotic, which antibiotic to use, and the appropriate duration of use—are incorrect in 30 to 50 percent of cases, said Tracey L. Cohen (Distinguished Visiting Scholar, Institute for Bioethics & Health Policy, University of Miami Miller School of Medicine) (Ventola, 2015). When clinicians are unable to rapidly identify a causative pathogen, this may lead to the following scenarios:

- a patient is prescribed an antibiotic that is unwarranted (e.g., for a viral infection);
- a patient is prescribed an incorrect antibiotic;
- a patient is prescribed a powerful, broad-spectrum antibiotic to cover the widest range of possible bacteria;
- a patient is denied antibiotics until test results are available;
- a patient is denied antibiotics altogether.

In each of these scenarios, said Cohen, healthcare providers are harming their patients. Giving the wrong antibiotic or broad-spectrum antibiotics increase the risk of resistance within the patient, which increases the likelihood of treatment failure. Delaying or denying treatment can lead to deterioration of the condition and/or dangerous complications (e.g., bronchitis leading to pneumonia, strep leading to heart damage). The harms that result from improper antibiotic decision-making violate the bioethical duties that healthcare providers owe to their patients, said Cohen. These duties include the responsibility of beneficence (to do good, to heal) and

non-maleficence (to do no harm). In addition, the healthcare provider's duty to respect the patient's autonomy is infringed. Cohen explained that patients are owed the right to full informed consent, which includes the risks and benefits of a proposed treatment and of any alternatives. However, when providers are lacking information about pathogens, patients are not given accurate information about risks, benefits, and alternatives. This results in patients relying on treatment plans to their detriment, emphasized Cohen.

Rapid point-of-care diagnostics, said Cohen, can help ensure that treatment decisions are made based on empirical data rather than supposition. They could assist providers in upholding their bioethical duties to patients, while also helping to combat the antibiotic resistance crisis. Cohen pointed out that pharmaceutical and biotechnology companies also have an obligation of non-maleficence; they should ensure that rapid diagnostics do not sacrifice accuracy for speed because inaccurate results can lead to harmful treatment decisions.

New diagnostics may be significantly more expensive than traditional methods, a distinction that requires bioethical and equity considerations among several different parties according to Cohen. Healthcare providers and institutions must offer life-saving diagnostics to all patients, regardless of their ability to pay. Pharmaceutical and biotechnology companies should find ways to keep costs low to promote accessibility. State and federal governments have an ethical obligation to help forestall the antibiotic resistance crisis to ensure the health of citizens. These stakeholders should work towards subsidizing rapid tests (as happened with COVID-19) to ensure they are available to all. Further, governments should ensure that diagnostics are widely distributed and available, particularly among healthcare providers working in low-income communities. Third party payers have an ethical obligation to cover the costs of these diagnostics. Cohen emphasized that rapid diagnostics should be regarded as routine tests rather than specialty tests, which can be excluded from coverage, and that failure of insurers to pay would be an unjustifiable interference with healthcare providers' ethical obligations to patients. She observed that it is more cost-effective for payers to pay for these tests because they will cut long-term costs by reducing morbidity and mortality.

In summary, said Cohen, rapid diagnostics will help healthcare providers mitigate improper treatment decisions which harm patients in violation of the bioethical principles. Stakeholders, including pharmaceutical and biotechnology companies, government entities, healthcare providers, and third-party payers, have corresponding bioethical imperatives to create, distribute, utilize, and subsidize reliable, rapid point-of-care diagnostics. However, Cohen emphasized that diagnostics must be justly distributed and financially accessible in conformity with the principle of social justice. As the WHO has observed, the antibiotic resistance crisis may seem slow-moving and abstract

compared to the COVID-19 pandemic. However, antibiotic resistance is a growing concern for everyone around the globe, and the problem demands a collective focused attention.

Clinical Microbiology Laboratory Perspective

Clinical microbiology laboratories largely depend on traditional culture-based techniques (e.g., inoculation of specimens to plated media). There are advantages to these techniques, Carroll said: they are cost-effective, they have undergone extensive clinical validation, and microbiologists are comfortable performing them. However, traditional techniques tend to be "very slow" (Miller et al., 2019). Newer methods have been developed, said Carroll, but these tend to be "add-on" approaches rather than a replacement for traditional diagnostic tests, in part due to limitations in the spectrum of pathogens that can be detected, variable specificity and sensitivity, lack of differentiation between living and dead cells, and cost. Further culture-based methods can test for multiple pathogens simultaneously, which may be particularly useful when there is no *a priori* knowledge of the causative pathogen.

According to Carroll, phenotypic susceptibility testing continues to be important in the detection of AMR. Antimicrobial susceptibility testing (AST) relies on semi-automated and automated devices that use microbroth dilution methods. This approach is standardized and quantitative, and there are interpretive guidelines to determine susceptibility versus resistance. However, Carroll emphasized that this approach is slow, not amenable for testing all bacterial pathogens, and there is a lag between the availability of new agents and incorporation into AST panels by manufacturers. Clinical and Laboratory Standards Institute (CLSI)[1] and the European Committee on Antimicrobial Susceptibility Testing (EUCAST)[2] are continually reevaluating the guidelines for susceptibility and resistance, said Carroll, which makes it challenging to incorporate new criteria for interpreting AST panels in a timely manner. A survey found that up to 70 percent of clinical laboratories in the United States are not using the current CLSI criteria for determination of resistance (Simner et al., 2022). This is a patient safety issue, she said; quality AST is critical for infection control, hospital and national surveillance, and antibiograms for empiric treatment.

Carroll noted that recent advances show some promise. For example, the Accelerate Pheno is a Food and Drug Administration (FDA)-approved platform that can identify organisms in positive blood cultures within one

[1] See https://clsi.org/standards/?page=1&sort=date&sortdir=desc&subcat=AST&area= (accessed January 25, 2023).

[2] See https://www.eucast.org/ast_of_bacteria (accessed January 25, 2023).

hour using fluorescence in-situ hybridization probes and detect phenotypic susceptibility within seven hours using microscopic image analysis (Marschal et al., 2017). This approach allows clinicians to rapidly tailor treatment within a reasonably short period of time (8 hours) and can improve antimicrobial stewardship. However, there are technical barriers for some "drug/bug" combinations that add time and cost to the process, and there is financial risk to the industry in bringing these to the market. There are other new approaches as well, said Carroll, such as deoxyribonucleic acid (DNA) amplification methods that target specific genes, immunochromatographic assays, and antibiotic degradations assays. These approaches can detect resistance very rapidly (within 15 to 60 minutes) and confirm phenotypic resistance, which improves antimicrobial stewardship and infection control. However, Carroll highlighted some limitations to these approaches. For example, a negative result does not imply susceptibility, a positive resistance marker does not necessarily confer phenotypic resistance, testing may be limited to certain antibiotics, and there are additional associated costs.

Over the last several decades, disruptive technologies have advanced diagnostics in clinical labs and made transformative changes. Some culture-based methods have been replaced by multiplexed molecular syndromic panel tests, and organisms can be identified faster using Matrix Assisted Laser Desorption Ionization Time of Flight Mass Spectrometry (MALDI-TOF MS). MALDI-TOF MS identifies organisms based on their unique protein profile and requires only a single colony rather than a large biomass. This approach is cost-effective, highly accurate, and can be used for bacteria, fungi, and mycobacteria. It has been shown to have a "tremendous medical impact," said Carroll, including reducing time to therapy and length of stay for patients (Miller et al., 2019). Beyond identification, mass spectrometry can be used for susceptibility testing and strain typing for epidemiology. Another notable advance has been the development of syndromic panel tests, which combine organism detection and resistance marker detection for bacterial pathogens. These can be used to detect the major causes of a particular syndrome such as respiratory infections, gastroenteritis, or meningitis. These tests have been particularly useful, said Carroll, in reducing the turnaround time for antiviral and antibacterial therapy. However, there are limited studies on patient outcomes, with most studies showing variable impact on outcomes such as length of stay and mortality (Ramanan et al., 2017). Carroll emphasized the need for guidelines for appropriate utilization of syndromic panel tests. Other transformative methods on the horizon include DNA-microarray based hybridization technology, T2MR technology[3], rapid phenotypic/genotypic

[3] See https://www.t2biosystems.com/products-technology/t2mr-technology/

susceptibility testing, total laboratory automation combined with artificial intelligence (AI), and next generation sequencing.

According to Carroll, next generation sequencing (NGS) is the "next paradigm shift" in diagnostics. There are many applications of NGS, including whole genome sequencing, targeted amplification, and metagenomic NGS (mNGS). Whole genome sequencing is already being used in public health labs for a variety of purposes, including identifying the resistance genes in an organism, and tracking outbreaks of foodborne illness. The real power of this technology, however, is in mNGS, said Carroll, where the genomes within a clinical specimen are subjected to massive parallel sequencing and sophisticated data analysis to arrive at a diagnosis. In traditional culture-based testing, a large proportion of samples are negative for a pathogen due to pretesting treatment, uncultivatable pathogens, or the need for special handling. In contrast, mNGS is effective at detecting a broad range of pathogens. However, Carroll noted that there are multiple disadvantages of mNGS. It is expensive (around $2500 per sample), it is complicated and has no reliable reference method, turnaround time is not fast (around 5 days on average), and it requires a huge investment in laboratory infrastructure. As a result, according to Carroll, mNGS is currently used as a "method of last resort." To overcome these challenges, Carroll highlighted several potential solutions, including utilizing existing molecular workflows, implementing newer technologies to speed up actionable results, and developing universal well-standardized metrics (Table 2-1).

In summary, Carroll said that despite technological advances in AMR testing in clinical microbiology, there remain several challenges. Issues including workforce shortages, lack of institutional investment in clinical laboratories, and regulatory impediments are hindering the development and implementation of new tools that could transform testing and the care of patients. Further, she noted a need for diagnostic stewardship and the implementation of guidelines to help ensure appropriate test utilization and optimize patient care.

Point-of-care diagnostics

There are a number of exciting new tools in the point-of-care (POC) testing toolbox, said Carroll. The WHO developed criteria for POC tests: they should be affordable, sensitive, specific, user-friendly, rapid, equipment-free, and deliverable to where the patient is located (ASSURED) (Figure 2-1).[4] While these criteria were developed with sexually transmitted infections in mind, she said, they can be applied to all rapid diagnostics. In

[4] See https://apps.who.int/iris/bitstream/handle/10665/68990/TDR_STI_IDE_04.1.pdf (accessed January 25, 2023).

TABLE 2-1 Challenges to the Use of mNGS and Potential Solutions

Current Challenges	Potential Solutions
Requires investment in laboratory infrastructure • Information technology; database storage • Separate sample prep/library prep areas • Specialized equipment • Unique validation processes • Specialized personnel • Variable sensitivity and specificity caused by unbiased approach (host and all organisms) are sequenced	Use of existing molecular workflows • Validation of user-friendly specialized commercialized and free software • High quality databases • Sequencing negative controls; removal of post-sequencing contamination • Quantification of pathogen abundance • Ultraclean nucleic acid extraction kits
Costs	Use of commercially available systems Limit use to diagnostic dilemmas Prospective cost-effectiveness studies
Not amenable to immediate to fast TAT (5 days on average) • Deeper sequencing limits number of samples per run	• Implementation of newer technologies that can speed up actionable results (e.g. Oxford Nano-pore technology) • Transition to POC environment
Complicated validation (Laboratory developed tests, no reliable reference method)	Use of published protocols More universal well-standardized metrics needed

NOTE: POC = point-of-care; TAT = turnaround time
SOURCE: Presented by Karen Carroll, October 13, 2022.

2019, Land et al. (2019) added two more criteria—Real-time connectivity and Ease of specimen collection—making the acronym REASSURED.

Emerging POC testing technologies include microfluidics, biosensors, digital droplet polymerase chain reaction (PCR), and paper-based devices. Carroll noted that these technologies show promise; for example, microfluidics combined with isothermal amplification allows for fast thermal cycling and high sensitivity at the POC. However, there is a need for more research on the barriers to realizing the REASSURED criteria, specifically, the cost of translating these technologies into the clinical environment. During the COVID-19 pandemic, diagnostic development accelerated: clinical labs created lab-developed tests, labs partnered with industry to fast-track technologies, and the government provided research support and regulatory flexibility. Carroll shared several examples of microfluidics-based technologies that were used for POC testing for COVID-19 (Table 2-2).

The promise of POC testing is most evident for certain conditions, said Carroll, including sexually transmitted infections (STIs), tuberculosis, urinary tract infections (UTIs), respiratory infections, malaria, and neglected tropical diseases. There are more than 2.4 million cases of

FIGURE 2-1 Criteria for point-of-care testing
SOURCE: Presented by Karen Carroll, October 13, 2022.

syphilis, gonorrhea, and chlamydia in the United States each year, and resistance among *Neisseria gonorrhoeae* isolates is high (CDC, 2019b). Other STIs of interest include emerging Mycoplasma genitalium, human papilloma virus, Trichomonas vaginalis and herpes simplex 1 and 2. There are several current and future POC tests for STIs; most provide results within 30 minutes and are comparable to the high-throughput instruments currently in clinical labs. Carroll emphasized that the short timeframe is critical because studies show that patients presenting to STI clinics or the emergency department (ED) do not want to "hang around" for more than 45 minutes; the ability to see a patient, diagnose them, and treat them within a 45-minute window is "very powerful." A workshop participant added that there is a need to create a system for simultaneous testing for STIs and resistance markers, rather than conducting them serially, due to these time constraints.

TABLE 2-2 Examples of Microfluidics-Based Tests Developed for SARS-CoV-2

POC Test	Assay Chemistry	Sample Type	Fluid Activation/Control	Signal Detection	Connectivity
Cue Health https://cuehealth.com/	Isothermal	Nasal swab	Capillary/wax valves Fluid mixing by sonication	Electrochemical	Portable Bluetooth connected reader/mobile app
Visby Medical https://www.visbymedical.com/	RT-PCR	Nasal swab	Gear motor/rotary on chip valves	Colorimetric (LFA)	None
Abbott ID Now https://www.abbott.com/	Isothermal	Nasal/NP/ throat	Manual/Manual	Fluorescence	Portable instrument with LED screen

NOTE: LCD = liquid-crystal display; LFA = lateral flow assay; NP = nasopharyngeal; POC = point-of-care; RT-PCR = reverse transcription-polymerase chain reaction
SOURCE: Presented by Karen Carroll, October 13, 2022.

Prior to the pandemic, studies demonstrated the effectiveness of tests using self-collected samples (e.g., I Want the Kit, I Know, and TakeMeHome). In combination with telemedicine, STI clinics turned to home collection tests in the early days of the pandemic. Carroll highlighted the benefits and challenges associated with self-collection tests. They are convenient, private, cost-effective, accurate, and readily accepted by patients; these benefits lead to increased testing and thus increased detection and treatment of STIs. The challenges of self-collection tests include language or literacy barriers for some patients (including those most at need), low specimen return rates, difficulty with surveillance and contact tracing, regulatory issues, and concerns about false positives or negatives.

In summary, said Carroll, there have been unprecedented technological advances that hold promise for enhanced diagnostics in labs and at the point-of-care, but there are a fair number of hurdles that need to be addressed to optimize implementation. These hurdles include

- technical barriers and costs to mass production/commercialization;
- need for better outcome studies to understand patient impact;
- need for studies to understand workflow barriers in clinics and laboratories;
- quality management considerations (e.g., contamination, poor user performance);
- data management;
- regulatory and reimbursement issues for laboratories and industry.

Developer Perspective

The test development process, said Craig Whiteford (Senior Director R&D, Becton Dickinson) starts with the basic question: "What is the need?" Based on the answer to this question, design requirements are developed to describe how the test will fulfill the need. In the case of AMR, he said, the need is for rapid antimicrobial testing for susceptibility or resistance, and design requirements include

- time to results;
- target (e.g. bacteria);
- specimen (e.g., whole blood, respiratory specimen);
- impact on clinical workflow (e.g., does a new test require additional time and staff?);
- regulatory considerations;
- cost.

There are almost always tradeoffs among these design details, said Whiteford, for example, a test may be able to deliver results very quickly but be cost-prohibitive. Developers must also decide on the appropriate technological approach; in the case of AMR, will a test use a phenotypic, genetic, or genomic approach? Phenotypic approaches are limited due to cell division, which takes time and cannot be sped up. Genetic approaches (e.g., PCR) work well and are fairly quick, said Whiteford, but are limited in terms of targets. Genomic approaches (massive parallel sequencing) are the "great promise" of testing in this area.

Whiteford shared a Pugh Matrix that illustrates the benefits and drawbacks of different types of AST and AMR testing (Table 2-3). In the first two columns, traditional manual or automated tests (e.g., disk diffusion) have many advantages but they take more time. The third column shows the limitations of rapid traditional tests (e.g., microfluidic phenotypic systems) in terms of targets, specimen, costs, and clinical workflow. Whiteford explained that these tests are adjunct to other testing, putting a burden on the laboratory and the cost. Genomic predictive tests, seen in the fourth column, are a new approach that hold great promise; however, they are currently limited due to the reliance on AI. Whiteford emphasized a need to build and share a database of information for AI to work with, but there is no current regulatory guidance on AI. Moreover, there is a need for further discussion and collaboration among stakeholders for approaches that use AI, and, additionally, genomic predictive tests are currently quite expensive.

On the right-hand side of the matrix, genetic AMR tests (e.g., PCR) can produce results within 8 hours, but they are limited in terms of targets and the impact on workflow. These tests usually only provide information on resistance markers, which tells a provider what not to treat with but not what should be used. The pros and cons of the genomic approach for AMR testing are similar to the genomic approach for AST. There are also technological barriers to both AST and AMR tests, he said, including the "needle in the haystack" issue: if there are only a few colony-forming units (CFUs) per milliliter of specimen, it can be difficult to ensure that the CFUs are detected by the test.

Reimbursement Perspective

Susan Van Meter (President, American Clinical Laboratory Association) indicated that during the COVID-19 pandemic, the importance of leveraging every modality for testing became clear. Developing and utilizing tests for a variety of settings (e.g., inpatient, ambulatory, consumer) reduced barriers to access and supported clinicians in their workflow. Similarly, Van Meter emphasized a need to think broadly about the kinds of tests that will be useful for antimicrobial resistance. There is tremendous value in

TABLE 2-3 Pugh Matrix of AST and AMR Testing Approaches

Requirements	AST				AMR		
	Trad. Manual*	Trad. Automated	Rapid Trad.	Genomic Predictive	Genetic PCR/Iso	Genomic	
						Targeted	Metagenomic
Time to Results (≤8 hrs.)	x	x	✓	Library Prep	✓	Library Prep	Library Prep
Target(s)	✓	✓	Limited	✓	Limited	✓	✓
Specimen(s)	✓	✓	Limited	Limited	✓	Limited	Limited
Clinical Workflow	✓	✓	Adjunct	SA	Adjunct	SA	SA
IVDD/IVDR	Gold Std	✓	✓	AI	✓		AI
Cost	$	$	$$	$$$	$$	$$$	$$$

	Comprehensive
	Limited / Potential
	X / $$$

✓ Available * Baseline SA = Stand Alone

NOTE: AI = artificial intelligence; AMR = antimicrobial resistance; AST = antimicrobial susceptibility testing; Iso = isothermal; IVDD = In Vitro Diagnostic Medical Devices Directive; IVDR = In Vitro Diagnostic Medical Devices Regulation; PCR = polymerase chain reaction; Std = standard; Trad = traditional

SOURCE: Presented by Craig Whitford, October 13, 2022.

diagnostic tests that help ensure the right patient gets the right treatment at the right time; effective diagnostics save time and effort for both patients and providers and ultimately reduce costs. However, the value of a test is not always easily translated into an appropriate reimbursement. Van Meter added that oversight of the development to tests can cause uncertainty for developers, explaining that there is a lack of an overarching regulatory apparatus for diagnostic tests and technologies. Some tests are developed in laboratories; these laboratory developed tests (LDTs) are regulated by the Clinical Laboratory improvement Amendments (CLIA) under the Centers for Medicare & Medicaid Services (CMS). Other tests are developed for the commercial market and regulated by the FDA. There is some discussion in Congress about modernizing the regulation of diagnostics to create a single risk-based framework, but Van Meter said she does not think the chances of this becoming law are particularly high.

When it comes to bringing a test to market, Van Meter noted that developers need to consider whether there is an existing Current Procedural Terminology (CPT) code for the test. Applying to the American Medical Association for a new code can take between six months and two years. Payer coverage for tests can be complicated and may vary among geographic regions. For example, contractors who provide services to Medicare patients may make local coverage decisions and coverage may vary depending on whether the patient is in an inpatient or ambulatory setting. Within hospitals, coverage for a test is generally rolled into an inpatient Diagnosis Related Group (DRG) rather than reimbursed separately. Coverage in the ambulatory setting is more complicated. If a physician's office provides a test onsite, they will generally bill the payer directly, whereas if samples are collected and sent to a commercial lab, the lab will generally bill the payer. Van Meter noted that Medicare reimbursement amounts for clinical laboratory fees have been reduced several times in recent years, although Congress has repeatedly delayed the reductions. This unpredictability makes it difficult for test developers to contemplate what the market for a particular test might look like, she said. In addition, the reduction in Medicare reimbursement threatens the stability of the clinical laboratory infrastructure, which is critical to the wellbeing of the country.

Other issues to consider when bringing a test to market include clinical guidelines and clinical/consumer uptake. Van Meter said that clinical guidelines often take years to be updated and thus may not reflect the most recent technologies; this can have a negative impact on accessibility and use of new tests. In addition, it can be difficult for clinicians to keep abreast of what diagnostic tests are available and how to employ them. There is a need, said Van Meter, to pursue new innovations in testing but also to leverage and improve the uptake of tests that are available today.

Discussion

Cost

One workshop participant observed that cost underpins many of the issues discussed during this session, including the cost of development, use of diagnostics, and reimbursement. They suggested that one roadblock may be reluctance on the part of hospitals to invest in new instrumentation and a reliance on outsourcing of testing to clinical laboratories. Whiteford agreed and added that outsourcing diagnostic tests also introduces transportation issues. He said that stakeholders should work together to figure out how to fund laboratory testing so that the potential of new technologies is realized. Van Meter emphasized that laboratory substructure—whether commercial labs, hospital labs, or point-of-care testing used in physician office labs—is part of the nation's critical infrastructure. The recent reductions in Medicare reimbursement threaten the stability of this groundwork, and it is essential that the nation makes the necessary investments in building infrastructure to serve patients and communities, noted Van Meter. Technology is advancing to make new things possible but requires the infrastructure to support it.

Development and uptake

Workshop participants asked the panelists to comment on the role of different types of tests, specifically, lateral flow assays and multiplex tests for UTIs. Whiteford said that at-home tests that use lateral flow have been shown to be useful during COVID-19 for triaging patients. Daniel Bausch (Director of Emerging Threats & Global Health Security, FIND, The Global Alliance for Diagnostics) observed that many of the types of tests discussed thus far at the workshop are "near" point-of-care tests and that lateral flow assays can be used as "true" point-of-care tests in the hands of individuals at home. He added that there is an important role for these tests in the United States, but their utility is even more obvious in low- and middle-income countries, where infrastructure, electricity, and price can be barriers to testing in formal healthcare settings. Regarding multiplex tests, Van Meter said that such tests would be useful. For example, a patient presenting with respiratory symptoms could be efficiently tested for COVID-19, flu, and respiratory syncytial virus (RSV), however, it is unclear what the regulatory pathway for such a test would be, how it would be reimbursed, and what clinical guidelines would direct its use. Multiplex testing holds tremendous promise, but there is a need to clarify these issues to encourage development, she said. Jean Patel (Principal Scientific Affairs, Microbiology, Beckman Coulter Diagnostics) agreed that the issues of reimbursement

and guidelines influence test development and uptake. However, there are also examples of tests that are recommended for use and supported by reimbursement but are still not being widely used by clinicians (e.g., detecting colonization with carbapenem-resistant Enterobacterales [CRE] to prevent transmission in a healthcare setting). Van Meter agreed and suggested that there are mechanisms that can be leveraged to promote uptake in these circumstances. For example, public-private partnerships could fund a new technology add-on payment for tests that improve outcomes and enhance stewardship. Clinical guidelines can serve as substantial barriers to uptake and reimbursement, said Van Meter; new technologies often take years to make it into guidelines. She wondered aloud if there was a role for groups such as the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) to highlight key areas and support efforts to develop recommendations that payers can use to make decisions.

Carroll observed that CRE testing is largely used for surveillance, rather than diagnosis, and suggested that one mechanism to promote uptake in this area is to include in budgets funds for CRE and other multidrug resistant (MDR) organism colonization for inpatient care units. Data on key MDR organisms are reported to the National Healthcare Safety Network, so the hospital has a vested interest in reducing indicator organisms. Carroll noted that using public health to leverage these types of AMR testing is one creative solution for getting tests paid for.

Another potential approach for improving development and uptake, said Burnam, is declaring a national health emergency. As seen during COVID-19, an emergency situation (and the associated regulatory flexibility) gives everyone "a big shot of espresso." "Everything just starts working faster and better," he said; investors look for opportunities to fund development and infrastructure, and stakeholders work together to find quick solutions. Declaring a national emergency for antimicrobial resistance could be the solution for many of the issues discussed today.

Bioethical considerations for clinical laboratories

Robin Patel (ID Physician, Clinical Microbiology Laboratory Director, Mayo Clinic) asked Cohen to comment on the bioethical considerations for clinical microbiology laboratory directors in the AMR space. Cohen responded that she would argue that directors do have bioethical duties and that a surveillance approach may be helpful when directors are considering what tests to bring in and how to offer them. For example, directors should be aware of what diseases are coming into their hospitals and what technologies are available for testing. Cohen said that physicians and lab directors "stand in the same kinds of shoes" in terms of their shared bioethical obligations to the patient to do no harm and to act for the good

of the patient. However, before they can do so, they need to be aware of what diagnostics are available; Cohen said there is a need to communicate better about new technologies and how they can improve clinical decision-making. Physicians in particular, she said, are overloaded with information and need support in staying up to date.

Coordination

A workshop participant observed that many speakers had mentioned the need for stakeholders to work together on guidelines for new diagnostics as well as issues around development, reimbursement, and delivery. They asked panelists to comment on the potential for a coordinating body to unite these efforts and to address issues simultaneously. R. Patel responded that developing guidelines can be a lengthy, intense process, in part because of the need for a body of published evidence. It is possible to develop guidelines quickly; for example, during the COVID-19 pandemic the Infectious Diseases Society of America (IDSA) expeditiously put out guidelines. However, this required long hours of work and resources to facilitate the process. J. Patel noted that IDSA has published guidelines for treating infections caused by multi-drug resistant organisms; this can be an invaluable resource for clinicians and other stakeholders making decisions about what tests to provide.

Tradeoffs

A virtual workshop participant asked panelists how stakeholders could balance the tradeoffs between maximizing pathogen or resistance marker coverage versus practical point-of-care needs (i.e., tests that quickly inform clinical decisions). For example, should point-of-care tests broadly cover resistance markers, or should tests focus on common resistance markers? Carroll responded that priorities for testing will depend on the needs of the individual institution, the patient population, and the type of laboratory. However, it does not need to be an either/or situation. Carroll emphasized a need to simultaneously push point-of-care testing to inform treatment decisions and diagnostic tests that enable the collection of public health data for surveillance purposes.

Van Meter took a broader view of prioritization and said that efforts could be focused based on a variety of criteria: the type of bug, the areas where there is the most inappropriate prescribing, or care settings for which tools are available but are not being used. For example, she said, a study found that 30 percent of patients with upper respiratory symptoms who test positive for flu walk out of the doctor's office with a prescription for antibiotics (Havers et al., 2014).

3

Lessons Learned from the COVID-19 Pandemic

Key Points Made by Individual Speakers:

- The ongoing COVID-19 pandemic has highlighted how diagnostic testing is a critical component of the response to a public health threat and shown how nontraditional approaches for testing can be useful (e.g., screening asymptomatic patients, at-home testing, testing on wastewater). (Lutgring)
- As the number of analyses to diagnose antimicrobial susceptibility mount, reimbursement cannot keep pace, nor does scale necessarily add value. To keep costs down, however, the government can play an important role to ensure that bacterial panels to validate targets are readily available. (Greninger)
- Innovation in AMR diagnostics should center on the needs of patients and the realities of the environments where they need the care; the COVID-19 pandemic has demonstrated that an infusion of resources and political will can lead to improvement in testing capacity. (Rodriguez)
- There are resources and support available through the National Institute of Allergy and Infectious Diseases (NIAID) for the development of diagnostics. (Eder)
- The FDA responded to the COVID-19 pandemic with increased flexibility and streamlined processes; these changes may be beneficial for addressing drug-resistant infections more broadly. (Roth)

- Given the complexity of diagnostic technologies and drug-resistance mechanisms, public-private partnerships are critical for development and regulatory approval of innovations. (Persing)

In this session of the workshop, speakers and participants considered the unique challenges for the development of rapid point-of-care diagnostics to address antibiotic resistance. Speakers shared lessons learned from other disease areas, including COVID-19, discussed the development and use of rapid diagnostics to address drug-resistant bacterial infections, and considered generalizable applications and practical approaches to overcome barriers to innovation.

LESSONS LEARNED FROM THE COVID-19 PANDEMIC

From a U.S. perspective, there are three key lessons learned during COVID-19 that are applicable to combating AMR, said Joseph Lutgring (Medical Officer, Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention):

- Testing is not just for symptomatic patients;
- There is a need for more than one type of test for a given disease; and
- Testing is not just for people.

Relatively early in the pandemic, said Lutgring, it became clear that asymptomatic and presymptomatic people could transmit severe acute respiratory syndrome coronavirus 2 (SARS CoV-2), which had a major impact on testing approaches and recommendations. However, screening of asymptomatic people is only beneficial if there are interventions that can protect that person and/or prevent transmission to others. As an example, Lutgring noted if someone receives a positive COVID-19 test result, they could reduce the risk of transmission by self-isolating, wearing a face covering, or avoiding contact with high-risk patients. Over the course of the pandemic, testing of asymptomatic people was recommended for a number of populations, including nursing home residents, K-12 students and staff, hospitalized patients, and workers and residents in correctional facilities. Screening of asymptomatic individuals has also had applications in the context of drug-resistant bacterial infections, particularly for hospital-acquired infections, said Lutgring. For example, the Department of Veterans Affairs (VA) implemented a methicillin-resistant *Staphylococcus*

aureus (MRSA) nasal swab screening program for hospitals; hospitals in Israel have implemented active screening of CRE to reduce infections; and the Netherlands has a policy for active MRSA screening, which may account for the low rates of MRSA in that country (Health Council of the Netherlands, 2007; Schwaber and Carmeli, 2014; VA, 2007). Screening for other organisms—including Vancomycin-resistant enterococci (VRE) and bacteria that produce extended spectrum beta-lactamase (ESBL)—has been attempted, but Lutgring said the utility of such screening depends on whether there are interventions that can be implemented when a person tests positive. For multi-drug resistant organisms, the main interventions are contact precautions (e.g., providers wear gowns/gloves) or isolation. However, in the future there may be decolonization interventions that could reduce the organism burden of the individual and prevent transmission to others. Screening and interruption of transmission have the potential to reduce infection even more than the development of a new treatment. He pointed to a recent workshop hosted by the Centers for Disease Control and Prevention (CDC) and FDA to discuss the state of evidence supporting decolonization and pathogen reduction in colonized patients as a strategy to prevent infection.[1]

According to Lutgring, the second key lesson learned from the COVID-19 pandemic is that more than one type of test is needed for a given disease. As of October 2022, the FDA had issued EUAs for a variety of SARS-CoV-2 tests, including almost 300 molecular tests, 51 antigen tests, and 85 serology tests (FDA, 2022). These tests, said Lutgring, vary in terms of performance characteristics, costs, turn-around times, specimen types, and can be utilized in different ways. For example, patients admitted to the VA hospital in Atlanta are tested using both an antigen and a molecular test; antigen results are faster while molecular tests are more sensitive. A combination of test results can be helpful to inform decisions about bed placement or whether a patient should be quarantined in an airborne isolation room. Clinicians have become savvier about using both types of tests for clinical decision-making, he said. For example, if a patient tests positive on both antigen and molecular tests, that patient likely has an active COVID-19 infection and should be treated. However, if a patient has a negative result on an antigen test but a positive result on a molecular test, more consideration may be given to whether or not that patient has an active COVID-19 infection requiring treatment. In the area of AMR, said Lutgring, a similar testing strategy can be used for *Clostridioides difficile*. There is debate about the best strategy for detecting *C. diff*, with some arguing for nucleic acid amplification tests (more sensitive) and others arguing

[1] See https://info.rescueagency.com/en-us/drug-development-consideration-virtual-public-workshop-cdc-fda (accessed January 25, 2023).

for toxin enzyme immunoassays (more specific). There are facilities that perform a combination of these tests, e.g., screening with the more sensitive molecular test and then performing the more sensitive test to give indications about disease severity, likelihood, or true current infection. Lutgring cautioned that there can be unintended consequences of using multiple diagnostics, particularly if clinicians do not understand what a positive or negative result means. For example, a patient with a positive nucleic acid amplification test and a negative toxin enzyme immunoassay test might be treated with antibiotics even if they do not have an active infection. Lutgring emphasized that as testing strategies become more complex and as more diagnostics become available, it will be important for clinicians to understand how results should be interpreted to best care for their patients.

Finally, Lutgring said, the COVID-19 pandemic has indicated that testing is not just for people. Early detection and containment of pathogens are crucial, but individual patient testing is time- and resource-intensive. The National Wastewater Surveillance System (NWSS)[2] was launched by the CDC in September 2020, to coordinate and build the nation's capacity to track the presence of SARS-CoV-2 in wastewater samples. Information about the presence and level of SARS-CoV-2 in the wastewater combined with other community-level information can help track the impact of COVID-19 on a community. There is ongoing research about how to use this type of surveillance system for antimicrobial resistance detection, particularly for rare pathogens like carbapenemase-producing organisms. For example, a new CDC initiative, the Healthcare Wastewater Antimicrobial Resistance Network, will be conducting research on how to best use wastewater testing, with an initial focus on carbapenemase-producing organisms and *Candida aureus*.

Lessons Learned from the "Access to COVID-19 Tools Accelerator" Program

AMR, like COVID-19, is a global crisis, said William "Bill" Rodriguez (Chief Executive Officer, FIND, The Global Alliance for Diagnostics). FIND is aimed at supporting equitable access to diagnostics everywhere in the world, with a focus on diseases of poverty such as tuberculosis, malaria, hepatitis, and schistosomiasis. When SARS-CoV-2 emerged, FIND's mandate and activities expanded dramatically, he said. The Access to COVID-19 Tools Accelerator (ACT Accelerator)[3] initiative was designed by WHO to speed up efforts for development and deployment of tests, treatments, and vaccines; FIND co-led the diagnostics pillar of the initiative.

[2] See https://www.cdc.gov/nwss/index.html (accessed March 9, 2023).
[3] See https://www.act-a.org/ (accessed January 25, 2023).

Before delving into the lessons learned from COVID-19, Rodriguez gave workshop participants a brief overview of the landscape of diagnostics around the globe. Almost half of the world's population, he said, lacks access to essential diagnostics for diseases such as tuberculosis, HIV, hepatitis, diabetes, and hypertension (Fleming et al., 2021). Basic diagnostic capacity is available in only 1 percent of primary care clinics and 14 percent of hospitals in some low- and middle-income countries (Leslie et al., 2017). Further, 47 percent of the world's population cannot receive a diagnosis when sick, and diagnostic gaps for diseases like diabetes, Hepatitis C, and HIV are significantly larger than treatment gaps, meaning treatments are available but not able to be deployed due to a lack of diagnoses (Fleming et al., 2021). The diagnostic gap is greatest at the primary care level, Rodriguez said, but not much better at most district hospitals and referral hospitals; for example, basic technologies such as tests for pregnancy and syphilis, microscopes, and X-rays are not readily available at most hospitals in some low- and middle-income countries (Leslie et al., 2017). Rodriguez urged workshop participants to keep this "stark environment" in mind when thinking about the global capacity to test for AMR. FIND divides diagnostics into three levels (Figure 3-1). Self-tests are those administered at home or in the community and do not require power, water, or lab equipment. True point-of-care tests are delivered in a primary care facility and do not require lab equipment or reliable power to be stored and administered. Near-patient point-of-care tests are conducted in district hospitals and may

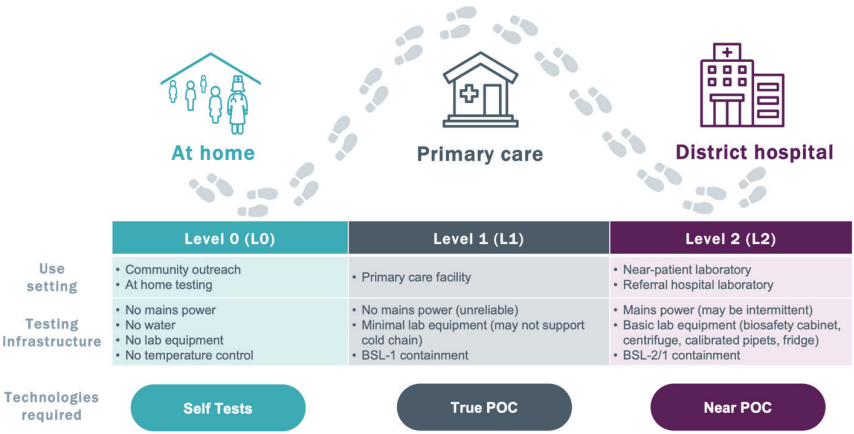

FIGURE 3-1 Fit-for-purpose testing
NOTE: BSL = biological safety level; POC = point-of-care
SOURCE: Presented by William Rodriguez, October 13, 2022; Image courtesy of FIND (www.finddx.org), 2023.

require basic lab procedures such as centrifuges and biosafety containment measures. Rodriguez emphasized that when considering diagnostics—whether for COVID-19 or AMR pathogens—it is essential to meet patients where they are and where they present for care.

The COVID-19 pandemic put testing in the spotlight as it has never been before, said Rodriguez. Before the pandemic, most non-expert stakeholders he talked with were unfamiliar with tools such as PCR tests or rapid tests, but "everyone understands testing now everywhere in the world." Rodriguez noted that this change put a new emphasis on what testing can accomplish and set a new global priority on testing for all diseases. The COVID-19 pandemic also demonstrated what a large investment of resources can do. Over the first nine months of the pandemic, testing capacity went from nothing to dramatically high capacity in most places in the world, including most of Africa and parts of Southeast Asia. It took about five years to develop a molecular test for tuberculosis that could be used globally and a few years for hepatitis C. In contrast, the first commercially available molecular tests for COVID-19 took only 64 days, and noncommercial tests were developed a mere 72 hours after the genome of the virus was identified (Molecular Devices, 2022). The first rapid test for COVID-19 available at scale globally took 236 days, while rapid tests for tuberculosis and hepatitis C are still "pipe dreams." The lesson, said Rodriguez, is that when resources are applied and the prioritization is high enough, a lot can be accomplished. He noted, however, that there remain barriers to the development and deployment of tests around the globe, including regional manufacturing capacity and regulations. Rodriguez asserted that expansion and diversification of local production is needed to meet the global needs for testing, and regulators need to be more responsive. He noted that more complex tests, such as multiplex molecular tests, will likely have an even greater challenge getting through regulatory hurdles.

In addition to advancing the development and deployment of molecular and rapid tests, Rodriguez noted that the ACT Accelerator also dramatically improved the global capacity to perform genomic sequencing tests. Nearly every country can now do sequencing at a reasonable level, and many countries can do sequencing at high levels and have national genomic programs. At the time of the workshop, nearly 13 million sequences of SARS-CoV-2 had been contributed from 215 countries and territories (GISAID, 2023). Global capacity to perform sequencing is important for COVID-19 but is also critical to the future of efforts on AMR.

Rodriguez said that issues like COVID-19 or AMR are like climate change; they are complex, political, health-related, and fragmented. Similarly, the response requires close coordination and a shared agenda across many agencies that are all trying to respond to the crisis. One of the

major successes of the ACT Accelerator was bringing everyone together on a weekly basis to share successes, challenges, and priorities for testing, research and development, commercialization, and policy. This model, he said, needs to be applied to other diseases, especially AMR. However, despite collaboration and investment of resources, gaps persisted in procurement and uptake among countries. To control the spread of SARS-CoV-2, stakeholders developed a consensus goal of one test per 1000 people per day. Over the first two years of testing, low-income countries were conducting about 0.02 tests per 1000 people, middle-income countries were conducting 0.15 tests per 1000 people, and high-income countries were vastly exceeding the target with a high mark of 7 tests per 1000 people per day (Figure 3-2). Rodriguez said that while stakeholders attempted to provide equitable access to COVID-19 testing, they "didn't come close" to meeting their target to address the pandemic.

With lessons from the COVID-19 pandemic in mind, Rodriguez stressed that "the patient journey needs to be at the center" of a diagnostics strategy. Many of the emerging platforms for AMR—including POC platforms for sepsis and triage, and near-POC multiplex molecular platforms—would not be fit-for-purpose in many settings around the world. Rodriguez laid out a few challenges during the COVID-19 pandemic that may be relevant for AMR, including

- complexity of the global problem requiring collaboration among clinicians, epidemiologists, and politicians;
- limited evidence to inform policy;

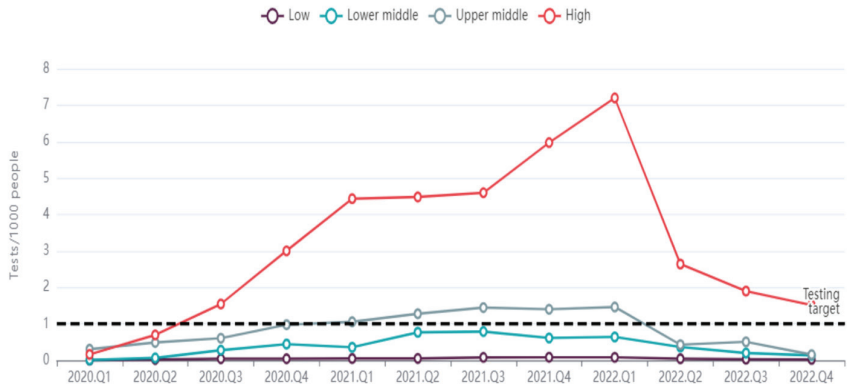

FIGURE 3-2 COVID-19 tests conducted per 1000 individuals per day
SOURCE: Presented by William Rodriguez, October 13, 2022; Image courtesy of FIND (www.finddx.org), based on data from the FIND COVID-19 test tracker, 2023.

- underprepared market;
- lack of clear product requirements;
- insufficient regulatory harmonization.

Rodriguez said that collaboration between academia and industry resulted in the rapid development and approval of COVID-19 tests, and government investment helped reduce costs for diagnostics, thus increasing manufacturing capacity and capability and improving access globally. The question, said Rodriguez, is whether these lessons learned can be applied to "rise to the challenge of AMR" over the years to come.

PROGRAMS TO ACCELERATE THE DEVELOPMENT OF DIAGNOSTICS

Paul Eder (Senior Scientific Officer, Concept Acceleration Program—Diagnostics, National Institute of Allergy and Infectious Diseases) began by describing what he means by "AMR" and "AST," noting that these terms are used in different ways by different people. For the purposes of his talk, AMR means antimicrobial resistance prediction based on genotypic data, while AST refers to antibacterial susceptibility characterization through empirical data.

At NIAID, said Eder, there are a number of programs and resources aimed at accelerating the development of diagnostics for AMR. NIAID supports Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) Diagnostics, Therapeutics, and Preventives, and offers pre-clinical services for diagnostic development. Additionally, the Concept Acceleration Program (CAP)[4]—which helps support innovative technologies, platforms, and provides strategic advice to help shepherd candidate products through the research and development (R&D) and regulatory processes—at NIAID is well-established in the areas of vaccines and therapeutics, while the focus on diagnostics is newer. CAP has worked closely with the CARB-X and FIND to gather expertise and fill gaps in knowledge of the R&D and regulatory processes. He noted that CARB-X is currently in its second round of funding, which includes a focus on developing cost-effective and quick testing for gonorrhea. Bringing new technologies and assays to market quickly, and ensuring their success, said Eder, will improve the nation's response to future emerging infectious diseases.

[4] See https://www.niaid.nih.gov/about/biodefense-research-resources-contacts (accessed March 6, 2023).

NIAID's Omnibus Broad Agency Announcement (BAA)[5] is an annual solicitation for proposals to combat antimicrobial resistance. The areas of focus for 2023 include

- Faster bacterial identification direct from whole blood in under 4 hours;
- AST from positive blood culture or bacterial isolate in less than 2 hours;
- Improved performance in nucleic acid sequencing, mass spec sensitivity, protein sequencing, antigen or toxin capture and detection.

The awards for BAA are based on milestones and successful deliverables, based on a negotiated statement of work. This process—in which success must be made at each phase to proceed—is different from the traditional grant process. The budget for 2023 is up to $12.8 million for contracts across multiple research areas (NIH, 2022). Eder noted that contract awards are based on agency priorities, and currently they will not support development of diagnostic tests for pathogen ID from culture or isolate (bacterial plate), diagnostics that rely solely on the detection of host-response proteins, basic research and discovery of new host-based diagnostic targets, or diagnostic efforts that will require significant hardware development. Eder explained that other opportunities exist for these areas of development, but the hardware development is often an "albatross" that can significantly delay the process.

Pre-Clinical Services (PCS) is another way in which NIAID supports the development of diagnostics, said Eder. Helping product developers with PCS lowers their risk and encourages commitment to product development to reduce the burden on infectious disease. The program provides expertise and capability in product development to accelerate promising discoveries and fill gaps along the product development pathway. The agreements between NIAID and the developer, said Eder, assure confidentiality, maintain intellectual property of the developer, and encourage publication. Services provided by NIAID include specimen acquisition, reagents and assays, and product development support (e.g., design control, risk management). Services that are not provided include testing in animal samples and instrument and consumables development. Applying for support is a simple process, and most groups are eligible, including non-U.S. entities, academics, start-ups, NGOs, companies, and government entities. NIAID makes decisions based on priority, significance, innovation, preliminary data, value, and product development plan.

[5] See https://sam.gov/opp/70720b778a894ce2ae311cc844f2a410/view (accessed March 6, 2023).

Finally, said Eder, NIAID offers research resources for diagnostics developers. These resources include organisms and reagents; resources for basic, bioinformatics, and 'omics research; structure determination of proteins; and biocontainment facilities.

PANEL PERSPECTIVES

The panel brought together individuals with different perspectives to discuss the challenges in development and use of rapid diagnostics in healthcare settings. Eder moderated the panel, as well as a question-and-answer session that followed.

Clinical Pathologist Perspective

The COVID-19 pandemic led to advancements in medicine that were accomplished in a short amount of time, said Alex Greninger (Assistant Professor and Assistant Director of the Clinical Virology Laboratories, University of Washington Medical Center). Greninger said it is possible to capture this energy again for an issue like AMR, but the volition is lacking. There have been significant advances in rapid diagnostics in the healthcare space in recent years. Multiplex testing platforms, such as the BioFire FilmArray Pneumonia plus Panel, have demonstrated rapid automated testing of more than 30 targets with turnaround time of about an hour and hands-on time expected to be about a minute (Buchan et al., 2020). As panels grow to include ever-increasing numbers of analytes, reimbursement becomes a major issue. Greninger shared the 2022 Clinical Laboratory Fee Schedule (CLFS) rates for testing for respiratory viruses: with 3-5 analytes, the National Limitation Amounts (NLA) is $143; for 6-11 analytes, it is $218; and for 12-25 analytes, it is $417 (Centers for Medicare and Medicaid Services, 2023). The question, said Greninger, is how to value scale. There are efforts within the federal government to reduce reimbursement for laboratory testing, but with the government looking to cut costs while laboratory tests increase in complexity, said Greninger, this may not be a sustainable path forward.

Greninger shared a few thoughts on the development and use of rapid diagnostics in the healthcare setting from his perspective as a clinical pathologist. First, he said, "flexibility matters." Multiplex tests and other rapid tests may end up in a wide variety of settings, from a quaternary hospital with AMR experts to a community hospital that doesn't have the relevant antibiotics on formulary. Second, interpretation of tests should be "baked in" to their design. Greninger said that many people, including clinical pathologists, do not have an expert-level understanding of AMR and the tests used. Third, he said that reimbursement will be a major issue,

particularly for tests with a high number of targets. There is no way to pass along costs for highly complex inpatient testing with expensive reagents, and this is money "leaving the system." Instead of using a complex machine to run tests automatically, Greninger said he would rather hire a technician who can run tests manually as well as answer the phone and fill out paperwork. Fourth, it is a challenge to get specimens for validation of new markers. As there are greater numbers of esoteric antimicrobial resistance markers, labs need to be able to order bacterial panels to validate targets. Greninger said there is an opportunity for a government agency to make these panels available so that tests can be brought online more quickly; he suggested that the Biological Exposure Indices (BEI) Resources Repository could play a role in distribution.[6] Finally, he said that there is a need for research on whether separating AMR detection from a given species is appropriate or useful.

Regulatory Perspective

Kristian Roth (Deputy Director, Division of Microbiology Devices, FDA) shared his perspective as part of the review organization that authorizes tests for infectious disease. He said that companies are sometimes hesitant to bring new technology and new approaches to the FDA for review, particularly when there are no established clinical practice or clinical guidelines. Tests can sometimes also be well-established in clinical practice but not yet reviewed by the FDA. He gave several examples of how the FDA deals with these types of situations. When there is a low burden pathway to catch up with clinical practice, it is fairly simple to grant a claim (e.g., reviewing a quantitative test for cytomegalovirus when there are a number of qualitative cytomegalovirus tests on the market). The FDA has also used master protocols to grant new claims, for example, extragenital testing for gonorrhea. When multiple sponsors are following a master protocol, the FDA can grant a claim that would be difficult to validate to several sponsors in parallel. The FDA has also used a combination of existing literature and smaller clinical studies; for example, procalcitonin was used for years and was finally authorized after a process that included a panel meeting, outside opinion, evidence from the literature, and a small clinical study that validated each test's performance. The final approach, said Roth, is the "brick-by-brick approach" in which data comes in and allows the granting of new claims for different intended uses.

Roth turned to lessons learned from the COVID-19 pandemic. He said that accelerated FDA review times are "good for everybody," including

[6] See https://www.niaid.nih.gov/research/bei-resources-repository (accessed January 25, 2023).

developers and the public. At-home testing for COVID-19 paved the way for at-home testing for other infectious diseases and more of these advancements are on the horizon. However, Roth noted a major negative impact of the pandemic has been the reduced level of clinical data that is expected. Manufacturers are in favor of the lower burden, but Roth questioned if it is good for public health. The EUA process greatly reduces the quality requirements that test manufacturers are responsible for; this has resulted in a tremendous number of recalls. According to Roth, Class I recalls, the most serious risk recall, nearly tripled in the last two and a half years. Further, the FDA has had considerable integrity concerns with the clinical data that are submitted, such as clinical studies that are too good to be true or biased clinical studies. These issues, said Roth, take "tremendous resources to address in a manner where all developers get an equal chance to get an EUA."

Industry/Economic Perspective

There are several challenges in moving a new AST test from development to clearance, said David Persing (Head of Research and Development, Cepheid). There is growing complexity of resistance mechanisms for each antimicrobial class; complex issues including the numbers of sample types, different transport media, and CLIA waivers; and accessing the required specimens for clinical trials is difficult given the decreasing number of labs willing to participate. Given these complexities, said Persing, public-private partnerships may be a useful mechanism for moving tests into clinical use. Persing shared his experience of developing an assay called "MTB/RIF" that simultaneously and quickly tests for Mycobacterium tuberculosis (MTB) and resistance to rifampin (RIF). The test uses species-specific, nested PCR amplification of the MTB drug resistance target, and detection of rifampin resistance-conferring mutations via molecular beacons (Boehme et al., 2010; Hunt et al., 1994). MTB/RIF was the first demonstration of scalable implementation of direct-from-specimen detection of drug resistance, which started in 2005 with support from FIND. It was launched globally in 2010 with WHO endorsement and received 510(K)-clearance in the United States in 2015 with data from a National Institutes of Health (NIH) supported clinical trial. Persing shared that since 2015, 112 million test cartridges have been produced.

Since launching MTB/RIF, Persing has been asked a number of questions from people around the world. Investigators and clinicians want to know if they can get the equivalent of MTB/RIF for NG ceftriaxone resistance or a cartridge for NG fluoroquinolone susceptibility. They want a direct-from-urine test for ESBL-producing organisms, or a cartridge for direct detection of ESBLs, and carbapenemases for severe lower respiratory

infections and complicated UTI/urosepsis cases. However, said Persing, it is important to consider whether it is acceptable to test for a drug-resistance allele while not also identifying the organism at the species level. For example, does it matter if a UTI is caused by *Escherichia coli* (*E. coli*) or by klebsiella, or is it enough to detect the resistance allele to predict the likelihood of being resistant? The connection between predicting phenotypic resistance from genotypic information is "strong and getting stronger," said Persing, but it is not as strong for predicting susceptibility. For now, conventional susceptibility testing is still required to fine tune drug selection.

Persing shared his experience working on the Xpert® Carba-R Test to detect carbapenem-resistance genes. The cartridge detects five families of resistance genes and can use specimens from rectal swabs, peri-rectal swabs, or carbapenem non-susceptible colonies (Jin et al., 2020). Persing emphasized that one important feature of this test is that it differentiates between metallo-beta-lactamases and non-metallo-beta-lactamases for the purpose of determining appropriate therapies. It is becoming "increasingly challenging" to keep up with the sheer number of targets that are emerging; because it is unknown which will become dominant, there is a need to maintain vigilance and modify tests as necessary to keep up with the variants. To obtain regulatory clearance, over 3,000 samples were tested, cultured, and sequenced as gold standards, and supplemental strains were used to evaluate the tests for contrived specimens. Government support was critical in validating the assays, said Persing. For example, the Antimicrobial Resistance Isolate Bank has bacterial isolates with emerging AMR genes that have been confirmed by DNA sequence analysis.[7] Persing said that this continually updated resource is very valuable due to its comprehensiveness. The Independent Test Assessment Program (ITAP) at NIH is another government resource that could help with the regulatory process through the FDA.[8] ITAP is aimed at accelerating regulatory review and availability of over-the-counter tests with an initial focus on COVID-19 tests. ITAP has recently expanded its purview to include mpox,[9] and it could be a potential mechanism to accelerate the availability of AMR tests.

In summary, said Persing, direct detection of drug resistance is possible and effective when results are delivered in an actionable timeframe. There is significant potential for high-impact rapid AMR testing in patients with

[7] See https://www.cdc.gov/drugresistance/resistance-bank/index.html (accessed January 25, 2023).

[8] See https://www.nibib.nih.gov/covid-19/radx-tech-program/ITAP (accessed January 25, 2023).

[9] Shortly after this workshop was held, the World Health Organization recommended changing the name of "monkeypox" to "mpox." These proceedings have been edited to use the updated language. https://www.who.int/news/item/28-11-2022-who-recommends-new-name-for-monkeypox-disease (accessed January 30, 2023).

sepsis and "sepsis-adjacent" conditions. In an environment where technologies and resistance mechanisms are increasingly complex, the pathway to FDA clearance will become more complicated; public-private partnerships may be a critical approach to facilitate timely FDA clearance of novel products.

DISCUSSION

Advantages and disadvantages of separating bug and drug testing

Eder pointed to the potential for separating "bug and drug" testing—for example, conducting a test to detect the presence of antimicrobial resistant genes rather than the pathogen responsible for the infection. Eder asked panelists to comment on the advantages and disadvantages of this approach.

Persing used sepsis as an example of a case in which testing for AMR but not the specific organism could be appropriate. About 20 to 40 percent of sepsis cases originate in the urinary tract and about 20 to 40 percent in the respiratory tract (Chou et al., 2020). The question, he said, is whether testing for resistance markers at these sites would be sufficient to direct therapy in a patient with sepsis, and what impact would this testing have on patient outcomes? Persing noted that studies on this approach would be complicated but worth doing because they could lead to dramatic improvement in antibiotic stewardship and antibiotic selection. R. Patel said that she has grappled with this issue in the area of UTI diagnostics and shared two key considerations. First, it is important to ensure the patient being diagnosed with an infection actually has an infection; for example, there are patients with asymptomatic bacteria who may be diagnosed with UTI. Second, there is debate over whether it is necessary to know the name of the responsible organism or whether knowing how to treat it is sufficient. This issue created a lot of controversy among R. Patel and her colleagues, and she observed that the field of medicine may not be quite ready to accept treating an infection without knowing what it is.

Carroll said that an important consideration is where the infection is located and what this means for interpretation of a test for resistance markers. For example, if a patient has signs and symptoms of a UTI and there are resistance markers in the otherwise sterile urine sample, Carroll would feel comfortable using this information to direct treatment without information about the specific pathogen. However, a respiratory infection is a "whole different quagmire." Resistance markers can be linked to normal respiratory flora or to the pathogens responsible for the infection. Because of this difference, she said, there is no universal approach for separating bug and drug testing, but there could be potential in areas that are otherwise sterile.

J. Patel agreed that there is likely no universal approach but pointed out that there are some resistance markers that lead to clearer decisions. For example, identifying a carbapenemases encoding gene in a urine specimen is very different than identifying ESBL in a urine specimen. There are more treatment options for an ESBL-producing organism, and J. Patel expressed worry that this type of testing might unnecessarily drive treatment escalation.

Rodriguez suggested that different types of clinicians might be amenable to using rapid diagnostics to inform decision-making. For example, emergency department physicians are accustomed to making decisions with minimal data to triage patients, while an infectious disease specialist may want a more comprehensive dataset. Ultimately, it may come down to regulators and payers and how they view the utility of these tests. In the global context, most clinicians would likely be willing to make decisions based on minimal data, but the future of these types of tests may depend on whether the WHO believes that it is sufficient to test for antimicrobial resistance without identification of the organism.

Following up on the importance of the regulatory perspective, Eder asked Persing and Roth to comment on the considerations for moving this type of approach through the regulatory process. Persing said that Cepheid does not have a particular strategy at this point but is interested in moving into the UTI space because of the potential for a significant impact. Roth said that in making a regulatory decision on this approach, the FDA would consider many issues, including sterile vs. non-sterile sites, potential for co-infections, and the availability of phenotypic data to validate claims.

Challenges of at-home testing

During the COVID-19 pandemic, at-home testing in the United States became more widespread and more user-friendly than it had ever been, said Eder. However, he noted that at-home testing requires self-collection of specimens, which may be prone to error. Roth pointed out that self-collection and interpretation improved as time went on during the COVID-19 pandemic. While there was a learning curve, people may now be as capable of collecting a sample as a health provider. However, this may not be the case for all types of samples. For example, it would be challenging for an mpox patient to collect a quality sample. Persing and Eder agreed that there is a need to design diagnostic tests in a way that enables users to collection specimens of adequate quality.

Another challenge of at-home testing, said Eder, is in the interpretation of results. He shared a story about a relative who called him after an at-home COVID-19 test and reported that his results were positive because there was a "huge line at the C, and C must mean COVID." Daniel Bausch (Director of Emerging Threats & Global Health Security, FIND, The Global Alliance

for Diagnostics) suggested that as the technology improves for at-home tests and it becomes possible to run multiplex tests, it may be beneficial to simplify the results. For example, instead of having seven lines on a lateral flow assay that tests for seven pathogens, there could be one line for "viral disease" and one line for "non-viral disease" Based on this simplified result, the patient could follow up with their provider as necessary and potentially forestall some AMR by reducing the use of unnecessary antibiotics.

While not the primary focus of this workshop, global applications should also be taken into account. Millions of people around the world do not have routine access to health facilities and clinical testing. When considering the value of self-tests on a global level, Rodriguez said, the comparison should not be between self-testing and clinic testing, but between self-testing and no testing. Some self-tests may not perform quite as well as clinical tests, but the choice for many people is between a test with a slight drop-off in performance or no test at all. Rodriguez said that the performance of a self-test depends in part on the ease of specimen self-collection and that some specimens are easier to collect than others; the utility of a self-test needs to be considered on disease-by-disease, test-by-test, and sample-by-sample bases. However, he emphasized that the ability to access a test usually "dramatically outweighs the small drop-off in performance from self-testing."

Leveraging pandemic collaborations for AMR

Eder shared a list of resources that NIAID offers to developers and stated that public-private partnerships bring together the resources of the government with the ingenuity of the private sector. Roth shared a project in which NIH collaborated with the University of Massachusetts to collect data on COVID-19 testing; these data were collected during an emergency situation and are now being used to make regulatory decisions. Roth said that they are hoping these sorts of partnerships can continue in more traditional settings and in other areas outside of COVID-19. Trainor asked Roth whether there are plans to leverage ITAP for other disease areas; Roth said he didn't know. ITAP was tremendously important for the FDA during COVID-19, he said, because it removed questions about data quality and integrity due to the master protocol style. Data were submitted on an ongoing basis, which allowed the FDA to make input or ask for corrections or interpretation as the program went on. It was a tremendous success, resulting in six over the counter COVID-19 tests and is now being used for mpox.

Leveraging pandemic data management processes and infrastructure for AMR

During the COVID-19 pandemic, data management processes and infrastructure were established to help manage the sheer number of tests

being conducted, said Trainor. When considering how these resources could be leveraged for AMR, Rodriguez said that FIND is actively working to apply COVID-19 tools and policies to the issue of AMR. Currently, there remains a significant gap in AMR data for many parts of the world. A new WHO hub for pandemic preparedness will consider global surveillance mechanisms and may yield insights that could apply to AMR (WHO, 2022b). The challenge, said Bausch, is figuring out how to integrate AMR surveillance into routine healthcare systems; parallel systems are infeasible and unsustainable.

A workshop participant observed that due to COVID-19, there has never been a more acute awareness of infectious disease. "Amidst chaos lies opportunity," he said, and this is the time to get out the message that antimicrobial resistance is a major threat to health.

4

Incentives at the Intersection of Drug Development and Complementary Diagnostics

Key Points Made by Individual Speakers:

- Partnerships between diagnostics and therapeutics companies can help optimize clinical trials by enabling the selection of patient population, saving time and cost, and limiting unnecessary patient drug exposure. (Raymond-Schwartzman)
- Innovation involves risk, and partnerships between diagnostics and therapeutics companies can help distribute the risk. (Frank)
- Market forces alone may not be sufficient to drive development of diagnostics and therapeutics; the government has an important role to play in supporting innovations in this area. (Sciarretta)

In the field of diagnostics and antibiotic development, said John Billington (Head of Commercial Pipeline & Health Security, Policy & Advocacy, GSK), there is a struggle to define the value proposition. Misalignment exists between the true value for patients in the marketplace and the reimbursement value; this misalignment makes for a "broken marketplace" for antibiotics and market weaknesses for diagnostics. Policy opportunities or incentives to correct these market inefficiencies are needed, said Billington. Speakers in this session explored incentives and disincentives for the development of rapid diagnostics and new antibiotics and discussed innovative approaches to foster innovation at the intersection

of complementary diagnostics and drug development. In this discussion, Billington said, "incentives" may be defined as key elements that will result in a more robust marketplace for diagnostics and antibiotics together. He noted that because of differences in the value propositions and market characterization of diagnostics and antibiotics, there may be divergence in the kinds of incentives that are appropriate for each type of product.

PANEL DISCUSSION

Case Study: Partnership Between bioMerieux and Entasis Therapeutics

Clinical trials for therapeutics are long, costly, and risk failure, said Valérie Raymond-Schwartzmann (Companion Diagnostics Senior Program Director, bioMerieux). Partnerships between diagnostic and therapeutic companies can help optimize clinical trials by enabling the selection of the right patient population, saving time and cost, and limiting unnecessary patient drug exposure. In addition to increasing the probability of clinical trial success, if the drug and diagnostic reach the marketplace, the partnership can help ensure that patients receive the best course of treatment. A personalized medicine approach that combines diagnostics and therapeutics, explained Raymond-Schwartzmann, could help ensure the most appropriate choice of drug given to a patient increases the chances of a positive outcome, while reducing the risk of undesirable side effects; this in turn leads to safer drug adoption and prescription practices.

The diagnostic-therapy combination has key benefits for patients, pharmaceutical companies, and diagnostics companies, she said. Patients experience quicker selection of the optimal therapy, improved outcomes, reduced side effects, and a deeper understanding of the disease and medical decision. Pharmaceutical companies gain an increased probability of clinical trial success, safer drug prescription practices that protect drug efficacy and prevent misuse, and the opportunity to get a premium reimbursement because a higher medical value is being delivered to patients. For diagnostics companies, there is increased recognition of their medical value and opportunities for collaboration on market access, medical education and promotion, and reimbursement.

Raymond-Schwartzmann described the BIOFIRE® Pneumonia Panel (BPP) as an FDA-cleared and CE-marked multiplex PCR system that integrates sample preparation, amplification, detection, and analysis into one closed system, and requires two minutes of hands-on time with results available within one hour (Buchan et al., 2020). It is a comprehensive panel with multiple targets, including bacteria, viruses, and resistance markers. It is intended for use in diagnosing direct-from-sample lower respiratory tract infections and uses samples from sputum or bronchoalveolar lavage.

It can be used in outpatient, inpatient, or emergency department settings. Next, she described how the BPP could be used to optimize a clinical trial for a new antibiotic (Figure 4-1). Potential subjects for the trial would be hospitalized adults with respiratory symptoms; Raymond-Schwartzmann noted that infections could be caused by different pathogens with similar clinical symptoms. With a drug targeted at *Acinetobacter baumannii*, it would be critical to identify which patients were infected with this specific pathogen. The BPP can be used to quickly screen patients, and those with a positive result are enrolled. Raymond-Schwartzmann observed that if only one patient was enrolled out of every 6 to 10 patients screened, screening would help a large proportion of patients avoid exposure to an unnecessary treatment.

Alita Miller (Chief Scientific Officer, Entasis Therapeutics) shared an example of how BPP was incorporated into a clinical trial comparing the safety and efficacy of sulbactam-durlobactam (SUL-DUR) vs. colistin for the treatment of carbapenem-resistant *Acinetobacter calcoaceticus-baumannii* complex (ABC) infections. The *Acinetobacter* Treatment Trial Against Colistin (ATTACK) trial[1] was a global Phase 3 study that enrolled 183 patients from 16 countries.[2] The study had two parts. In Part A, patients with documented ABC infections were randomized to receive either SUL-DUR or colistin, with a primary endpoint of all-cause mortality at day 28. In Part B, patients who were not eligible for Part A, because their infection was colistin resistant or the patient was intolerant to colistin, were given SUL-DUR. The data showed that SUL-DUR was non-inferior to colistin for all-cause mortality and was statistically significantly less nephrotoxic.

BPP was used in ATTACK to enable early identification of ABC in respiratory samples from patients being evaluated for enrollment eligibility, said Miller. Although the BPP test can detect multiple viral or bacterial pathogens, only positive results for ABC were considered or documented for enrollment purposes in ATTACK. All 83 sites were given the device and encouraged to use it, but it was not required. The study protocol required each patient to have a respiratory sample processed for standard culture in a lab. Patients who met all other enrollment criteria and had a positive ABC result on the BPP test were enrolled in the study while awaiting culture results; if the culture was negative, the patient was withdrawn from the trial. Of the 83 sites, 73.5 percent used BPP to evaluate pneumonia patients,

[1] See https://clinicaltrials.gov/ct2/show/NCT03894046 (accessed January 31, 2023).

[2] Results from the ATTACK study are expected to be published in the second half of 2023 but were not yet public at the time of the workshop. See https://investors.entasistx.com/news-releases/news-release-details/entasis-therapeutics-initiates-global-phase-3-pivotal-trial (accessed January 25, 2023).

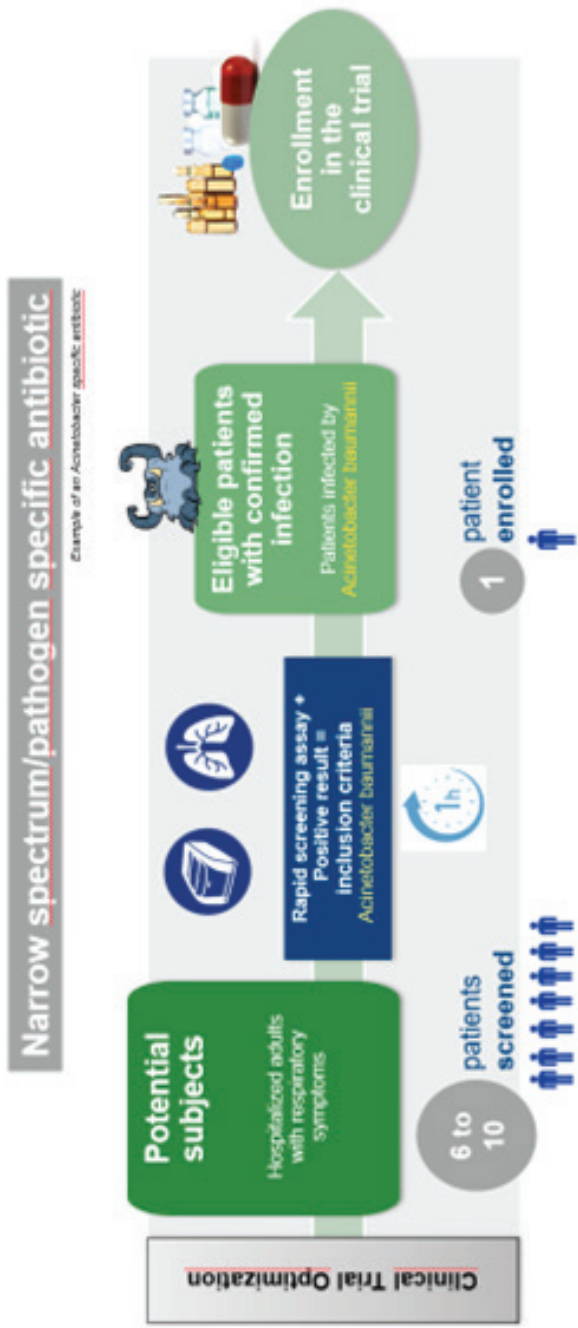

FIGURE 4-1 Clinical trial with diagnostic screening
SOURCE: Presented by Valérie Raymond-Schwartzmann, October 13, 2022; BIOMÉRIEUX, the BIOMÉRIEUX logo, PIONEERING DIAGNOSTICS are used, pending and/or registered trademarks belonging to bioMérieux, or one of its subsidiaries.

and a total of 422 BPP tests were performed for ATTACK. Of these, 123 patients tested positive for ABC on the BPP, and 106 of these were also culture positive for ABC.

This trial represents the first successful competition of a clinical trial to evaluate pathogen-directed therapy for a drug resistant gram-negative infection, said Miller, and a key component of that success was the ability to make enrollment decisions within 48 hours using a rapid test. Most sites that were provided with the test used it, and 70 percent of patients were able to be excluded from enrollment by using the BPP. Further, there was a high correlation between the rapid test and culture results. Miller said that these data suggest the enrollment of pathogen-directed clinical trials can greatly benefit from the use of a rapid diagnostic test, and personalized antibacterial therapy can lead to better patient outcomes.

Biotechnology Perspective

Despite the need for new antibiotics, there are challenges when it comes to financing clinical trials, obtaining FDA approval, and moving a new antibiotic onto the market, said Gregory Frank (Director, Global Public Policy, Merck). Many antibiotic companies, particularly small biotechnology companies, have entered the market and faced intense challenges that often left them in bankruptcy or having to sell off the company. Frank noted that these examples speak to the need for collaboration between antibiotic and diagnostic developers to share the risks associated with antibiotic development and increase the chances of success, as seen in the BPP/ATTACK example discussed above. There are incentives available to support antibiotic development, said Frank, but it is unknown how effectively these incentives link support for antibiotic development with support for complementary susceptibility testing. Billington added that in addition to risk-sharing among companies, a third party (e.g., the government) could play an important part in collaboration and sharing risk.

Biomedical Advanced Research and Development Authority Perspective

Kim Sciarretta (DRIVe Launch Office Branch Chief, Biomedical Advanced Research and Development Authority (BARDA)) focused her remarks on three areas: preparation for emerging threats, the clinical value of products, and the role of BARDA in catalyzing innovation in this area.

Preparedness

As a preparedness and response organization, BARDA focuses on responding to current threats as well as developing the flexibility and agility

for responding to future threats, said Sciarretta. One way in which BARDA pursues this goal is by considering antibiotics and diagnostics that target more than just one pathogen. This could take the form of platform-type diagnostics that are multiplex or that can rapidly adapt to new pathogens. Another area of focus is on the host-response in disease. For example, sepsis is a host dysregulation and organ dysfunction that occurs because of infection. Monitoring and targeting the host response through diagnostics and therapeutics may be an appropriate means to address AMR threats. Sciarretta noted that close to 80 percent of sepsis cases arise outside of the hospital setting, and she emphasized the importance of early identification and mitigation in multiple types of settings (Novosad et al., 2016).

Role of BARDA

BARDA's mission is to secure the nation from threats, such as pandemics and emerging infections, through advanced development of medical countermeasures. This mission, said Sciarretta, enables BARDA to establish public-private partnerships, which have led to 64 FDA approvals, licensures, and clearances to date (BARDA, 2022). BARDA's 2022-2026 strategic plan contains a prominent commitment to combat antimicrobial resistance through approaches including reinvigorating the antibiotic pipeline and catalyzing innovation across the medical countermeasure pipeline.[3]

Sciaretta said that BARDA is more than a funding agency and is available to provide wraparound support and expertise in any stage of the product development cycle, including regulatory approval. Funding is provided by BARDA through several mechanisms, including

- BARDA Broad Agency Announcement:[4] focused on topics that align with BARDA's strategic plan, including the antibacterials division and diagnostics division;
- DRIVe EZ-BAA:[5] rapid turnaround, smaller dollar value funds aimed at de-risking innovative and promising technologies;
- Project BioShield:[6] supporting advanced development and procurement of products.

In addition to funding, BARDA has an accelerator network to support entrepreneurs and early technology development as well as strategic

[3] See https://medicalcountermeasures.gov/barda/strategic-plan/ (accessed January 27, 2023).
[4] See https://medicalcountermeasures.gov/barda/barda-baa/ (accessed January 27, 2023).
[5] See https://drive.hhs.gov/partner.html (accessed January 27, 2023).
[6] See https://www.medicalcountermeasures.gov/barda/cbrn/project-bioshield (accessed January 27, 2023).

public-private partnerships such as CARB-X. Finally, BARDA recently established a ventures program in which BARDA can take an equity stance in financing companies to provide a unique means of funding and support to technologies that are relevant to BARDA's mission.

DISCUSSION

Challenges of partnerships

Raymond-Schwartzmann said that one challenge in collaboration is finding the right time to form a given partnership. If an agreement is made too early in the drug development process, there is the risk that the drug may fail before trials begin. If an agreement is made too late in the drug development process, the diagnostics company might not be able to develop a test in time. Raymond-Schwartzmann suggested that the right time to begin discussions is during Phase II, and both parties should anticipate that it will take time to agree on the details of the collaboration. During the development process, the drug and the diagnostic follow separate pathways, but those pathways will have to link up at some point. Regulatory approval for each product type depends on the success and approval of the other, and each may need support from the other to collect the right evidence. Miller added that an additional challenge from the perspective of the pharmaceutical company can be the cost of diagnostic. In the case of the SUL-DUR drug to combat *Acinetobacter*, it was not feasible to launch the drug with the BPP advanced diagnostic device due to cost, she said. Although the device and drug are very effective, *Acinetobacter* infection is rare in the United States.

Incentives

Given the potential benefits of co-developing drugs and diagnostics, Billington asked panelists to discuss specific types of incentives that might work in this context. Frank replied that the first step would be to assess existing incentives for antibiotic development and examine whether, and to what extent, they support co-development. With existing structures and funding streams in place, Frank noted "there is a conversation to be had" with funders about what they are doing and what more could be done. He emphasized that it may be difficult to adjust existing funding programs, but this would still be easier than establishing a new incentive program solely dedicated to co-development. In terms of market incentives, Frank suggested that one approach could be a temporary add-on reimbursement for a new susceptibility test that, if crafted properly, could support more rapid uptake of susceptibility testing and help de-risk the process of bringing these diagnostic products to market. J. Patel added that test developers need help obtaining characterized isolates, so the CDC Antibiotic Resistance

Isolate Bank is a valuable resource. R. Patel added that another resource for isolates is the Antibacterial Resistance Leadership Group Biorepository.[7]

Financial benefit of collaboration

In terms of the financial benefit of co-development, Miller said that ability to complete the trial quickly was invaluable. The ATTACK trial was expensive, in part due to the cost of the diagnostic, but the BPP allowed a design that rapidly excluded most screened patients and focused on those with *Acinetobacter* infection. For a small company, being able to do the trial quickly and efficiently was critical. Frank added that the cost of enrolling patients in an antibiotic trial may be close to one million dollars, which is not a sustainable price for small or large companies. The more collaboration encouraged between diagnostics and pharmaceutical companies to de-risk the process and make trials more efficient, the better.

[7] See https://arlg.org/laboratory-center-strain-access/ (accessed January 25, 2023).

5

Health Equity Considerations

Key Points Made by Individual Speakers:

- AMR is a "complex, unpredictable, irreversible, progressive, painful, suffocating, choking weed." Sharing stories about the experiences of people living with and dying from AMR is one way to raise awareness and advocate for change. (Shader Smith)
- Ethical considerations for AMR have not received much attention, but there are pressing bioethical issues that merit further exploration when it comes to the development and use of rapid diagnostics. (Evans)
- To be sustainable, systems for detecting and addressing AMR should be integrated into routine health systems so that they offer regular value to patients, clinicians, and the public health enterprise. (Bausch)
- There is a need to better quantify and characterize the intersection between AMR and health inequities and carry out studies that enroll participants who are representative of the populations that bear the burden of disease. (Pettigrew)
- Equity may be path-dependent, so innovating AMR diagnostics for low- and middle-income countries requires designing, not just adapting, technologies for this context. (So)

PATIENT STORY: MALLORY SMITH

"We're losing the battle against bacteria," stated Diane Shader Smith (Mother of the late Mallory Smith, author of *Salt in My Soul*, and AMR advocate). According to Shader Smith, despite years of messaging on the part of scientists and thought leaders, the issue has not penetrated the American consciousness the way it needs to. Shader Smith, whose daughter, Mallory, died in 2017 due to an antibiotic-resistant bacterial infection, emphasized that it is critical to hear the voices and understand the experiences of people living with and dying from AMR. Shader Smith suggests that storytelling is one way to get there.

Mallory was diagnosed with cystic fibrosis at the age of three. She had a happy childhood with no significant health challenges until she was colonized by *Burkholderia cenocepacia*, an opportunistic bacteria that commonly infects immunocompromised patients, at the age of 12. Suddenly, as her mother put it, "Mallory had an expiration date." By high school, Mallory was in and out of the hospital, each time needing IV antibiotics for weeks to months. Despite her health challenges, Mallory was a typical, high-achieving teenager who got straight As and played three varsity sports. However, in the second half of her senior year, Mallory got very sick. She ended up attending her high school prom and was voted prom queen. Unfortunately, a student threw a smoke bomb into the venue, searing Mallory's lungs, and she began coughing up blood.

These experiences instilled in Mallory a profound understanding of how precarious life is, said Shader Smith. Over the coming years, she was hospitalized repeatedly. These visits followed the same routine: cultures were taken, antibiotics were prescribed, drug susceptibility tests were performed, and antibiotic cocktails were adjusted. Shader Smith said that based on her lay understanding, antibiotic use is what leads to resistance. Better diagnostics could have helped Mallory.

AMR is a "complex, unpredictable, irreversible, progressive, painful, suffocating, choking weed," said Shader Smith. As Mallory's body deteriorated, her mind sharpened and she honed her writing skills. She spent the next 10 years documenting what it was like to live with a drug-resistant bacteria. Mallory graduated from Stanford University and wrote her first book, but AMR continued to wreak havoc on her life. Eventually, said Shader Smith, the only option left for Mallory was a lung transplant. Her insurance company initially denied the transplant; she was finally approved because her family "knew someone who knew someone." Shader Smith said that skewed social and economic policies and care practices made things easier for Mallory than for others, and Mallory wanted to use her privilege and power of the pen to expose these injustices. While waiting for her transplant, Mallory wrote, "*I want to maintain dignity to whatever*

extent possible, to receive whatever lifesaving tactic is appropriate, to be able to communicate in some way, to have the blinds open for natural light, to have calming music to listen to, to have my mom or dad with me always. I want to live."

The call for a lung transplant finally came, and despite a grueling recovery, Mallory celebrated her 25th birthday without supplemental oxygen. It was a happy time, said Shader Smith, and they dared to dream about a new life. However, a few weeks later, the *B. cenocepacia* infection returned, and Mallory was out of options. Mallory's father reached out to Stephanie Strathdee, an epidemiologist who had used phages to help save her husband (Macpherson, 2021). Strathdee amplified the call on Twitter and pleaded with researchers around the globe for help in finding phage matches. Mallory was on a ventilator but scribbled a note to her loved ones: "*Can't talk at all, but so grateful you are all here for the hardest part."* A phage match was found, and Mallory became the first patient in the United States with cystic fibrosis to receive phage therapy. "We were filled with hope," said Shader Smith, but the next morning the family had to make the "gut-wrenching decision" to remove Mallory from life support. The autopsy revealed that the therapy had started to work but not in time to save Mallory's life.

Mallory's writings were published posthumously as *Salt in My Soul*, which led to a documentary of the same name (Smith, 2019; 3Arts Entertainment, 2022). The Lancet published the largest study to date about superbugs at the same time the New York Times referred to *Salt in My Soul* as an awareness raising tool about the possibilities of bacterial phages (Antimicrobial Resistance Collaborators, 2022; Kenigsberg, 2022). "The seeds of my advocacy were planted by Mallory," said Shader Smith. Mallory's writing has enabled Shader Smith to share the patient voice, raise awareness, advocate for phage therapy, and address the need for better diagnostics. Shader Smith has taken on this advocacy role in a variety of settings, speaking at medical schools, bookstores, community events, conferences, Capitol Hill, and the White House. "I'm not a doctor, a scientist, a lobbyist, or a paid publicist," said Shader Smith, "just a grieving mom trying to make sense of the world and my place in it."

PANEL DISCUSION

Bioethics Perspective

Nicholas Evans (Chair, Associate Professor, University of Massachusetts, Lowell) observed that discussions about AMR rarely include a focus on bioethics or justice. Evans referenced several decades' worth of National Academies' publications on AMR and found no mention of "health equity."

He did find one mention of "justice" in the context of AMR, but it was in a small subsection of a larger report about infectious disease research. A search on PubMed, said Evans, reveals only 16 articles that discuss bioethics and antimicrobial resistance. Evans suggested a few reasons for this gap. First, there may already be moral clarity on the issue of AMR; as he put it, "Antimicrobial resistance is bad. We should fix it." Second, the field of bioethics has not historically focused on infectious disease. More recently, there have been bioethics discussions in areas of infectious disease, but they have tended to emphasize high-profile pathogens such as SARS or Ebola. The third reason, said Evans, is that AMR has received little public attention in general and for this reason may not be a priority for bioethicists. The published literature that addresses AMR mainly explores issues of distributive justice; that is, certain groups of people have access to antimicrobial medications while other groups have limited access.

In the context of rapid diagnostic development and use, Evans identified three pressing bioethical issues:

- Use of AMR diagnostics in research
- Diagnostic data and sample sharing
- Cost and access

Use of AMR diagnostics in research

In the United States, Federal Policy for the Protection of Human Subjects ('Common Rule') defines research as "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge" (45 CFR, §46.102l). Public health surveillance activities are exempted from this policy. Evans argued that research using AMR diagnostics should be considered under the Common Rule given that diagnostics can be used to track the movement and evolution of resistant pathogens, thus contributing to generalizable knowledge. Evans recognized that this shift in policy would require diagnostics researchers to engage with an institutional review board (IRB), which can be a cumbersome process. To facilitate the process, there would need to be better data management, data harmonization, and data standards in place for rapid diagnostics for AMR. Elevating AMR diagnostics to research status under the Common Rule, said Evans, could open opportunities for product development pipelines and standard setting for treating drug-resistant bacterial infections.

Diagnostic data and sample sharing

In past public health efforts, there has been a lack of consistent attention and commitment to domestic and international data and sample sharing, said Evans. For example, during the 2006 avian influenza pandemic,

Indonesia decided to withhold avian influenza A H5N1 samples from the WHO due to concerns about global inequities and lack of access to vaccines for developing countries (Fidler, 2008). Another example was seen when Sierra Leone was unable to retrieve Ebola virus disease samples from the United Kingdom due to national security restrictions (Evans et al., 2020). Data and sample sharing are core concerns when it comes to global health equity and justice, said Evans, and ensuring access to results and samples is critical for controlling infectious disease and AMR.

Cost and access

Evans highlighted that the key equity drivers for AMR are cost and access as bioethicists regard AMR as an issue of distributive justice. Evans further explained that the cause of AMR is largely an issue of unequal distribution of resources: antibiotics are often overprescribed in wealthy countries and underprescribed in poor countries (Selgelid, 2007). This inequity represents a failure of market-based healthcare allocation. Equity concerns may also arise for diagnostics that are not affordable or universal in design. Evans argued that it is essential to encourage collaboration across nations and public health authorities so that diagnostics are ethically designed and implemented in a manner that can be delivered at any point-of-care globally.

Research Perspective

AMR is an ongoing pandemic and like all pandemics there are equity issues in terms of who gets resources and how those resources are distributed at the national- and community-levels, said Daniel Bausch (Director of Emerging Threats & Global Health Security, FIND, The Global Alliance for Diagnostics). People who are disenfranchised and on the margins of society are nearly always the ones who suffer the most, however, Bausch offered four potential ways to address some of these inequities.

First, there is a need for effective messaging, both to the public and political leaders. Bausch noted that progress is often driven by constituents demanding change. For example, patient advocacy led to progress in HIV research and development. Despite powerful stories, like the ones shared at this workshop, this has largely not happened for AMR. There is a need to build a constituency that will come together, speak frankly with political leaders, and give AMR the attention it deserves.

Second, there is a need to move beyond the concept of binary diagnostics—tests that indicate whether or not a patient has a particular disease. Bausch said that when patients are told they do not have a disease—whether Ebola or COVID-19—they might be happy for a moment but then the focus turns to figuring out what they *do* have. There are new

diagnostic tools that will help with this issue, but these products must be available at a price point that makes them globally accessible.

Third, said Bausch, it is critical that systems for detecting and addressing AMR are integrated into routine health systems. Parallel systems are often established during outbreaks but become obsolete once the outbreak is resolved. Instead, surveillance should be built into existing systems and sustained in a way that offers value for patients, clinicians, and the public health enterprise.

Finally, there is a need to build equity into health systems to reduce vulnerabilities and inequities. For example, Bausch advocated that manufacturing be distributed around the world so that product pipelines are not dependent on just a few countries, and that health coverage and access to care should be universal.

Public Health Perspective

"Profound inequities are woven into the U.S. healthcare and public health systems," said Melinda Pettigrew (Professor of Epidemiology and Interim Dean, Yale School of Public Health) and these inequities are inextricably linked to structural factors and social determinants of health and can manifest across the trajectory of care. Inequitable outcomes in health can be a result of inequitable access to care, including a lack of fair and just access to diagnostics. Data that would help elucidate and identify disparities in AMR are not routinely collected, but there are some cases of well-documented disparities. For example, rates of gonorrhea vary by race and ethnicity and disproportionately impact members of certain racial and ethnic groups (Lieberman et al., 2021). Pettigrew pointed to employment, access to care, housing, health literacy, and behavioral factors that can alter an individual's exposure and risk for AMR infection. Some of these behaviors, said Pettigrew, are highly stigmatized, putting individuals at extra risk and influencing how they interact with the public health and healthcare system.

According to Pettigrew, in order to address health inequities, the first step is to identify groups that are at risk and to better understand the drivers and mechanisms behind these inequities. For example, race is a major driver of health inequities. Pettigrew stressed that it is important to identify the mechanisms, which could be socially constructed as well as biology- or genetic-based. For instance, if there are differences between men and women in terms of treatment efficacy, this could be due to a difference based on biology or how men and women interact with the healthcare system and what options they are offered. These types of questions are not always explicitly asked, and they are not always appropriately addressed.

While there are organizations working to improve health equity, Pettigrew emphasized a need for more work, particularly in the AMR space. There is a need to better quantify and characterize the intersection between AMR and inequities and carry out studies that enroll participants who are representative of the populations that bear the burden of disease, she said. In 1993, the NIH was given explicit authority to direct investigators of funded research to improve representation in trials with respect to gender, race, and ethnicity, but these policies do not apply to private industry. The FDA requires sponsors of new drug applications to present efficacy and safety data by gender, age, and racial subgroups, and in 2014, the FDA published an Action Plan for encouraging more inclusive trial participation.[1] However, after decades of voluntary and aspirational initiatives, there remains a lack of diverse representation in clinical trials, said Pettigrew.

Draft legislation passed by the U.S. House of Representatives in June 2022 would require study sponsors to submit a diversity action plan, including a description of how they plan to increase access for certain demographic groups.[2] However, these provisions would not fully resolve the barriers to diverse participation, including restrictive eligibility criteria, costs associated with participation, and limited outreach. Pettigrew said there is also a need for federal incentives, standards for diversity in research standards, and post-marketing surveillance to monitor effectiveness.

Access and Innovation Perspective

In 2019, 255,000 people in Sub-Saharan Africa died because of AMR and over half were children under 5, said Anthony So (Professor of the Practice; Director, Innovation + Design Enabling Access (IDEA) Initiative, Johns Hopkins Bloomberg School of Public Health) (Antimicrobial Resistance Collaborators, 2022). At the same time, the 2022 Mapping Antimicrobial Resistance and Antimicrobial Use Partnership (MAAP) project (MAAP, 2022) found that laboratory services were largely inaccessible:

- Only 1.3% of the 50,000 medical laboratories in the 14 countries studied conducted bacteriology testing;
- In 8 out of 14 countries studied, bacteriology labs were geographically accessible to less than 50% of the population;
- 80% of the 205 labs surveyed performed fewer than 1000 antimicrobial susceptibility tests per year.

[1] See https://www.fda.gov/media/89307/download (accessed January 23, 2023).

[2] *Consolidated Appropriations Act,* 2023, Public Law 117-328, 117th Cong., 2d sess. (December 29, 2022).

For patients in resource-limited settings, the barriers to access extend across the entire value chain, said So. On the development end, there are challenges with the value proposition for investing in a point-of-care diagnostics suited for resource-limited settings. Once a product is on the market, it may be priced out of reach and healthcare workers may opt for antibiotics because there is no available diagnostic nearby. These barriers to equitable access at the technology, financial, and structural levels are deeply intertwined. Both push and pull incentives can be used to address barriers and increase access. So identified a need for strategic thought on how push incentives—paying for the inputs of R&D—and pull incentives—paying for the outputs of R&D—can work to build the innovation ecosystem and contribute to the access that is needed globally. Pull incentives, however, typically benefit groups that already have capital to run the race for a prize. To address this, the Longitude Prize on Antimicrobial Resistance, a prize competition for innovation in point-of-care diagnostics, offered discovery awards to provide seed funding for teams to get their ideas off the ground.[3] There is a need for more effort on push incentives to encourage those who may have an alternative approach that is focused on low- and middle-income countries (LMIC).

Bringing diagnostics into the healthcare systems of LMIC often requires tradeoffs between efficiency and accuracy. So shared a table (Figure 5-1) that demonstrates the tradeoffs in implementing a diagnostic for bacterial pneumonia. Implementing a test that has perfect performance but requires advanced infrastructure would result in fewer lives saved than a test with good performance that can be used in environments with minimal infrastructure. So emphasized that care must be taken to avoid the perception of double standards and to navigate regulatory approval for diagnostics that are designed for conditions of minimal infrastructure.

Even when diagnostic technology is effective and affordable, said So, there can still be unintended consequences from implementing it. For example, a clinical algorithm applied by healthcare workers to manage patients presenting with fever used a combination of respiratory rate and rapid diagnostic tests for malaria to determine if antibiotic treatment, not just antimalarial treatment, were needed (Mukanga et al., 2012). He explained that some providers did not prescribe antibiotics when the malaria test was positive, even if the respiratory rate was high enough to diagnose pneumonia, but providers would also prescribe antibiotics when the respiratory rate was normal and the malaria test was negative; So suggested this overuse may have stemmed from the healthcare provider's interest in providing some kind of treatment to the pediatric patient. To help ensure equitable results from diagnostics, So suggested wraparound implementation

[3] See https://longitudeprize.org/ (accessed January 23, 2023).

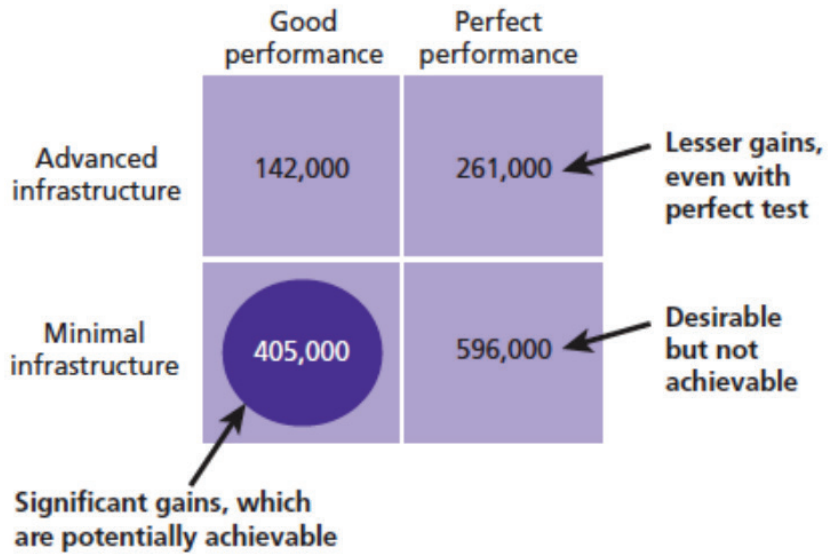

FIGURE 5-1 Comparison of lives saved by a new diagnostic for bacterial pneumonia SOURCE: Presented by Anthony So, October 14, 2022; Burgess et al., 2007. See https://www.rand.org/pubs/research_briefs/RB9293.html (accessed March 1, 2023).

research to improve our understanding of what happens when technologies are deployed.

There are important lessons that can be learned from previous experiences in AMR diagnostics, said So. The GeneXpert System was an important advance that allowed for diagnoses of tuberculosis and rifampicin resistance. The technology platform is proprietary and pricey at around $17,000 per machine; test cartridges are just under $10 at the volume-discounted price. Public funders contributed over $250 million to its development, said So (Gotham et al., 2021). With this type of investment, should funders have insisted on an interoperable platform rather than a proprietary one? Should funders have insisted on more transparency on pricing? These types of questions, said So, can help better assess fair return on public financing in the future.

So shared the details of two innovations that were motivated by equity considerations, both of which were supported by Doctors without Borders (MSF). Antibiogo is an AI-based mobile app that is designed to help interpret AST, particularly where trained technicians may not be available.[4] The Mini-Lab is a core laboratory system designed for rapid setup in field set-

[4] See https://antibiogo.org/ (accessed January 23, 2023).

tings, from conflict-ridden areas to refugee camps.[5] Both of these developments approach innovation with equity and accessibility built into design.

In conclusion, So shared three final thoughts. First, a systems perspective would enable strategic consideration of how to nurture dual markets in high-income countries and resource-limited markets that support equitable and sustainable access to diagnostics. For example, diagnostic platforms could serve to monitor and track emerging infections in health care settings as well as monitor prevalence of pathogens in wastewater. Second, there is a need to consider how to bundle the development, use, and reimbursement of diagnostics with drugs to lower costs and improve treatment. Finally, said So, diagnostics should be considered as part of a "best buy bargain" to address AMR. He said that "no one blinks" when billions are spent in public financing for new drugs, but there is a need to consider the opportunity costs of such funding if effectively deployed on complementary technologies like diagnostics. AMR-related complications in the Organization for Economic Co-operation and Development (OECD) and European Union (EU) countries are estimated to cost up to $3.5 billion each year; investing just $2 per capita per year in a comprehensive public health package, including diagnostics, to tackle AMR would avert 47,000 deaths per year in OECD countries and would pay for itself in under a year (OECD, 2018).

DISCUSSION

Gathering evidence and turning evidence into action

Evans described three barriers to gathering data necessary to understanding the extent of disproportionate impacts of AMR. First, the fragmentation of the health system makes it difficult to collect data, in sufficiently high levels of granularity, and then share data among researchers, administrators, and other stakeholders. Second, there are competing and incompatible platforms for storing data, which exacerbates the difficulties of producing and sharing. Third, many labs simply do not have the capacity to collect these types of data. Pettigrew added that while collecting and managing data are challenges, it is important to first identify the types of data that are being collected and those that should be collected. Many of our definitions and labels are ill-defined and not always useful; for example, when considering the impact of race on AMR, is it the biological aspects or sociocultural determinants that matter? Collecting data using standard definitions will help identify who is at risk and where resources are needed but will not address the underlying mechanisms. Other data points that may be useful—such as insurance status or socioeconomic status—are very challenging to collect, particularly within healthcare systems. In addition,

[5] See https://fondation.msf.fr/en/projects/mini-lab (accessed January 23, 2023).

there is a need to improve the diversity of those who participate in studies by addressing barriers to access and lack of trust. Despite these challenges, however, Pettigrew said "we have to start somewhere." It would be beneficial to have macro-level data on race and ethnicity to assess disparities and identify groups that need special attention.

So said that as important as collecting data is, it does not always translate into increased action. For example, a study published in *The Lancet* said that 1.27 million people per year are dying of drug resistant bacterial infections, and the World Bank estimates that if AMR goes unchecked, 24 million people will be forced into extreme poverty by 2030 (Antimicrobial Resistance Collaborators, 2022; World Bank, 2017). Unfortunately, these numbers have not been enough to move policy makers to provide the necessary and commensurate resources. Addressing inequity cannot be done through data alone; sometimes it requires "putting a face to inequity." Stories of people like Mallory Smith are so important to helping the public understand the scope of threat that AMR poses. Additionally, said So, there is a need to translate and communicate data in ways that are simple, straightforward, and lead to actionable results. AMR comprises a constellation of issues rather than one specific disease, meaning it can be particularly difficult to garner support and get results.

Bausch agreed that while better data are needed, it would be naïve to think data alone could spur action. In addition, equity arguments alone will not make the case; Bausch noted that there are data about inequities in multiple areas of health, but global resources are limited and economic constraints exist. What is needed, he said, are real-world political and economic arguments and a constituency of people who will demand change from decision makers. The "unfortunate reality" of our system is that politicians are looking for things that will benefit them and get them votes. Political cycles are short, so politicians need clear economic arguments about short-term benefits.

Shader Smith agreed with So that putting a face to the disease is critical for getting decision makers on board. Whether it is her daughter Mallory, patients with Valley Fever, or amputees, decision makers need to be able to see and understand the real-world impact on individual people. In addition, Shader Smith said, AMR discussions tend to happen in an echo chamber that is full of "alphabet soup" (i.e., acronyms). While these discussions are useful for sharing information, people on the outside of the echo chamber, or without specialized medical knowledge, are largely unaware of the problem or potential solutions.

Diversifying clinical trials

So encouraged stakeholders to consider diversity within a global context. He pointed out that depending on the setting, a diagnostic or

treatment may play out very differently. Based on experiences during the ongoing COVID-19 pandemic, clinical trials tend to rely on existing infrastructure, which may not overlap with places of diverse populations. Unless the clinical trials infrastructure extends into more diverse communities, said So, AMR researchers will continue to only "look at the light under the lamp post."

Bausch said the entire system of research, development, and deployment of drugs and diagnostics is "haphazard" and "disjointed" with different stakeholders, barriers, and incentives at each step along the way. As a result, it is difficult for people to see the value in clinical trials, particularly for something like AMR. In contrast, his experience enrolling patients in a trial for an Ebola vaccine in the Democratic Republic of the Congo was relatively straightforward because there was an ongoing Ebola outbreak. There is a need to communicate the value of clinical trials and for people to see there is value for themselves and their communities in participating in research.

One marginalized group that is not often talked about, said Evans, is the community of people with disabilities. AMR-related issues appear to be more likely for people who have a disability or chronic disease (e.g., cystic fibrosis, amputee). These individuals are generally empowered to want to engage in the research process, he said, in part because medical care is a lifeline that allows them to live their lives as fully as possible. There is an urgent need for research that examines the interactions between AMR and different kinds of chronic conditions, comorbidities, and disabilities.

Pettigrew said that it can be difficult to know which populations should be included in a clinical trial. For example, if an infection is six times more prevalent in one population than another, should the enrollment reflect this ratio or should it reflect census data? Should trials focus the people who are most impacted by a condition or address more generalizable questions?

Incorporating diversity and equity from the beginning

A virtual participant asked panelists to comment on how considerations for diversity and equity can be intentionally incorporated from the very beginning of the development process for AMR diagnostics. Pettigrew responded that the first step is to look at the diversity of the field itself. "We all approach the world and research problems and challenges with our own lens based on our own experiences," so if there are not enough diverse investigators running trials, there will not be diverse trial participants. In terms of barriers to trial participation, Pettigrew said that investigators need to consider issues such as access to the trial site, reimbursement for travel, and taking time off work. In addition, she agreed with Bausch that people need to see the value in participating in a trial. People need to understand the potential impact of AMR on themselves and their communities, and

they need to believe that their communities will benefit from the trial. For example, she said, trials where a product is tested in community A but will be used in community B are not useful.

Bausch agreed and said that investigators should be realistic and concrete about the benefits for clinical trial participants, rather than framing participation as a general benefit to humankind. The development process takes time, so investigators should be honest when engaging trial participants and communities. Evans referred to his earlier example of Indonesia withholding avian flu samples because they believed their nation would not benefit from the research (Fidler, 2008). This example drives home the importance of ensuring that research is designed in a way to benefit the populations participating in a trial.

So added that it can be challenging to enroll diverse populations if they will not be able to afford or benefit from a given technology. One approach for addressing this issue could be to design and target rapid diagnostics for use in resource-limited settings rather than trying to adapt technologies once they have been developed for a higher resource setting. Evans added that fundamental design principles in addition to price points, trial participation, and other issues, should include engagement from people who have a disability or chronic disease.

Building momentum and public engagement

As speakers have noted, said Kester, it can be challenging to build momentum and public engagement behind the issue of AMR because it is such a broad and variable condition. Visible diseases like polio or Ebola are more likely to get traction, whereas AMR is a hidden epidemic. Bausch and Evans underscored the value of consistent and focused messaging. Speaking from a marketing perspective, Shader Smith posited that if a popular and accessible platform, such as the *Today Show*, had an amputee, a cystic fibrosis patient, and a caregiver of a deceased patient share their stories this could be a powerful way to educate and reach people. Shader Smith pointed out the need for a global marketing plan that includes people from outside of the insulated community of existing AMR experts and stakeholders. The discussions at this workshop are important, said Shader Smith, but it is essential that the messaging be spread into the general public.

6

Diagnostic Stewardship

Key Points Made by Individual Speakers:

- Antimicrobial stewardship and diagnostic stewardship are complementary practices that go hand in hand to guide therapeutic decisions. (Burnham)
- The impact of a rapid diagnostic use will vary depending on local resistance rates, antibiotic prescribing practices, patient populations, the availability of stewardship programs, and baseline laboratory practices. (Banerjee)
- There would be value in establishing metrics to drive diagnostic use and antibiotic stewardship and to better understand how antibiotics are being used within healthcare systems. (Flayhart)

LABORATORY CLINICIAN PERSPECTIVE

Antimicrobial stewardship and diagnostic stewardship are complementary practices that go hand in hand to guide therapeutic decisions (Figure 6-1), said Carey-Ann Burnham (Chief Clinical Officer, Pattern Bioscience). Diagnostic stewardship can be defined as:

> Coordinated guidance and interventions to improve appropriate use of microbiological diagnostics to guide therapeutic decisions. It should promote appropriate, timely diagnostic testing, including specimen collection,

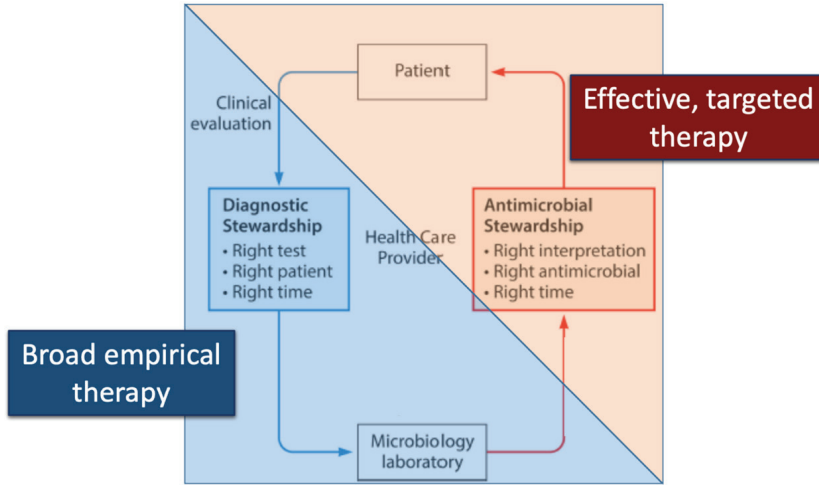

FIGURE 6-1 Diagnostic and antimicrobial stewardship
SOURCE: Presented by Carey-Ann Burnham, October 14, 2022; adapted from Messacar et al., 2017.

> and pathogen identification and accurate, timely reporting of results to guide patient treatment. (WHO, 2016)

Or stated more simply as, "getting the right test to the right patient at the right time."

Considerations for determining the right test include: the analytical performance characteristics (e.g., sensitivity/specificity), the diagnostic yield, and the context of local epidemiology. Choosing the right patient depends on appropriate use criteria, the patient population, and pre-test probability. The right time for a test, said Burnham, is a time during which the test results fit into the clinical workflow and will have an impact on patient care. Laboratory management and capacity should also be considered by assessing factors such as space, cost, hands-on time, and throughput.

Diagnostic stewardship occurs throughout the lifecycle of a test, although most decisions are made in the preanalytical phase. At this phase, decisions must be made about test ordering, specimen collection and transport, specimen acceptance and rejection criteria, and specimen processing. The next stage of testing is the analytical phase, said Burnham; at this point, diagnostic stewardship includes decisions about methodology, batch vs. on demand processing, and where a test will be processed (central laboratory vs. point-of-care). Finally, the postanalytical phase includes

considerations about how results are reported, what interpretation is provided, and whether notification of results is active or passive. Conversations about diagnostic stewardship often focus on reducing testing that is inappropriate or unnecessary, said Burnham. However, both overutilization and underutilization of testing are problematic. The failure to order a necessary diagnostic test at the right point in the workflow has been shown to be one of the most common medical errors in ambulatory practice settings (Gandhi et al., 2006).

Diagnostic stewardship—and its relationship with antimicrobial stewardship—will vary depending on the practice setting. Burnham considered practice settings across four categories, each of which has a different approach to diagnostic stewardship: outpatient, emergency department, inpatient, and critical care inpatient. In each of these settings, she said, a diagnostic stewardship program should consider:

- Where will testing take place (e.g., at the patient's bedside, local laboratory, central laboratory, pharmacy, or patient's home)?
- Who will collect the specimens and what guidance should they receive?
- How will test results be reported and communicated, and what guidance will be provided for interpretation of results?
- What, if any, action will be taken based on test results?

Burnham suggested that some laboratorians have concerns about testing that takes place in pharmacies or in the home. However, testing in these locations is already taking place; from a diagnostic stewardship standpoint, the best approach may be to provide guidance across settings to support accurate test results.

While there are several rapid diagnostics available and coming on the horizon, said Burnham, there are challenges in getting these tests into clinical practice. Clinical guidelines are important to encourage uptake and should include guidance on when and how to use a given test and information that is specific to users in working in different settings (e.g., critical care, surgery). Rapid diagnostics can be expensive but can also have high clinical value, so uptake may also require a shift in reimbursement policy. There is a need for more research on the impact of rapid diagnostics on multiple outcomes including clinical outcomes, workflow, and decision-making. In addition, said Burnham, there is a need for formal mechanisms for ongoing evaluation of the performance of rapid diagnostics; this will require strong partnerships between microbiology and antimicrobial stewardship programs.

ANTIBIOTIC STEWARDSHIP PROGRAM PERSPECTIVE

When a clinician is faced with a patient who has possible sepsis, the clinician will obtain cultures and then prescribe empiric antibiotics, said Ritu Banerjee (Medical Director, Pediatric Antimicrobial Stewardship Program, Vanderbilt University). Banerjee identified a couple of ways in which empiric antibiotic selection can go wrong. First, a clinician may prescribe an antibiotic that is ineffective against the infecting organism, resulting in poor outcomes including death. Second, a clinician may prescribe antibiotics that are unnecessarily broad-spectrum; the treatment may be effective but unnecessarily contribute to the emergence of resistance. The challenge, said Banerjee, is that conventional bacterial blood cultures and antibiotic susceptibility testing methods typically take days to yield actionable information. Rapid diagnostics can shorten this time, but the clinical impact must be demonstrated.

Banerjee shared evidence from observational studies (Table 6-1) and randomized controlled trials (RCTs) (Table 6-2) that looked at the outcomes associated with the use of rapid diagnostics. Banerjee observed that a variety of tests and methods are in use, but not all tests are implemented with antibiotic stewardship program oversight. Most observational studies demonstrated a decrease in time to optimal therapy for patients but results (e.g, mortality, length of stay, and cost savings) were mixed. The RCT studies also demonstrated a decrease in time to optimal therapy but only one demonstrated improvement in mortality.

Banerjee and colleagues conducted the Blood Culture Identification (BCID) trial, which was a single center, prospective RCT (Banerjee et al., 2015). All patients with positive blood culture were randomized in the laboratory to one of three arms: control (conventional culture and susceptibility testing), BCID (conventional culture and susceptibility testing plus BCID rapid test), or BCID plus stewardship (conventional culture and susceptibility testing, BCID rapid test, and treatment recommendations). In the two arms that included rapid testing, the organism was identified earlier and antibiotic escalation for patients on ineffective therapy happened more quickly (Figure 6-2). Importantly, said Banerjee, antibiotic de-escalation—narrowing a broad-spectrum therapy to target the cultured organism—was only faster in the arm that included the oversight of an antibiotic stewardship team. Banerjee said that this demonstrates the value of integrating a rapid test with stewardship. Clinical outcomes—including mortality, length of stay, adverse events, and cost—were not significantly different between the different arms (Table 6-3).

The Randomized Trial Evaluating Clinical Impact of Rapid Identification and Susceptibility Testing for Gram-negative Bacteremia (RAPIDS GN) was another prospective RCT carried out by Banerjee and colleagues. For

TABLE 6-1 Observational Studies: Rapid Blood Culture Diagnostic and Outcomes

Test	ASP	Decrease TOT	Mortality benefit	ΔLOS (days)	Cost Savings	Study
PNA FISH	Y	Y	Y	N	-	Forrest, 2008
Xpert MRSA	Y	Y	Y	-6.2	21K	Bauer, 2010
MALDI-TOF	Y	Y	Y	-1.8	19K	Perez, 2013
MALDI-TOF	Y	Y	Y	-2.8	-	Huang, 2013
Verigene GP	Y	Y	N	-21.7	60K	Sango, 2013
mecA PCR	Y	Y	-	-3	-	Nguyen, 2010
PNA FISH	N	N	-	N	-	Holtzman, 2011
Verigene	N	Y	Y	-	Y	Suzuki, 2015
BCID	Y	Y	-	-	-	Messacar, 2016
MALDI-TOF	Y	Y	N	N	-	Malcolmson, 2017
BCID	Y	N	N	N	-	Tseng, 2018
Accelerate Pheno	Y	Y	-	-	-	Robinson, 2021
Metaanalysis (31 studies)	Y/N	Y	Y (ASP only)	Y	-	Timbrook, 2017

SOURCE: Presented by Ritu Banerjee, October 14, 2022.

TABLE 6-2 Randomized Controlled Trials: Rapid Blood Culture Diagnostic and Outcomes

Test	Org.	SS	ASP	Decreased TOT	Mortality benefit	ΔLOS (days)	Cost savings	Study
Same day Microscan	All	573	N	Y	Y	N	Y	Doern, 1994, US
Multiplex PCR	All	250	N	Y	N	N	-	Beuving, 2015, Netherlands
BCID	All	617	Y	Y	N	N	N	Banerjee, 2015, US
MALDI-TOF	All	425	Y	Y	N	N	-	Ostoff, 2017, Switzerland
Accelerate Pheno	GN	448	Y	Y	N	N	N	Banerjee, 2020, US
MALDI-TOF	All	3127	Y	N	N	N	N	MacGowan, 2020, England and Whales
QMAC-dRAST	All	89	Y	Y	N	N	N	Kim, 2021, Korea
Accelerate Pheno	GN	205	Y	Y	N	-2	-	Christensen, 2022, US

NOTE: ASP = antibiotic stewardship program oversight; GN = gram-negative; LOS = length of stay; Org = organism; SS = subjects selected; TOT = time to optimal therapy
SOURCE: Presented by Ritu Banerjee, October 14, 2022.

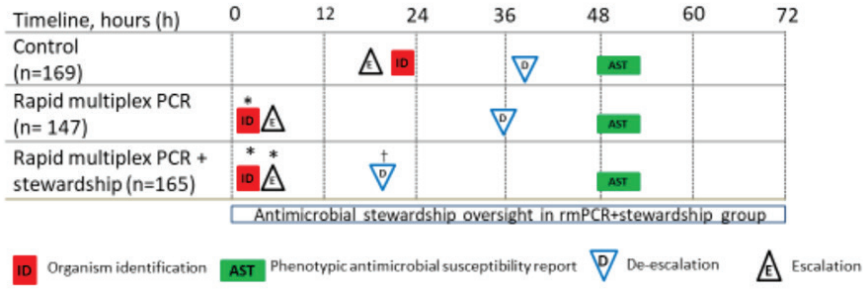

FIGURE 6-2 Comparison of median time to identification, susceptibility results, and time to antibiotic modifications
NOTES: PCR = polymerase chain reaction; * = significant vs. control; † = significant vs. control and Blood Culture Identification
SOURCE: Presented by Ritu Banerjee, October 14, 2022; Banerjee et al., 2015.

TABLE 6-3 Clinical Outcomes in BCID trial

Outcome	Control (n=207)	BCID (n=198)	BCID + Stewardship (n=212)	P-value
Length of stay (days)	8 (5,15)	8 (5,15)	8 (5,16)	0.60
ICU within 14 days	16 (7.7%)	5 (2.5%)	10 (4.7%)	0.06
30-day mortality	22 (10.6%)	20 (10.1%)	18 (8.5%)	0.74
30-day readmission[a]	6 (2.9%)	6 (3%)	8 (3.8%)	0.88
Toxicity/ adverse drug rxn	3 (1.4%)	3 (1.5%)	2 (0.9%)	0.82
Blood cx clearance in 3d	147 (71%)	131 (66%)	146 (69%)	0.79
C. difficile/ MDRO in 30d[b]	15 (7.2%)	16 (8.1%)	21 (9.9%)	0.62
Overall costs[c]	$65,450 ($27,192)	$66,887 ($23,935)	$68,729 ($29,064)	0.78

NOTE: BCID = Blood Culture Identification; *C. difficile* = *Clostridioides* difficile; cx = culture; ICU = intensive care unit; MDRO = multidrug resistant organisms; rxn = reaction
[a] with same organism
[b] VRE, MRSA, ESBLs, Gram-negatives resistant to ≥ 3 drug classes
[c] Mean (median) among inpatients with available data (n= 544)
SOURCE: Presented by Ritu Banerjee, October 14, 2022; adapted from Banerjee et al., 2015.

this study, patients were randomized to either a control arm (conventional culture and susceptibility testing) or a rapid testing arm (conventional culture and susceptibility testing plus rapid test); both arms included oversight by an antibiotic stewardship team. The results of the trial showed that patients who had resistant organisms detected in their blood and were on ineffective therapy initially were switched to effective therapy almost two days faster than patients in the control arm. Unfortunately, said Banerjee, the trial did not find significant differences in mortality, length of stay, readmissions, or other clinical outcomes (Banerjee et al., 2021).

While the BCID and RAPID GN trials did not find significant differences in clinical outcomes between traditional culture testing and rapid testing, Banerjee said that there were important lessons learned from both trials. First, rapid blood culture diagnostics, when implemented in collaboration with antibiotic stewardship teams, can improve treatment optimization for patients with bloodstream infections. Optimized treatment means faster antibiotic modifications, more judicious antibiotic use, and more timely antibiotic administration. Second, Banerjee said that understanding the local context is important for study design and interpretation. The impact of a rapid diagnostic will vary depending on local resistance rates, antibiotic prescribing practices, patient populations, the availability of stewardship programs, and baseline laboratory practices. Another lesson learned from these trials is that clinical outcomes (e.g., mortality or length of stay) may not be appropriate endpoints. These outcomes are dependent on many factors, Banerjee said, and de-escalation or targeted antibiotic treatment "should be sufficient justification for implementing a novel diagnostic." Other downstream impacts of improved medical decision-making should also be selected as endpoints for clinical utility studies, including laboratory workflow efficiencies and infection control activities such as time to isolation.

Banerjee closed by saying that she has "a lot of hope" that there are novel and innovative diagnostics on the horizon. Her "wish list" for diagnostics would include direct-from-specimen testing, point-of-care testing, tests that can rule bacterial infection in or out, and tests that could distinguish bacterial colonization from bacterial infection.

INDUSTRY/DEVELOPER PERSPECTIVE

Diane Flayhart (Global Program Leader, Becton, Dickinson and Company) focused her presentation on four main questions:

1. How effectively do current diagnostics inform antibiotic stewardship?
2. Is there enough data to understand how drug-resistant infections affect specific patient populations?

3. Are new metrics needed to drive diagnostic use and antibiotic stewardship efforts?
4. Are more advocates needed to drive awareness for Diagnostic and Antibiotic Stewardship?

To address the first question about how effectively current diagnostics inform antibiotic stewardship, Flayhart's company and its partners conducted a study, which included a literature review followed by interviews with frontline clinicians and a survey of an additional 50 clinicians (BD, 2022). The study was designed to examine how diagnostics are currently used to combat AMR, capture lessons learned on better use of current diagnostics, estimate the value of diagnostics, describe how the use of diagnostics can be improved, highlight priority unmet needs, and inform guidelines (Figure 6-3).

Flayhart shared a selection of preliminary results from the first two phases of the study. They found that the guidelines on antimicrobial stewardship programs recommend the use of rapid diagnostics in combination with traditional methods and that most guidelines for individual practice areas recommend traditional methods. Sporadic recommendations for point-of-care or rapid testing were not specific about how and when to use these diagnostics. Another key finding, said Flayhart, was that minimal data were being gathered about how surveillance and diagnostics have impacted hospital formulary access policy. Flayhart explained that to tie the impact of a diagnostic to antibiotic stewardship, it is necessary to have these data. Interviews with clinicians revealed several issues, including heterogeneity of diagnostic availability, the cost of diagnostics, and a lack of awareness of AMR and the utility of rapid tests. Flayhart said that this study was motivated in part because her company spends a lot of time and money developing diagnostic tests, so it is critical to understand how and why they are or are not being used by frontline clinicians.

Next, Flayhart addressed the issue of whether there are enough to data to understand how drug resistant infections affect specific patient populations. She shared data about age and geographic distribution of antibiotic-resistant bacterial infections. Further, she noted that the CDC is undertaking efforts to understand the links between health inequities and antibiotic resistance. A 2022 CDC presentation described a few associations:[1]

- Community-associated ESBL-Enterobacterales: Higher incidence rates in areas with lower median incomes, lower high school

[1] Information from Dawn Siewert, Antimicrobial Resistance Coordination and Strategy Unit, National Center for Emerging and Zoonotic Infectious Diseases, U.S. Centers for Disease Control and Prevention; presented at World AMR Congress in September 2022.

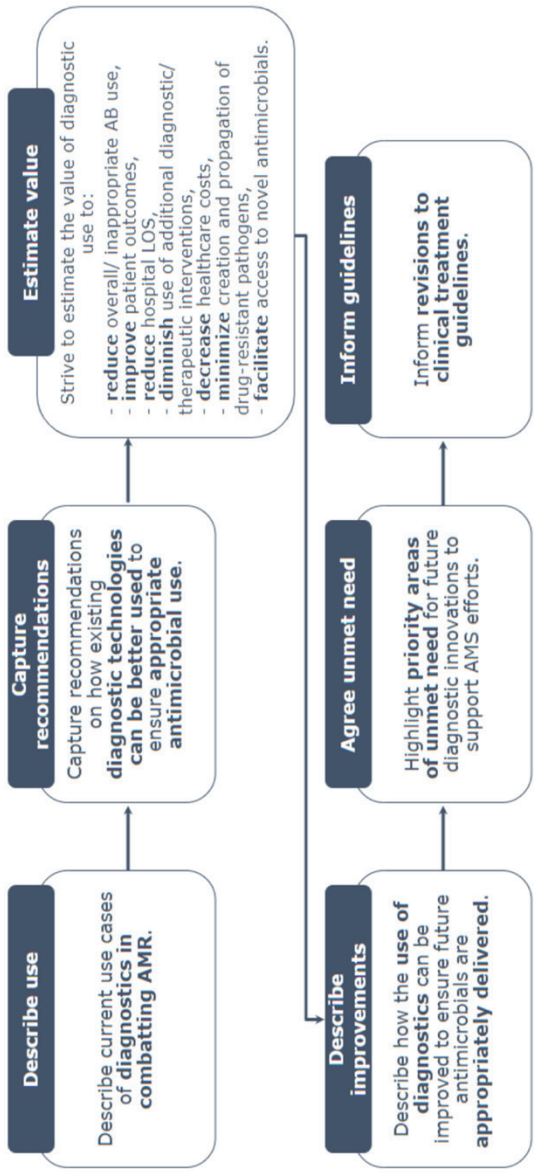

FIGURE 6-3 A multinational survey on antimicrobial stewardship program practice and rapid diagnostic utilization
NOTE: AB = antibiotic; AMS = antimicrobial stewardship; AMR = antimicrobial resistance; LOS = length of stay
SOURCE: Presented by Diane Flayhart, October 14, 2022; Survey Study Design, BD, Wellcome, Pfizer.

education rates, higher percentages of persons without health insurance, and those with limited English proficiency.
- Community-associated *C. difficile* infections: Higher incidence rates in communities with low-incomes, foreign-born populations, non-English speaking households, and crowding in the home.
- Candidemia and MRSA: Higher rates in Black individuals, possibly reflecting differences in medical conditions, healthcare access, socioeconomic status, and access to housing.
- Antibiotic prescribing and/or inappropriate prescriptions: Higher volumes/rates in rural areas, non-Hispanic White individuals, pediatric populations, and older persons with viral respiratory diseases.
- Antibiotic prescribing or diagnosis with bacterial pathogen: Lower volumes in Black individuals.

Flayhart considered whether new metrics are needed to drive diagnostic use in antibiotic stewardship or to understand how antibiotics are being used within healthcare systems. Flayhart suggested there is a need for national metrics for antibiotic use at the hospital level. There are complexities and challenges with accomplishing this, but it would allow antibiotic stewardship teams to measure how diagnostics are impacting antibiotic use. Antibiotic use increases during cold and flu season, which could offer an opportunity for stewardship programs to track and evaluate appropriate antibiotic use and the role of diagnostics (Yu et al., 2022).

Finally, Flayhart turned to the role of advocacy in improving diagnostic and antibiotic stewardship. She emphasized the importance of engaging outside of the "AMR bubble." For example, when new rapid diagnostics for sepsis are brought to market, there is a need to engage and involve organizations such as the Sepsis Alliance,[2] ENDSEPSIS,[3] and the Global Sepsis Alliance.[4] In addition, there may be creative ways, such as the use of film or other media, to better engage the lay public.

DISCUSSION

Role of policy

Banerjee suggested that policies in the form of clinical guidelines "would go a long way" towards integrating diagnostics into care. When clinicians, administrators, and payers can refer to one set of guidelines that recommend when and how to use diagnostics, those guidelines determine the new standard of care. Another effective approach would be a policy that

[2] See https://www.sepsis.org/ (accessed January 23, 2023).
[3] See https://www.endsepsis.org/ (accessed January 23, 2023).
[4] See https://www.global-sepsis-alliance.org/ (accessed January 23, 2023).

mandates diagnostic stewardship programs that are conducted in partnership with microbiology laboratories. These programs would help support uptake of diagnostics and appropriate use of diagnostics.

Role of guidelines

Burnham pointed out that guidelines are typically developed by volunteers who have many other duties, so it would be useful to have financial resources for professional help with tasks such as literature reviews to help speed up the process, particularly given that this field evolves quickly over time. Additionally, guideline development should be useful for the end users, so it is important to incorporate the input of people who might rely on diagnostic tests, including laboratory directors, medical specialists and infectious disease experts. When considering policy levers for supporting the development guidelines (e.g., CDC or specialty societies), Flayhart and R. Patel agreed that more work is needed.

Role of reimbursement and incentives

Flayhart stated that it can be challenging to assess and demonstrate the value of diagnostics because patient health and outcomes are complex and multi-factorial. She emphasized the importance of collaborating with laboratories and stewardship teams to design clinical trials in a way that captures meaningful measurements. If a trial shows how a diagnostic can plug into the clinical pathway for patient care and improves outcomes, it is more likely to be deployed and reimbursed.

Opportunities for public awareness

Flayhart said that AMR should be viewed as a global phenomenon that impacts humans, animals, and the environment. There are public conversations about issues, such as antibiotic use in animal food products and environmental contamination of public waterways, she said, but what "we haven't cracked yet" is getting people to ask questions about their own use of antibiotics. According to Flayhart, people should be having conversations with their doctors about why an antibiotic is being prescribed and if there is a diagnostic available to help make more informed treatment decisions. Bausch said that stakeholders should be more forthcoming about the potential harms of antibiotics so patients can weigh the pros and cons of taking a drug. The message for patients, said Flayhart, is that unlike other medications, taking antibiotics does not just impact the patient but everyone in their ecosystem.

Buy-in from hospital leadership

Diagnostic stewardship programs seem to be beneficial for many reasons, said Van Meter. However, how can hospital leadership be convinced

to invest in them? Burnham said that there is a delicate balance between a desire for physician autonomy and a desire to deploy resources appropriately. Like many things, she said, it starts with a "gentle approach." For example, an alert could be built into the electronic health record that would simply ask the physician to confirm a prescribing choice. Eventually this could progress to a hard stop where the physician cannot take a certain step (e.g., prescribing or ordering a test) without following a certain pathway. Along the way, said Burnham, it is critical to include stakeholders in the process and focus on adding value whenever possible. Often, the lab might have to take on the initial burden of choosing a use case and a clinical partner to deploy the tool; once value is demonstrated, they can "take that on the roadshow" and champion it.

Following up on this, a virtual participant asked Banerjee to discuss how hospital leadership can be convinced of the value of diagnostics if they do not improve the metrics that are most important to hospitals (e.g., length of stay, mortality). Banerjee said that the value can be demonstrated through other metrics, for example, savings on the cost for antibiotics, or long-term savings due to faster infection control. There is value in reducing societal levels of AMR, and this should be reflected in accreditation or joint commission surveys. For example, if a survey asks hospitals if they monitor certain metrics related to AMR, hospital leadership is likely to adopt new practices to maintain accreditation and ratings.

Mechanism to measure performance

As new diagnostics are developed and deployed, said a participant, it will be critical to have an ongoing mechanism for ensuring performance. She asked panelists to comment on how this could be accomplished. Burnham said that there will need to be different approaches for ongoing evaluation of diagnostics. Putting this burden on device manufacturers is not realistic, said Burnham; it will need to be a coordinated effort among hospitals, laboratories, device manufacturers and government. If a shift in performance occurs or a new mechanism of resistance is detected, these results will need to be reported so that appropriate steps can be taken.

Clinical outcome studies

A participant commented that conducting clinical outcome studies poses a considerable challenge for test developers; studies may need to be conducted in multiple centers and in areas with high resistance. Banerjee responded that it can be difficult for companies, particularly smaller companies, to conduct studies that can adequately show the value of a new diagnostic. Partnering with larger organizations can be one approach to support these types of studies. However, at the end of the day, clinical outcome studies should be "diagnostic agnostic." In other words, if it can

be demonstrated that a diagnostic provides actionable results within a certain timeframe and has downstream clinical benefit, then those benefits should be applied to equivalent tests as they move through clinical outcome studies.

7

Exploring Potential Policy Options

Workshop participants discussed a "menu" of potential policy options (Box 7-1) for incentivizing the development and use of rapid diagnostics, important issues to consider, and next step opportunities.

POLICY OPTIONS

Mark McClellan (Duke Margolis Center for Health Policy) laid out a "menu" of potential policy options to encourage the development and appropriate use of rapid diagnostics. Panelists, each representing a different stakeholder perspective, made brief remarks, followed by a discussion moderated by McClellan. The discussion is presented by topic area rather than by speaker. The panelists were:

- Industry perspective: Phyllis Arthur (Vice President, Infectious Diseases & Emerging Science Policy, BIO)
- Research perspective: Sarah McClelland (Health Policy Analyst, U.S. Department of Health and Human Services)
- Policy perspective: Jaclyn Levy (Director, U.S. Policy, AMR Action Fund)
- Law and economics perspective: Kevin Outterson (Professor of Law, Boston University, Executive Director, CARB-X)

Before exploring the suggested policy options outlined in Box 7-1, several speakers discussed why policy levers are appropriate or necessary for spurring diagnostic development. Arthur stated that one barrier to

BOX 7-1[a]
Menu of Policy Options

Based on the needs discussed during this panel session and drawing from past experience and examples from other therapeutic areas, panelists discussed a "menu" of policy options. Policy options fell into two main categories:

- Options for encouraging the development of rapid diagnostics; and
- Options for encouraging the appropriate uptake and use of rapid diagnostics.

Panelists pointed to initiatives, including CARB-X,[b] PACCARB,[c] and the AMR Action Fund,[d] which have worked to incentivize diagnostic and antibiotic development. Levy noted that while progress is being made, the incentives currently in place are just one step in the right direction— more is needed to determine which incentives are working and how to improve upon them. Panelists considered three types of policy options: incentives to promote coordination, cooperation, and efficiency; regulatory approaches; and pull incentives.

Options for Encouraging the Development of Rapid Diagnostics

Coordination, Cooperation, and Efficiency

- Accelerator programs (e.g., CARB-X) (McClellan)
- Clinical trial networks (McClellan)
- Master study protocols (McClellan)
- Coordinating organizations (McClellan)

Regulatory Approaches

- Implementing reforms that remove barriers and help streamline regulatory processes (McClelland)
- Supporting clinical trial networks with common rules and shared IRBs, in part to reduce regulatory burden of test approval (McClelland)

New Incentives

- Using financial incentives to encourage co-development of new antibiotic susceptibility tests and new antibiotics (e.g., tax credit for portion of qualified clinical testing expenses) (McClelland)

diagnostic development lies in the valuation of diagnostics and antibiotics; these products are essential to the public's health and for the longevity of effective treatments, but the market does not value them in this way. Given this reality, Arthur noted the options are to either allow diagnostic products to be valued for what they bring to the marketplace or to find substitutions for the valuation that allow companies to invest in the work without losing money. Policy interventions can be used to address the valuation issue and encourage investment in the area.

On a similar note, Outterson said that while the use of rapid diagnostics has benefits—including better care, reductions in cost of care, and curtailing

- Creating federal small-business grant opportunities for diagnostic developers (Levy)

Options for Encouraging Appropriate Uptake and Use of Rapid Diagnostics

Demonstrating Clinical Value

- Funding research that investigates the clinical outcomes and benefits to patients related to diagnostics (Outterson)
- Promoting collaboration between diagnostic companies and other stakeholders to ensure optimal test development to meet clinical needs and to increase the likelihood of adoption of test (McClelland)
- Providing clinician education on the use and interpretation of diagnostic tests to spur uptake in clinical practice (McClelland)

Development of Guidelines

- Expanding capacity by supplying funding and more resources (Levy)

Reimbursement Reform

- Shifting toward a reimbursement system that prioritizes patient outcomes rather than cost minimization (McClellan)
- Using a reimbursement-plus system to realign reimbursement with value (McClelland)
- Using conditions of participation in Medicare to encourage uptake of diagnostics (Outterson)

---

[a] This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They are not intended to reflect a consensus among workshop participants.

[b] See https://carb-x.org/ (accessed January 27, 2023).

[c] See https://www.hhs.gov/ash/advisory-committees/paccarb/index.html (accessed January 27, 2023).

[d] See https://www.amractionfund.com/ (accessed January 27, 2023).

AMR—the financial return for using a diagnostic does not usually flow back to the entity that makes the initial payment. Diagnostics are currently more expensive than empirical prescribing an antibiotic, said Outterson, so there is not a financial incentive for key stakeholders to incorporate the use of these products. As noted by Anthony So in Chapter 5, bundling the development, use, and reimbursement of diagnostics with drugs may be one way to manage this issue.

Outterson highlighted that hospitals are reimbursed through Medicare based on a DRG system. Patients are classified based on DRGs, which determines how much money the hospital will receive on a per case basis.

The DRG system is designed to drive cost-cutting for inpatient expenses, such as nursing, facilities, food, bed, and pharmacy costs. Patients with a particular type of bacterial infection may be assigned the same DRG whether they are prescribed a relatively inexpensive generic antibiotic or if the hospital deploys a costly new diagnostic test that determines the generic drug is not effective, in which case the hospital may be obligated to prescribe a more expensive antibiotic. Each step of this process, said Outterson, incurs costs—space for the diagnostic test, staff to run the test, expense of running the test, and prescribing a more expensive drug—without additional reimbursement through the DRG system. When a hospital CEO or CFO considers the financial implications of adopting a new diagnostic tool, there are more costs to be controlled than incentives for improving patient care.

In the emergency department, the financial incentives look a bit different, said Outterson. A rapid diagnostic could help a provider to make a quick decision about whether to admit a patient or send them home. Testing in the ED is paid for through CPT codes, or if a patient is admitted that cost is rolled into the DRG payment. CPT codes can be confusing for new diagnostics, he said, but if a test is billed correctly and a patient is not admitted, it could result in a small positive margin for the ED.

According to Outterson, given these types of misaligned incentives, hospitals are not financially motivated to adopt new (more expensive) diagnostic tools; add newer antibiotics to AST panels and breakpoints; add new antibiotics to the hospital formulary; use a higher-priced antibiotic; or identify a hospital-associated infection. As a result, timely diagnosis and appropriate treatment for patients are often delayed.

Encouraging the Development of Rapid Diagnostics

Incentives to Promote Coordination, Cooperation, and Efficiency

In response to the ongoing COVID-19 pandemic, the diagnostics industry has built up core capability, said Arthur, and policy solutions should leverage this capacity and direct resources towards better point-of-care rapid diagnostics. Policies and approaches that can help promote coordination include accelerator programs (e.g., CARB-X), clinical trial networks, master study protocols, and coordinating organizations, said McClelland. She pointed to the PACCARB, which recommended the following:

> Federal government agencies (e.g., HHS, FDA, CDC, NIH, DoD, USDA) should come together to create a list of the most critically needed diagnostics for combating AMR. (PACCARB, 2017)

McClelland said this list could help spur collaboration between diagnostic companies and stakeholders in the AMR arena and accelerate the development of diagnostic tools. Levy added that challenges like the Rapid Acceleration of Diagnostics (RADx) and the NIH/ASPR AMR Diagnostic Challenge, which have been successful in accelerating the development timelines for other products, could be applied to AMR diagnostics to promote collaboration and partnerships between companies and funders. Crowdsourcing and citizen science also present opportunities for public-private partnerships. Advocacy and patient coordination are particularly challenging with infectious diseases due to the variety of patient groups, said Levy, but coordinating these groups within the AMR space and connecting their experiences to the need for diagnostics continues to be important work.

Regulatory Approaches

Regulatory approaches, said McClelland, could include reforms that remove barriers and simplify the process of obtaining regulatory approval, similar to the regulatory flexibility that the FDA showed during the COVID-19 pandemic. In addition, clinical trial networks with common rules and shared IRBs could reduce the regulatory burden of test approval. Arthur suggested that given the ongoing pandemic, there may be more pressure for companies to concurrently develop rapid diagnostics alongside new therapeutics. Levy highlighted the need for balance between the regulatory system and the rapid deployment of new technologies. She added that there is a need to retain the ability of clinical laboratories to develop rapid diagnostics, particularly for pediatric and immunocompromised patient populations. There may be opportunities to address these needs, in part, through post-market data and real-world evidence.

New Incentives

Tax credits are one pull incentive that PACCARB has recommended, which would pair funding for the development of new antibiotic susceptibility tests with the development of new antibiotics by providing a tax credit for a portion of clinical testing expenses (PACCARB, 2017). Arthur pointed to the need to incentivize developers of antibiotics to work with diagnostic companies. She suggested that incentives could focus on a core set of pathogens that would most benefit from a paired diagnostic and drug. Outterson added that drugs and diagnostics should be developed in similar time frames because it could take years after the introduction of a new drug before a physician could get information about susceptibility or resistance.

An additional benefit of co-development of drugs and diagnostics is that it can reduce the cost of clinical trials, said Arthur; a diagnostic allows patients to quickly be differentiated and eligible patients enrolled in relevant clinical trials. Jean Patel (Principal Scientific Affairs, Microbiology, Beckman Coulter Diagnostics) cautioned that while co-development can be advantageous, there are also risks involved. She mentioned that she has seen cases in which diagnostics were developed or redesigned to include a specific drug, but the drug did not make it to market. These experiences could serve as a disincentive for these types of partnerships, but policy approaches could help mitigate some of these risks.

Arthur stressed that incentives should be focused on the most urgent antimicrobial threats and that putting incentives toward the right drug and the right tool being developed and deployed "at the same time" will result in the best outcomes in healthcare. She added that there are lessons to be learned from the oncology field. When companies are creating an oncology treatment, they are encouraged to develop a companion diagnostic that allows clinicians to use the product on the right patient to optimize outcomes. Using this approach for antibiotics, said Arthur, means that clinicians would have the data they need to direct treatment to the patient rather than "empirically trying every antibiotic in the pharmacy." A rapid diagnostic that would lead to the most effective drug being prescribed to a patient, she said, is the "holy grail" of what stakeholders in rapid diagnostic development are trying to achieve.

Encouraging Uptake and Use of Rapid Diagnostics

Demonstrating Clinical Value

According to McClelland, successful development and regulatory approval of a diagnostic test is only the first hurdle; to be impactful, the test must be appropriately used during patient care. There are a variety of policy approaches for incentivizing the uptake of diagnostics, said McClelland, including policies in the areas of clinical value, guidelines, and reimbursement reform.

Clinicians want a test that will make a difference in the care of their patients, said McClelland. If doctors and administrators had more information about what works, said Outterson, uptake would improve. Policy approaches that could increase the likelihood that the diagnostics that are developed are taken up by clinicians include

- Funding for research that investigates the clinical outcomes and benefits to patients related to diagnostics (Outterson);

- Promoting collaboration between diagnostic companies and other stakeholders to help ensure optimal test development to meet clinical needs and to increase the likelihood of adoption of test (McClelland);
- Providing clinician education on the use and interpretation of diagnostic tests to spur uptake in clinical practice (McClelland);
- Increasing collection and analysis of post-market data and real-world evidence (Levy).

Development of Guidelines

Several speakers mentioned the need for timely guidelines for new diagnostics, and how these could prompt improvements in uptake and reimbursement, said McClellan. Arthur said that the value of clinical guidelines is that they set a drug or a diagnostic apart from others and empower clinicians to get access to the product for their patients. McClellan asked panelists how policy could be used to support rapid guidelines development when there is a breakthrough diagnostic. Levy said that during the COVID-19 pandemic, IDSA was able to get guidelines out "incredibly rapidly," but it took a global emergency and an enormous amount of effort. Guideline development takes manpower, time, and work, and is usually carried out by volunteers. There is a need for more resources and expanded capacity to enable guidelines to be developed more quickly.

Reimbursement Reform

Once a product reaches the market, said Levy, clinical uptake can be a significant challenge due to misaligned financial incentives—for example, hospital administrators are reluctant to use a $50 test to prescribe a $5 antibiotic. While using a diagnostic to find the right antibiotic has the potential to save money in terms of patient care and patient outcomes, said Levy, the current reimbursement structure does not reflect this value. Realigning incentives to encourage uptake will require reimbursement reform for diagnostics; Arthur added that reform for reimbursement of antibiotics may be necessary as well. Speakers suggested several policy approaches:

- A shift toward a reimbursement system that prioritizes patient outcomes rather than cost minimization (McClellan);
- A reimbursement-plus system to realign reimbursement with value (McClelland);
- Using conditions of participation in Medicare to enhance diagnostic use; this approach was "transformative" for antibiotic stewardship (Outterson).

Several speakers suggested that new technology add-on payments (NTAPs) could play a role in incentivizing the uptake of diagnostics.[1] However, Outterson pointed out that these have not generally been effective for AMR-related products thus far. NTAPs were created in 2001 to deal with the unanticipated consequences of Medicare reform, and they provide separate reimbursement for up to 50 percent of the added cost to hospitals for selected clinically valuable products for two to three years. However, the funds do not return to the cost center (hospital pharmacy or lab), which undermines the goal of the policy. In the hospital laboratory, he said, there are four major financial concerns: space, time, people, and costs. A company with a new diagnostic tool is asking for all four of these and any extra reimbursement goes to another account in the hospital. For example, if an antibiotic diagnostic has a NTAP, the NTAP may reduce the cost of each test by $50. However, the hospital still incurs the costs of buying the technology, conducting the tests, and potentially paying for more expensive medications. Even with the NTAP, Outterson said, the diagnostic may cause the hospital to lose money on a patient. Evans agreed that in his view, NTAPs are not effective because they do not offer enough of an incentive, and the likelihood of a provider receiving the passthrough payment is low. However, he said, there is an opportunity to bolster the program and remove some of these barriers.

Considerations for Policy Interventions

In addition to discussing specific policy options, panelists reflected on a variety of issues to consider when implementing policies directed at improving the development and uptake of diagnostics for AMR.

Role of the Federal Government

The federal government has a unique and important role to play in incentivizing development and uptake of diagnostics, said Levy. The federal government can use its resources and position to fund research, create tax credits, change reimbursement policies, simplify regulatory requirements, and facilitate collaboration among developers and clinical investigators. In addition to these critical incentives, the federal government could develop a list of the highest priority areas in which diagnostics are needed (similar to WHO's Essential Diagnostics List[2]). This list could help guide both public and private decisions about funding, research, and incentives, said Levy.

[1] See https://www.federalregister.gov/documents/2001/09/07/01-22475/medicare-program-payments-for-new-medical-services-and-new-technologies-under-the-acute-care (accessed January 27, 2023).

[2] See https://www.who.int/teams/health-product-policy-and-standards/assistive-and-medical-technology/medical-devices/selection-access-and-use-in-vitro (accessed January 27, 2023).

Levy said that the types of incentives discussed at the workshop provide a good opportunity for engagement across different agencies and organizations. For example, NIAID has experience with small-business grants, while the FDA and Internal Revenue Service (IRS) have experience with tax credits for clinical testing expenses (i.e., the Orphan Drug Tax Credit[3]). Partnerships and collaborations are critical for moving efforts forward, she said, and there are existing models that can be leveraged for AMR. For example, RADx initiative at NIH supported innovative and non-traditional diagnostic approaches for COVID-19;[4] a similar initiative could be explored for AMR diagnostics. PACCARB and the CARB Task Force are examples of collaborative bodies convened by the government that are working on issues surrounding AMR (Box 7-2).

An Ethical Dilemma

Burnam suggested that if a brand-new drug for MRSA were released, is it would be the clinician's ethical responsibility to "lock it in a safe" and not use it until it is absolutely needed. As soon as people are exposed to a new drug, the bacteria will begin evolving resistance, he said, so from a "do no harm" perspective, a clinician should be extremely cautious about using new drugs. However, if a drug does not get used, the pipeline of new drugs dries up because the business model is unsustainable. Arthur said that this is a "chicken or the egg" problem, in which physicians feel like they have to "hold everything behind glass" because they want to have something in reserve when resistance occurs. McClellan said that this dilemma demonstrates the value of having accurate, rapid diagnostics that can give physicians confidence about using a specialized drug in a particular patient who needs it.

Global Implications

Even if the problems discussed during this workshop were resolved, there would still be an ongoing AMR pandemic throughout the rest of the world, stated Bausch. Most of the solutions suggested so far are not applicable outside of the United States. For example, even if a diagnostic were developed that costs two dollars, amoxicillin can be purchased on the market for 50 cents. Whether the antibiotic works or not is "almost immaterial," said Bausch, because patients and clinicians are generally inclined to use the easier and more affordable solution. In the context of an LMIC, Bausch suggested that it will take long-term investment

[3] See https://www.irs.gov/forms-pubs/about-form-8820 (accessed January 27, 2023).

[4] See https://www.nih.gov/research-training/medical-research-initiatives/radx (accessed January 27, 2023).

BOX 7-2
Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

PACCARB was created in 2014 to provide advice and recommendations to the Secretary of Health and Human Services (HHS) on all things related to combating antibiotic resistance, said Sarah McClelland (Health Policy Analyst, U.S. Department of Health and Human Services). The PACCARB sits at the nexus of federal and public, said McClelland; it is composed mostly of nongovernment subject matter experts to help ensure public engagement in the policy making process. In contrast, said McClelland, the CARB Task Force is an effort that pulls together federal agencies to promote collaboration and communication on federal antibiotic resistance efforts. Since its establishment, the PACCARB has published ten reports, all of which address the key issues of development and uptake of diagnostics. Diagnostics are a "pivotal component" of this work, said McClelland, and antibiotic stewardship can only be accomplished with the inclusion of diagnostics. The recommendations in the PACCARB reports addressed market-based and reimbursement incentives, as well as use and uptake. McClelland noted that all PACCARB's recommendations come from a OneHealth perspective, which incorporates human as well as animal health.

In the spring of 2022, PACCARB was tasked by the Secretary of HHS to evaluate pandemic preparedness policies in terms of how AMR could be included and could bolster pandemic-related efforts, said McClelland. PACCARB created a Pandemic Preparedness Working Group,[a] which held a public meeting to examine critical aspects of pandemic preparedness infrastructure, including surveillance, diagnostics, vaccines and therapeutics, and infection prevention and control. The PACCARB members and speakers worked through a mock pandemic scenario to highlight key gaps; for diagnostics, this meant examining steady state versus surge capacity needs of laboratories, as well as highlighting barriers in the development of new diagnostics. McClelland encouraged workshop participants to engage with PACCARB by attending meetings or submitting stakeholder input.

[a] See https://www.hhs.gov/ash/advisory-committees/paccarb/working-groups/index.html (accessed January 27, 2023).

and creative financing and approaches that are not entirely based on short-term economics. Arthur added that regardless of the incentives for development and uptake, behavioral change is needed, and this applies to care settings in the United States and LMICs. Clinicians and patients hold certain views about antibiotic use, and these views impact their behavior: "The right drug in your hands" will not make a difference without behavior change, she said.

CONSIDERING A PATH FORWARD

AMR is a complex term that involves multiple bacterial species and multiple clinical syndromes, so there will likely need to be multiple ways for diagnostics to help manage AMR, said J. Patel. She noted, for example, that the bacterium that Mallory Smith was infected with—*Burkholderia cenocepacia*—is not on the list of CDC antibiotic resistance threats.[5] For an individual patient, antimicrobial resistance is a problem regardless of which bacterium is causing their infection, so diagnostic-based solutions should address AMR broadly and across all patient populations. At the same time, J. Patel pointed out, clinical microbiology laboratory staff has been decimated because of the ongoing COVID-19 pandemic. "We cannot go on with diminished technical expertise in infectious disease diagnostics," she stated, and replenishing the workforce is a responsibility that falls on all sectors of diagnostics and patient care.

In considering the path forward, panelists identified a few areas for which next steps could improve the development and uptake of AMR-related diagnostics: leveraging COVID-19, addressing regulatory barriers, policy reform to incentivize diagnostic development and use; prioritization of efforts based on pathogen, syndrome, or care settings; and collaboration to share information and resources, establish common metrics, and mobilize people and organizations to take action.

Leveraging COVID-19

"We are in a technology revolution, but we are also in an AMR pandemic" said Robin Patel (ID Physician, Clinical Microbiology Laboratory Director, Mayo Clinic). In response to the ongoing COVID-19 pandemic, there were remarkable advances in diagnostics development. There is an opportunity, said R. Patel, to apply lessons learned from COVID-19 towards AMR. This should be done in an expeditious way so that patients can get the treatments they need. Arthur added that the COVID-19 pandemic demonstrated how industry can make faster, better, and easier-to-use diagnostics. Leveraging these core capabilities to improve point-of-care and at-home diagnostics and ramping up partnerships for the development and use of diagnostics are two promising options for the AMR space.

Addressing Regulatory Barriers

Emerging technologies offer an opportunity to measure and see things in a different way than before, said Ribhi Shawar (Branch Chief, Division

[5] See https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf (accessed February 6, 2023).

of Microbiology Devices, Office of In Vitro Diagnostic and Radiological Health, Center for Devices and Radiological Health, FDA). However, these technologies come with challenges for regulators, particularly in determining a comparative reference method. For example, during the COVID-19 pandemic, a new test was proposed that could diagnose COVID-19 through the breath.[6] The only existing breath-based test, said Shawar, was a test for *H. pylori*.[7] He said that this required regulators to really think about how to evaluate a test that was operating in a "totally different paradigm." Collaboration and coordination are critical when developing, evaluating, and implementing these new technologies: some stakeholders bring expertise, others bring facilities and tools, and others bring specimen banks. The field will not advance without collaboration, he said.

Van Meter said that a program to provide transitional coverage for emerging technologies could help technologies that have been cleared and received breakthrough status from the FDA. Such a program might support device and diagnostic manufacturers work collaboratively with the government to generate evidence. However, she noted, this type of approach would not necessarily ensure an appropriate reimbursement rate or a market. Shawar added that there is an existing "pre-submission" program at the FDA that allows developers to ask questions before they formally submit a Premarket Approval Application.[8] This program helps developers conduct studies and gather evidence in a way that will be amenable to the FDA. J. Patel agreed that these types of programs for emerging and innovative technologies are useful in the AMR space, in part because clinical care practices are constantly evolving.

Addressing Reimbursement Barriers

Susan Van Meter (President, American Clinical Laboratory Association) offered a few suggestions for how reimbursement barriers to the development and uptake of diagnostics could be addressed through CMS. First, Medicare has conditions for participation that require antimicrobial stewardship programs in the inpatient setting. Work could be done to bolster these requirements and build diagnostic stewardship programs into conditions of participation. Another approach could be to include diagnostic stewardship as part of a value-based payment initiative. For example, a program launched by the Affordable Care Act holds back two percent

[6] See https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-covid-19-diagnostic-test-using-breath-samples (accessed January 27, 2023).

[7] See https://www.fda.gov/media/157723/download (accessed January 27, 2023).

[8] See https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program (accessed January 27, 2023).

of inpatient hospital payments and uses the money to reward hospitals for advancement compared to peers and improvement compared to baseline.[9] She highlighted that it would be important that incentive programs not be used to penalize hospitals. Underserved hospitals that are struggling for resources should be given the resources they need rather than penalized for not meeting certain metrics.

In ambulatory settings, said Van Meter, Medicare's Merit-Based Incentive Payment System (MIPS) for physicians could be used to encourage ambulatory diagnostic stewardship programs, particularly in areas that are most impacted by inappropriate prescribing. The Centers for Medicare and Medicaid Innovation Center has "extraordinary authority" to waive rules and regulations for pilot programs, she said. Their primary focus is on improving quality of care while reducing cost, but they also have authority to implement programs that increase costs to improve care. Together, Medicare and Medicaid reach a very high proportion of Americans throughout the country and leveraging this mechanism could help develop evidence about the value of diagnostics for AMR across the patient population.

Van Meter added that from her perspective, one of the most pressing priorities is to pass the Saving Access to Laboratory Services Act (SALSA)[10] to prevent cuts to Medicare payments for laboratory tests. Medicare is a large market, she said, and so SALSA would provide a more predictable pathway forward for developers. Another approach, said Van Meter, would be to encourage CMS to use existing authorities to put in place Medicare and Medicaid pilot programs that leverage diagnostic stewardship programs across communities. Finally, she pointed to Independent Test Assessment Program (ITAP), which helped small and large companies pull together diagnostic submissions to the FDA in an expedited fashion during the COVID-19 pandemic. A similar model, made permanent and adequately funded, could help ensure that there is a fast-track mechanism for getting needed diagnostics through the regulatory process as quickly as possible. Diagnostics account for two to three percent of total healthcare spending but drive around 70 percent of clinical decision-making (Rohr et al., 2016). The "investment in diagnostics is so worth it across the board," she said.

Pursuing Innovative Approaches

Joseph Larsen (Vice President, Clinical Development, Locus Biosciences, Inc.) said that innovative diagnostics in the AMR space would not only

[9] See https://www.cms.gov/newsroom/press-releases/affordable-care-act-program-improve-hospital-care-patients (accessed January 27, 2023).

[10] Saving Access to Laboratory Services Act, HR 8188, 117th Cong., 2d sess. (June 22, 2022).

improve treatment with traditional antibiotics but would also contribute to the development and use of nontraditional treatments such as genetically engineered bacteriophage. For example, Larsen's company is currently enrolling UTI patients in a clinical study for an *Escherichia (E.) coli* phage "cocktail."[11] Before enrollment and randomization, it must be confirmed that the patient is infected with *E. coli*. Current testing adds a delay of three days between the administration of a test and the interpreting of results after which a patient can enroll, and the trial itself is testing a five-day dosing regimen. Because of this time commitment, he said, many patients simply take their antibiotics and "go home." A diagnostic that would quickly confirm *E. coli* infection would remove some of the barriers to enrollment and allow evidence to be collected more quickly on these new approaches. Launches of new antibiotic agents over the last decade have been "atrocious" from a commercial standpoint, said Larsen, but innovative diagnostics have the potential to improve the commercial prospects for both new antibiotics and nontraditional approaches to infectious disease.

Levy agreed that innovative and nontraditional approaches to diagnostics are needed to meet the challenges in the area of AMR and diagnostics, including workforce shortages, the lack of a coordinated and robust patient advocacy community, and regulatory barriers. New and nontraditional approaches to diagnostics include

- community wastewater surveillance and analysis to identify pathogens and measure the spread of infection;
- novel analytical platforms (e.g., NGS) coupled with point-of-care, noninvasive sample collection;
- screening and home-based tests;
- integration of AI systems, novel diagnostics, and digital health technologies that can screen, diagnose, monitor, and predict disease severity;
- automatic, real-time detection and tracing to integrate virus-sensing elements with touchscreen or other digital devices.

Innovative approaches to developing diagnostics may also be needed, she said. For example, the AMR Diagnostic Challenge was a federal prize competition that sought innovative, point-of-care diagnostics to combat AMR; the winner received $19 million for a rapid diagnostic for gonorrhea that detected microorganisms and susceptibility to a single-dose antibiotic in under 30 minutes (NIH, 2020). This challenge, said Levy, spurred a number of paradigm-shifting and "moonshot" diagnostics. Another approach for encouraging innovation is crowdsourcing or "citizen science." This has

[11] See https://clinicaltrials.gov/ct2/show/NCT05488340 (accessed January 27, 2023).

become popular in adjacent fields, said Levy; for example, Foldit[12] is an online video game designed to advance research in protein folding. Foldit is also an example of a strong public-private partnership, she said, as its collaborators include University of Washington, Defense Advanced Research Projects Agency (DARPA), NIH, Amazon, Microsoft, Adobe, and others. A similar approach could be taken to generate data for the development of diagnostics and therapeutics. In fact, said Levy, Adaptive Phage Therapeutics has just announced a challenge to find bacteria that are resistant to their investigational phage bank, with any successful submission receiving $1000.[13]

CLOSING REMARKS

Given that cost underpins many of the challenges raised during the workshop discussions, Trainor suggested that rather than trying to "boil the ocean," it can be helpful to think about how the community could come together to support focused efforts on specific pathogens, syndromes, or care settings that would have the most impact. Priority areas might include care settings that have demonstrated high levels of inappropriate prescribing or conditions, such as sepsis, for which time has a significant impact on disease progression and patient outcomes. Eder suggested that one area in which investments could make a difference is asymptomatic monitoring. In some care settings, monitoring may not be cost-effective, he said, but in particular settings, such as nursing homes, diagnostics that help monitor patients and detect the onset of infection, could support more timely and effective treatment. As an example, Eder suggested that in a retirement facility setting, the use of wearables that detect UTIs could help inform the appropriate and timely use of antibiotics and mitigate the development of more serious conditions.

Trainor, Shawar, and Kester encouraged stakeholders to share information and resources through collaboration. Shawar pointed out that diagnostic developers need access to data, such as genetic information and its correlation to phenotype. Specimen banks are also critical for validating devices, particularly for rare pathogens and rare resistant organisms. Additionally, J. Patel and R. Patel highlighted the need for commonly accepted metrics for improving antibiotic use in hospital settings. If there were metrics upon which hospitals were responsible for improving prescribing, this could change how diagnostics are used and institutionalize

[12] See https://fold.it/ (accessed January 27, 2023).

[13] See https://aphage.com/adaptive-phage-therapeutics-announces-the-amr-rapid-challenge-for-the-infectious-disease-research-community-find-a-bacteria-resistant-to-apts-investigational-phage-ban/ (accessed January 27, 2023).

the benefits of appropriate antibiotic use. Trainor and Kester concluded that discussions such as these can help mobilize people, organizations, and the public to engage on the issue of diagnosis and appropriate treatment and take action.

References

3Arts Entertainment. *Salt in My Soul*. United States: 2022.

Antimicrobial Resistance Collaborators. 2022. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* 399(10325):629–655. https://doi.org/10.1016/S0140-6736(21)02724-0.

Banerjee, R., L. Komarow, A. Virk, N. Rajapakse, A. N. Schuetz, B. Dylla, M. Earley, J. Lok, P. Kohner, S. Ihde, N. Cole, L. Hines, K. Reed, O. B. Garner, S. Chandrasekaran, A. de St Maurice, M. Kanatani, J. Curello, R. Arias, W. Swearingen, S. B. Doernberg, and R. Patel. 2021. Randomized Trial Evaluating Clinical Impact of RAPid IDentification and Susceptibility Testing for Gram-negative Bacteremia: RAPIDS-GN. *Clinical Infectious Diseases* 73(1):e39–e46. https://doi.org/10.1093/cid/ciaa528.

Banerjee, R., C. B. Teng, S. A. Cunningham, S. M. Ihde, J. M. Steckelberg, J. P. Moriarty, N. D. Shah, J. N. Mandrekar, and R. Patel. 2015. Randomized Trial of Rapid Multiplex Polymerase Chain Reaction-Based Blood Culture Identification and Susceptibility Testing. *Clinical Infectious Diseases* 61(7):1071–1080. https://doi.org/10.1093/cid/civ447.

BARDA (Biomedical Advanced Research and Development Authority). 2022. *BARDA announces the 64th FDA Approval/Licensure/Clearance for Simplexa™ COVID-19 Direct, the second standalone FDA cleared COVID-19 diagnostic test and supported by BARDA under Novel Public Private Partnerships*. https://www.medicalcountermeasures.gov/newsroom/2022/simplexa/#:~:text=BARDA%20announces%20the%2064th%20FDA,under%20Novel%20Public%20Private%20Partnerships (accessed January 25, 2023).

BD (Becton, Dickinson and Company). 2022. *Pfizer, Wellcome Collaborate to Improve Global Hospital Antimicrobial Stewardship Practices*. https://investors.bd.com/news-releases/news-release-details/bd-pfizer-wellcome-collaborate-improve-global-hospital (accessed March 6, 2023).

Boehme, C. C., P. Nabeta, D. Hillemann, M. P. Nicol, S. Shenai, F. Krapp, J. Allen, R. Tahirli, R. Blakemore, R. Rustomjee, A. Milovic, M. Jones, S. M, O'Brien, D. H. Persing, S. Ruesch-Gerdes, E. Gotuzzo, C. Rodrigues, D. Alland, and M. D. Perkins. 2010. Rapid molecular detection of tuberculosis and rifampin resistance. *New England Journal of Medicine* 363(11):1005–1015. https://doi.org/10.1056/NEJMoa0907847.

Buchan, B. W., S. Windham, J. M. Balada-Llasat, A. Leber, A. Harrington, R. Relich, C. Murphy, J. Dien Bard, S. Naccache, S. Ronen, A. Hopp, D. Mahmutoglu, M. L. Faron, N. A. Ledeboer, A. Carroll, H. Stone, O. Akerele, K. Everhart, A. Bonwit, C. Kwong, R. Buckner, D. Warren, R. Fowler, S. Chandrasekaran, H. Huse, S. Campeau, R. Humphries, C. Graue, and A. Huang. 2020. Practical Comparison of the BioFire FilmArray Pneumonia Panel to Routine Diagnostic Methods and Potential Impact on Antimicrobial Stewardship in Adult Hospitalized Patients with Lower Respiratory Tract Infections. *Journal of Clinical Microbiology* 58(7):e00135-20. https://doi.org/10.1128/JCM.00135-20.

Burgess, D. H., J. Wasserman, C. A. Dahl, F. Girosi, S. S. Olmsted, E. B. Keeler, Y. Lim, J. E. Aledort, M. E. Rafael, K. A. Ricci, R. Boer, L. H. Hilborne, K. P. Derose, M. Shea, C. Beighley, M. Steinhoff, D. Holtzman, H. Campbell, R. Black, K. Mulholland, A. Ronald, S. M. Le Blancq, R. Ridzon, A. Landay, J. Safrit, R. W. Peeling, N. Hellmann, P. Mwaba, K. Holmes, C. M. Wilfert, P. I. Tarr, C. Mason, M. Miller, J. Hughes, L. von Seidlein, J. M. Agosti, R. L. Guerrant, T. Taylor, A. Magill, R. Allan, M. D. Perkins, P. Small, C. Hanson, S. Reed, J. Cunningham, C. Dye, P. Vickerman, M. Urdea, L. A. Penny, M. Y. Giovanni, P. Kaspar, A. Shepherd, P. Wilson, S. Buchsbaum, and G. Moeller. 2007. Estimating the Global Health Impact of Improved Diagnostic Tools for the Developing World. Santa Monica, CA: RAND Corporation. https://www.rand.org/pubs/research_briefs/RB9293.html (accessed January 23, 2023).

CDC (Centers for Disease Control and Prevention). 2019a. *Antibiotic Resistance Threats in the United States, 2019*. http://dx.doi.org/10.15620/cdc:82532 (accessed February 1, 2023).

CDC. 2019b. *Sexually Transmitted Disease Surveillance 2018*. http://dx.doi.org/10.15620/cdc.79370 (accessed February 1, 2023).

Centers for Medicare and Medicaid Services. 2023. "Clinical Laboratory Fee Schedule, File no. 23CLABQ1." https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/Clinical-Laboratory-Fee-Schedule-Files (accessed March 10, 2023).

Chou, E. H., S. Mann, T. C. Hsu, W. T. Hsu, C. C. Liu, T. Bhakta, D. M. Hassani, and C. C. Lee. 2020. Incidence, trends, and outcomes of infection sites among hospitalizations of sepsis: A nationwide study. *PloS ONE* 15(1):e0227752. https://doi.org/10.1371/journal.pone.0227752

Dhingra, S., N. A. A. Rahman, E. Peile, M. Rahman, M. Sartelli, M. A. Hassali, T. Islam, S. Islam, and M. Haque. 2020. Microbial Resistance Movements: An Overview of Global Public Health Threats Posed by Antimicrobial Resistance, and How Best to Counter. *Frontiers in Public Health* 8:535668. https://doi.org/10.3389/fpubh.2020.535668.

Evans, N. G., K. Hills, and A. C. Levine. 2020. How Should the WHO Guide Access and Benefit Sharing During Infectious Disease Outbreaks?. *AMA Journal of Ethics* 22(1):E28–E35. https://doi.org/10.1001/amajethics.2020.28

FDA (U.S. Food and Drug Administration). 2022. *FDA Roundup: October 7, 2022*. https://www.fda.gov/news-events/press-announcements/fda-roundup-october-7-2022 (accessed January 26, 2023).

Fidler, D. P. 2008. Influenza Virus Samples, International Law, and Global Health Diplomacy. *Emerging Infectious Diseases* 14(1):88–94. https://doi.org/10.3201/eid1401.070700.

Fleming, K. A., S. Horton, M. L. Wilson, R. Atun, K. DeStigter, J. Flanigan, S. Sayed, P. Adam, B. Aguilar, S. Andronikou, C. Boehme, W. Cherniak, A. N. Cheung, B. Dahn, L. Donoso-Bach, T. Douglas, P. Garcia, S. Hussain, H. S. Iyer, M. Kohli, A. B. Labrique, L. M. Looi, J. G. Meara, J. Nkengasong, M. Pai, K. L. Pool, K. Ramaiya, L. Schroeder, D. Shah, R. Sullivan, B. S. Tan, and K. Walia. 2021. The Lancet Commission on diagnostics: transforming access to diagnostics. *Lancet* 398(10315):1997–2050. https://doi.org/10.1016/S0140-6736(21)00673-5.

Gandhi, T. K., A. Kachalia, E. J. Thomas, A. L. Puopolo, C. Yoon, C., T. A. Brennan, and D. M. Studdert. 2006. Missed and Delayed Diagnoses in the Ambulatory Setting: A Study of Closed Malpractice Claims. *Annals of Internal Medicine* 145(7):488–496. https://doi.org/10.7326/0003-4819-145-7-200610030-00006.

GISAID (Global Initiative on Sharing Avian Influenza Data). 2023. *GISAID*. https://gisaid.org/ (accessed January 26, 2023).

Gotham, D., L. McKenna, S. Deborggraeve, S. Madoori, and D. Branigan. 2021. Public investments in the development of GeneXpert molecular diagnostic technology. *PloS ONE* 16(8):e0256883. https://doi.org/10.1371/journal.pone.0256883.

Havers, F., S. Thaker, J. R. Clippard, M. Jackson, H. Q. McLean, M. Gaglani, A. S. Monto, R. K. Zimmerman, L. Jackson, J. G. Petrie, M. P. Nowalk, K. K. Moehling, B. Flannery, M. G. Thompson, and A. M. Fry. 2014. Use of Influenza Antiviral Agents by Ambulatory Care Clinicians During the 2012-2013 Influenza Season. *Clinical Infectious Diseases* 59(6):774–782. https://doi.org/10.1093/cid/ciu422.

Health Council of the Netherlands. 2007. *MRSA policy in the Netherlands*. The Hague: Health Council of the Netherlands. https://www.healthcouncil.nl/documents/advisory-reports/2006/10/16/mrsa-policy-in-the-netherlands (accessed January 22, 2023).

Hunt, J. M., G. D. Roberts, L. Stockman, T. A. Felmlee, and D. H. Persing. 1994. Detection of a genetic locus encoding resistance to rifampin in mycobacterial cultures and in clinical specimens. *Diagnostic Microbiology and Infectious Disease* 18(4):219–227. https://doi.org/10.1016/0732-8893(94)90024-8.

IOM (Institute of Medicine). 2010. *Antibiotic Resistance: Implications for Global Health and Novel Intervention Strategies: Workshop Summary*. Washington, DC: The National Academies Press. https://doi.org/10.17226/12925.

Jin, S., J. Y. Lee, J. Y. Park, and M. J. Jeon. 2020. Xpert Carba-R assay for detection of carbapenemase-producing organisms in patients admitted to emergency rooms. *Medicine* 99(50):e23410. https://doi.org/10.1097/MD.0000000000023410.

Kenigsberg, B. 2022. "'Salt in My Soul' Review: Living, Even Thriving, With Illness". *New York Times*. https://www.nytimes.com/2022/01/20/movies/salt-in-my-soul-review.html (accessed January 26, 2023).

Land, K. J., D. I. Boeras, X. S. Chen, A. R. Ramsay, and R. W. Peeling. 2019. REASSURED diagnostics to inform disease control strategies, strengthen health systems and improve patient outcomes. *Nature Microbiology* 4(1):46–54. https://doi.org/10.1038/s41564-018-0295-3.

Leslie, H. H., D. Spiegelman, X. Zhou, and M. E. Kruk. 2017. Service readiness of health facilities in Bangladesh, Haiti, Kenya, Malawi, Namibia, Nepal, Rwanda, Senegal, Uganda, and the United Republic of Tanzania. *Bulletin of the World Health Organization* 95(11):738–748. https://doi.org/10.2471/BLT.17.191916.

Lieberman, J. A., C. A. Cannon, and L. A. Bourassa. 2021. Laboratory Perspective on Racial Disparities in Sexually Transmitted Infections. *The Journal of Applied Laboratory Medicine* 6(1):264–273. https://doi.org/10.1093/jalm/jfaa163.

MAAP (Mapping AMR & AMU Partnership). 2022. *Incomplete Antimicrobial Resistance (AMR) Data in Africa: The Crisis Within the Crisis*. https://aslm.org/wp-content/uploads/2022/09/ASLM_MAAP-Policy-Brief_Embargoed-until-15-Sept-6AM-GMT.pdf?x26552 (accessed January 31, 2023).

Marschal, M., J. Bachmaier, I. Autenrieth, P. Oberhettinger, M. Willmann, and S. Peter. 2017. Evaluation of the Accelerate Pheno System for Fast Identification and Antimicrobial Susceptibility Testing from Positive Blood Cultures in Bloodstream Infections Caused by Gram-Negative Pathogens. *Journal of Clinical Microbiology* 55(7):2116–2126. https://doi.org/10.1128/JCM.00181-17.

Messacar, K., S. K. Parker, J. K. Todd, and S. R. Dominguez. 2017. Implementation of Rapid Molecular Infectious Disease Diagnostics: the Role of Diagnostic and Antimicrobial Stewardship. *Journal of Clinical Microbiology* 55(3):715–723. https://doi.org/10.1128/JCM.02264-16.

Miller, M. B., F. Atrzadeh, C. D. Burnham, S. Cavalieri, J. Dunn, S. Jones, C. Mathews, P. McNult, J. Meduri, C. Newhouse, D. Newton, M. Oberholzer, J. Osiecki, D. Pedersen, N. Sweeney, N. Whitfield, and J. Campos. 2019. Clinical Utility of Advanced Microbiology Testing Tools. *Journal of Clinical Microbiology* 57(9):e00495-19. https://doi.org/10.1128/JCM.00495-19.

Molecular Devices. 2022. *COVID-19 Timeline: Diagnostics, Vaccines, and Therapeutic Antibody Development*. https://www.moleculardevices.com/lab-notes/clone-screening/covid-19-timeline-diagnostics-vaccines-antibody-discovery (accessed January 26, 2023).

Mukanga, D., A. B. Tiono, T. Anyorigiya, K. Källander, A. T. Konaté, A. R. Oduro, J. K. Tibenderana, L. Amenga-Etego, S. B. Sirima, S. Cousens, G. Barnish, and F. Pagnoni. 2012. Integrated Community Case Management of Fever in Children under Five Using Rapid Diagnostic Tests and Respiratory Rate Counting: A Multi-Country Cluster Randomized Trial. *The American Journal of Tropical Medicine and Hygiene* 87(5):21–29. https://doi.org/10.4269/ajtmh.2012.11-0816.

NASEM (National Academies of Sciences, Engineering, and Medicine). 2017. *Combating Antimicrobial Resistance: A One Health Approach to a Global Threat: Proceedings of a Workshop*. Washington, DC: The National Academies Press. https://doi.org/10.17226/24914.

NASEM. 2022. *Combating Antimicrobial Resistance and Protecting the Miracle of Modern Medicine*. Washington, DC: The National Academies Press. https://doi.org/10.17226/26350.

NRC (National Research Council). 2014. *Technological Challenges in Antibiotic Discovery and Development: A Workshop Summary*. Washington, DC: The National Academies Press. https://doi.org/10.17226/18616.

NIH (National Institutes of Health). 2020. *Rapid diagnostic for gonorrhea wins $19 million federal prize competition to combat antibiotic resistance*. https://www.nih.gov/news-events/news-releases/rapid-diagnostic-gonorrhea-wins-19-million-federal-prize-competition-combat-antibiotic-resistance (accessed January 27, 2023).

Novosad, S. A., M. R. Sapiano, C. Grigg, J. Lake, M. Robyn, G. Dumyati, C. Felsen, D. Blog, E. Dufort, S. Zansky, K. Wiedeman, L. Avery, R. B. Dantes, J. A. Jernigan, S. S. Magill, A. Fiore, and L. Epstein. 2016. Vital Signs: Epidemiology of Sepsis: Prevalence of Health Care Factors and Opportunities for Prevention. *Morbidity and Mortality Weekly Report* 65(33):864–869. https://doi.org/10.15585/mmwr.mm6533e1.

OECD (Organization for Economic Co-operation and Development). 2018. *Stemming the Superbug Tide: Just A Few Dollars More*. OECD Publishing, Paris. https://doi.org/10.1787/9789264307599-en.

O'Neill, J. 2016. *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*. Government of the United Kingdom. https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf (accessed January 31, 2023).

PACCARB (Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria). 2017. *Recommendations for Incentivizing the Development of Vaccines, Diagnostics, and Therapeutics to Combat Antibiotic-Resistance*. https://www.hhs.gov/sites/default/files/paccarb-final-incentives-report-sept-2017.pdf (accessed January 24, 2023).

Ramanan, P., A. L. Bryson, M. J. Binnicker, B. S. Pritt, and R. Patel. 2017. Syndromic Panel-Based Testing in Clinical Microbiology. *Clinical Microbiology Reviews* 31(1):e00024-17. https://doi.org/10.1128/CMR.00024-17.

Rohr, U. P., C. Binder, T. Dieterle, F. Giusti, C. G. Messina, E. Toerien, H. Moch, and H. H. Schäfer. 2016. The Value of In Vitro Diagnostic Testing in Medical Practice: A Status Report. *PloS ONE* 11(3):e0149856. https://doi.org/10.1371/journal.pone.0149856.

Schwaber, M. J., and Y. Carmeli. 2014. An Ongoing National Intervention to Contain the Spread of Carbapenem-Resistant Enterobacteriaceae. *Clinical Infectious Diseases* 58(5):697–703. https://doi.org/10.1093/cid/cit795.

Selgelid, M. J. 2007. Ethics and drug resistance. *Bioethics* 21(4):218–229. https://doi.org/10.1111/j.1467-8519.2006.00542.x.

Simner, P. J., C. A. Rauch, I. W. Martin, K. V. Sullivan, D. Rhoads, R. Rolf, R. She, R. J. Souers, C. Wojewoda, and R. M. Humphries. 2022. Raising the Bar: Improving Antimicrobial Resistance Detection by Clinical Laboratories by Ensuring Use of Current Breakpoints. *Open Forum Infectious Diseases* 9(3):ofac007. https://doi.org/10.1093/ofid/ofac007.

Smith, M. *Salt in My Soul: An Unfinished Life*. New York: Random House, 2019.

VA (U.S. Department of Veterans Affairs). 2007. *VA National Campaign Takes Aim at Resistant Staph Infections*. https://www.va.gov/opa/pressrel/pressrelease.cfm?id=1396 (accessed January 25, 2023).

Ventola, C. L. 2015. The Antibiotic Resistance Crisis: Part 1: Causes and Threats. *Pharmacy and Therapeutics* 40(4):277–283.

WHO (World Health Organization). 2016. *Diagnostic stewardship: A guide to implementation in antimicrobial resistance surveillance sites*. https://apps.who.int/iris/bitstream/handle/10665/251553/WHO-DGO-AMR-2016.3-eng.pdf (accessed January 23, 2023).

WHO. 2019. *New report calls for urgent action to avert antimicrobial resistance crisis*. https://www.who.int/news/item/29-04-2019-new-report-calls-for-urgent-action-to-avert-antimicrobial-resistance-crisis (accessed January 19, 2023).

WHO. 2021. *Antimicrobial resistance*. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance (accessed January 19, 2023).

WHO. 2022a. *Lack of innovation set to undermine antibiotic performance and health gains*. https://www.who.int/news/item/22-06-2022-22-06-2022-lack-of-innovation-set-to-undermine-antibiotic-performance-and-health-gains (accessed January 19, 2023).

WHO. 2022b. *A new understanding of pandemic and epidemic risks*. https://pandemichub.who.int/ (accessed January 25, 2023).

World Bank. 2017. *Drug-Resistant Infections: A Threat to Our Economic Future*. Washington, DC: World Bank.

Yu, K. C., V. Gupta, H. Kabler, J. A. Watts, and A. Amiche. 2022. A multicenter analysis of inpatient antibiotic use during the 2015-2019 influenza seasons in the United States: Untapped opportunities for antimicrobial stewardship. *Antimicrobial Stewardship & Healthcare epidemiology* 2(1):e140. https://doi.org/10.1017/ash.2022.265.

Appendix A:

Workshop Agenda

DAY 1: THURSDAY, OCTOBER 13, 2022

8:30 am **Welcome and Opening Remarks**
Kent E. Kester, *Workshop Co-chair*
Vice President, Translational Medicine
International AIDS Vaccine Initiative

Betsy Wonderly Trainor, *Workshop Co-chair*
Alliance Director
CARB-X

8:50 am **SESSION I – Defining the Need for Rapid Diagnostics: Where do we go from here?**

Session Objectives:

- Examine the current state of rapid diagnostic development, including examples of successes and limitations of current approaches;
- Consider gaps that rapid diagnostics may be best-suited to address (e.g. tools to support targeted treatment decisions in the healthcare setting, tools to enable real-time surveillance based on routine hospital data);
- Discuss what "success" might look like in future.

8:50 am **Fireside Chat**
Karen C. Carroll, *Keynote Speaker*
Director, Division Medical Microbiology & Professor of Pathology
Johns Hopkins University School of Medicine

9:20 am **Panel Discussion**
Karen C. Carroll, *Moderator*
Johns Hopkins University School of Medicine

Patient Perspective
Bradley Burnam
Founder & AMR Survivor
Turn Therapeutics

Developer Perspective
Craig Whiteford
Senior Director R&D
Becton Dickinson

Bioethics Perspective
Tracey L. Cohen
Distinguished Visiting Scholar
Institute for Bioethics & Health Policy, University of Miami Miller School of Medicine

Reimbursement Perspective
Susan Van Meter
President
American Clinical Laboratory Association

10:00 am **Q&A/Audience Discussion**

10:30 am **Coffee Break (30 minutes)**

11:00 am **SESSION II – Challenges in Development and Use of Rapid Diagnostics in Healthcare Settings**

Session Objectives:
- Consider the unique challenges for the development of rapid point-of-care diagnostics to address antibiotic resistance;
- Discuss lessons learned from other diseases, including COVID-19, for rapid diagnostics development and use; and

- Consider generalizable applications and practical approaches to overcome barriers to the development and use/uptake of rapid diagnostics for drug-resistant bacterial infections.

11:00 am **Presentation 1**
Lessons Learned from COVID-19 in the U.S. that are Applicable to AMR
Joseph Lutgring
Medical Officer, Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

11:15 am **Presentation 2**
Lessons Learned from Abroad through the WHO's Access to COVID-19 Tools Accelerator Program
William "Bill" Rodriguez
Chief Executive Officer
FIND, the Global Alliance for Diagnostics

11:30 am **Presentation 3**
Lessons Learned from Programs focused on Accelerating the Development of Rapid Dx's To Date
Paul Eder
Senior Scientific Officer
Concept Acceleration Program – Diagnostics
National Institute of Allergy and Infectious Disease

11:45 am **Panel Discussion (30 mins)**
Paul Eder, *Moderator*
National Institute of Allergy and Infectious Disease

Clinician Perspective
Alex Greninger
Assistant Professor and Assistant Director of the Clinical Virology Laboratories
University of Washington Medical Center

Regulatory Perspective
Kristian Roth
Deputy Director
Division of Microbiology Devices, FDA

Industry/Economic Perspective
David Persing
Head of R+D
Cepheid

12:15 pm **Q&A/Audience Discussion**

1:00 pm **Lunch Break (1 hour)**

2:00 pm **SESSION III – Incentives at the Intersection of Diagnostics and Drug Development**

Session Objectives:

- Consider common incentives/disincentives for the development of rapid diagnostics and new antibiotics; and
- Discuss innovative ways to foster innovation at the intersection of complementary diagnostics and drug development.

2:00 pm **Setting the Stage**
John Billington
Head of Commercial Pipeline & Health Security, Policy & Advocacy
GSK

2:10 pm **Panel Discussion**
A Case Study: Partnership Between bioMerieux and Entasis Therapeutics
John Billington, *Moderator*
GSK

Developer Perspective
Valérie Raymond-Schwartzmann
Companion Diagnostics Senior Program Director
bioMerieux

Therapeutics Perspective
Alita Miller
Chief Scientific Officer
Entasis Therapeutics

Biotechnology Perspective
Gregory Frank
Director, Global Public Policy
Merck

HHS Perspective
Kim Sciarretta
DRIVe Launch Office Branch Chief
Biomedical Advanced Research and Development Authority (BARDA)

2:50 pm **Audience Q&A**

3:00 pm **Coffee Break (30 mins)**

3:30 pm **SESSION IV – Policy Levers: A Menu of Options**

Session objectives:
- Lay out a "menu" of policy options for incentivizing the development and use of rapid diagnostics.

3:30 pm **Panel Discussion**
Mark McClellan, *Moderator*
Duke Margolis Center for Health Policy

Industry Perspective
Phyllis Arthur
Vice President, Infectious Diseases & Emerging Science Policy
BIO

PACCARB Research Perspective
Sarah McClelland
Health Policy Analyst
U.S. Department of Health and Human Services

Analyst Perspective
Jaclyn Levy
Director, U.S. Policy
AMR Action Fund

Law & Economics Perspective
Kevin Outterson
Professor of Law, Boston University
Executive Director, CARB-X

4:30 pm **Q&A/Audience Discussion**

5:00 pm **ADJOURN WORKSHOP DAY 1**

DAY 2: FRIDAY, OCTOBER 14, 2022

8:30 am **SESSION V – Health Equity Considerations for Diagnostic Development and Use**

Session Objectives:

- Consider the health equity implications for the development and use of rapid point-of-care diagnostics in health care settings; and
- Discuss practical approaches for incorporating diversity, equity, inclusivity, and access into push and pull incentives for spurring diagnostic development.

Diane Shader Smith, *Keynote speaker*
Mother of the Late Mallory Smith
AMR Advocate
Salt in My Soul Co-author/Producer

9:00 am **Roundtable Discussion**
Amanda Jezek, *Moderator*
Infectious Diseases Society of America

Bioethics Perspective
Nicholas Evans
Chair, Associate Professor
University of Massachusetts, Lowell

Research Perspective
Daniel Bausch
Director of Emerging Threats & Global Health Security
FIND, The Global Alliance for Diagnostics

Public Health Perspective
Melinda Pettigrew
Anna M. R. Lauder Professor of Epidemiology and Interim Dean
Yale School of Public Health

Access and Innovation Perspective
Anthony So
Professor of the Practice; Director, Innovation+Design Enabling Access (IDEA) Initiative
Johns Hopkins Bloomberg School of Public Health

10:00 am **Discussion**

10:30 am **Coffee Break (30 minutes)**

11:00 am **SESSION VI – Integrating Rapid Diagnostics and Antibiotic Stewardship**

Session Objectives:

- Discuss practical and actionable policy options to integrate rapid point-of-care diagnostics and antibiotic stewardship in healthcare settings;
- Consider the role of reimbursement, incentives, and guideline development for rapid point-of-care diagnostics in healthcare settings.

11:00 am **Panel Discussion**
Robin Patel, *Moderator*
Mayo Clinic

Stewardship Program Perspective
Ritu Banerjee
Medical Director, Pediatric Antimicrobial Stewardship Program
Vanderbilt University

Lab Clinician Perspective
Carey-Ann Burnham
Chief Clinical Officer
Pattern Bioscience

Industry/Developer Perspective
Diane Flayhart
Global Program Leader
Becton, Dickinson and Company

11:30 am **Q&A/Audience Discussion**

12:00 pm **SESSION VII – A Path Forward**

Session Objectives:

- Based on a menu of policy options, consider practical and actionable next steps that would be most impactful for spurring the development and use of rapid diagnostics in healthcare settings; and
- Discuss practical short- and long-term opportunities for specific stakeholders to take action.

12:00 pm **Roundtable Discussion**
Betsy Wonderly Trainor, *Moderator*
CARB-X

Dx Developer/Public Health Equity Perspective
Jean Patel
Principal Scientific Affairs, Microbiology
Beckman Coulter Diagnostics

Pharma Perspective
Joseph Larsen
Vice President, Clinical Development
Locus Biosciences, Inc.

Clinician Perspective
Robin Patel
ID Physician, Laboratory Director
Mayo Clinic

Regulatory/Policy Perspective
Ribhi Shawar
Branch Chief, Division of Microbiology Devices, Office of In Vitro Diagnostic and Radiological Health
Center for Devices and Radiological Health, FDA

Health Equity Perspective
Susan Van Meter
President
American Clinical Laboratory Association

12:50 pm **Wrap Up Discussion and Closing Remarks**
Kent E. Kester, *Workshop Co-chair*
Vice President, Translational Medicine
International AIDS Vaccine Initiative

Betsy Wonderly Trainor, *Workshop Co-chair*
Alliance Director
CARB-X

1:00 pm **ADJOURN DAY 2**

Appendix B

Biographical Sketches of the Workshop Planning Committee and Speakers

PLANNING COMMITTEE BIOSKETCHES

Kent Kester, M.D. *(co-chair),* is currently Vice President, Translational Medicine, at IAVI. He was previously Vice President and Head, Translational Science and Biomarkers at Sanofi Pasteur, the vaccine business unit of the Sanofi Group. Prior to this, in the context of a 24-year career in the U.S. Army, he worked extensively in clinical vaccine development and led multiple research platforms at the Walter Reed Army Institute of Research, the U.S. Department of Defense's largest and most diverse biomedical research laboratory—an institution he later led as its Commander. His final military assignment was as the Associate Dean for Clinical Research in the School of Medicine at the Uniformed Services University of the Health Sciences (USUHS). During his military service, Dr. Kester was appointed as the lead policy advisor to the U.S. Army Surgeon General in both Infectious Diseases and in Medical Research & Development. In these capacities, he worked extensively in the interagency environment and developed a variety of Army and DoD medical policies related to infectious diseases.

Dr. Kester holds an undergraduate degree from Bucknell University and an M.D. from the Sidney Kimmel Medical College, Thomas Jefferson University, completing his internship and residency in internal medicine at the University of Maryland and a research fellowship in infectious diseases at the Walter Reed Army Medical Center. Currently a member of the U.S. Government Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB), the Department of Veterans Affairs Health Services Research & Development Service Merit Review

Board, the National Academy Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats, and the CEPI Scientific Advisory Committee, he previously chaired the Steering Committee of the NIAID/USUHS Infectious Disease Clinical Research Program, and has served as a member of the FDA Vaccines & Related Biologics Products Advisory Committee (VRBPAC), the NIAID Advisory Council, and the CDC Office of Infectious Diseases Board of Scientific Counselors. He is a Vice Chair of the National Academy of Medicine Forum on Microbial Threats. Board-certified in both internal medicine and infectious diseases, Dr. Kester holds faculty appointments at USUHS and the University of Maryland; and is a fellow of the American College of Physicians, the Royal College of Physicians of Edinburgh, the Infectious Disease Society of America, and the American Society of Tropical Medicine and Hygiene, where he also serves as the Society's Secretary-Treasurer. He is a member of the clinical faculty at the University of Maryland Shock Trauma Center in Baltimore and the Wilkes-Barre VA Medical Center in Wilkes-Barre, PA.

Betsy Wonderly Trainor *(co-chair)* brings over a decade of experience in the diagnostics industry, focused mainly on the validation and implementation of infectious disease diagnostics. Trainor has a background in clinical and behavioral research that started during her undergraduate studies at Cornell University. Her work initially focused on HIV in Africa and then on infectious diseases, globally, including HCV, TB, and Ebola. In addition to leading diagnostic validation studies, she has led the commercialization of diagnostic product lines and a variety of global partnerships on behalf of both private and public entities. She has supported the development of global guidelines and negotiated deals with large donor organizations as well as private entities. Trainor has recently led business development efforts at multiple innovative diagnostic companies, including Daktari Diagnostics and Aldatu Biosciences, in addition to leading product validation and implementation efforts at the Foundation for Innovative New Diagnostics (FIND) and the World Health Organization (WHO). She is looking forward to putting her experience to good use in supporting the CARB-X mission.

John Billington, J.D., M.P.H., is Head of Commercial Pipeline and Health Security Policy and Advocacy in the global corporate government affairs department of GSK. In this role, he is responsible for the company's policy and advocacy strategy for the commercial pipeline at the enterprise level, including a focus on pandemic preparedness and antimicrobial resistance (AMR). Prior to this role, Billington was director of science policy for the global vaccines business and director of U.S. vaccines policy before that. Before joining GSK, he was director of health policy at the Infectious

Diseases Society of America (IDSA). At IDSA, Billington served as lead subject matter expert on vaccines, antibiotics, and medical countermeasures policy. He also launched and coordinated the U.S. Stakeholder Forum on Antimicrobial Resistance (S-FAR), a national stakeholder partnership to advance U.S. and global policies and practices in response to AMR. Earlier in his career, John was a manager in the health reform practice at Avalere Health, a health policy advisory firm. He was also a legislative fellow for health policy in the office of U.S. Senator Sherrod Brown of Ohio. He received his Juris Doctor and Master of Public Health degree from the Ohio State University in Columbus, Ohio. He received his undergraduate degree from Colgate University in Hamilton, New York.

Carey-Ann Burnham, Ph.D., D(ABMM), FIDSA, F(AMM), is currently Chief Clinical Officer, Pattern Bioscience, and Professor of Pathology & Immunology, Washington University in St. Louis School of Medicine. She was previously Professor of Pathology & Immunology, Pediatrics, Molecular Microbiology, and Medicine at Washington University in St. Louis School of Medicine and Vice Chair for Faculty Mentoring & Advancement in Pathology & Immunology. In addition, for 11 years she served as Medical Director of the system clinical microbiology laboratory at Barnes-Jewish Hospital in St. Louis and the program director for the Medical and Public Health Microbiology Fellowship at Washington University. At Washington University, her research program focused on the development of new diagnostics for infectious diseases, antimicrobial resistance, and transmission and epidemiology of antimicrobial resistant microorganisms. Burnham is actively involved in several editorial roles, including serving as an editor for the *Journal of Clinical Microbiology*, *Clinical Microbiology Newsletter*, and *Clinical Microbiology Procedures Handbook, 5th ed*. Burnham has held leadership roles in professional societies, including the American Society for Microbiology, Clinical and Laboratory Standards Institute, the American Academy of Microbiology, and the Academy of Clinical Laboratory Physicians and Scientists. In 2020, Burnham received the prestigious American Society for Microbiology Award for Research and Leadership in Microbiology, and Burnham has published more than 200 articles in the area of diagnostic and clinical microbiology.

Paul Eder, Ph.D., is a Senior Scientific Officer and leads the Concept Acceleration Program for Diagnostics in the Division of Microbiology and Infectious Diseases (DMID) at NIAID. Previously he served for eight years as a Senior Medical Diagnostics Advisor at the Biomedical Advanced Research and Development Authority (BARDA) inside the U.S. DHHS. For seven years prior he served as the Director of Assay Development at Qiagen, where he used a Bill and Melinda Gates Foundation grant to create the

first WHO pre-qualified HPV screening test for utility in resource-limited communities worldwide. He completed postdoctoral fellowships in nuclear tRNA transport at the Howard Hughes Medical Institute at the University of Pennsylvania and in catalytic RNA with Nobel laureate Sidney Altman at the Department of Biology at Yale University. His Ph.D. is in biochemistry from the University of Iowa.

Deborah Hung, M.D., works at the interface of chemical biology, genomics, and bacterial pathogenesis to establish new paradigms for an antibiotic based on the essential biology required for a pathogen to cause disease within the host. Using her training as a synthetic chemist, bacterial geneticist, and clinical physician, she explores approaches to disrupting the pathogen-host interaction. Dr. Hung is a physician-scientist at the Broad Institute of MIT and Harvard, the Department of Molecular Biology at the Massachusetts General Hospital, and the Department of Genetics at Harvard Medical School, and is the Co-Director of the Infectious Disease and Microbiome Program at the Broad Institute. She is an attending physician at the Brigham and Women's Hospital in Boston in infectious diseases and critical care medicine.

Amanda Jezek is currently the Senior Vice President for Public Policy and Government Relations at the Infectious Diseases Society of America (IDSA), which represents more than 12,000 ID physicians and scientists. Amanda oversees IDSA's public policy and government relations department, with responsibility for policy development and advocacy on IDSA priority issues, including antimicrobial resistance, the infectious diseases workforce, pandemic preparedness and response, immunizations, federal funding, and other issues relating to public health and biomedical research. Jezek has been with IDSA since 2011, previously serving as IDSA's Government Relations Director. Prior to joining IDSA, she was the Deputy Director for Federal Affairs at the March of Dimes Foundation. In this capacity, Jezek led the March of Dimes' policy development and lobbying efforts on all issues related to access to healthcare for women of childbearing age, infants, and children, including the Foundation's work on the Affordable Care Act. She also lobbied for Mental Health America and worked as a legislative assistant and press secretary for U.S. Representative Grace Napolitano (D-CA). Jezek holds a B.A. in Political Science from Dartmouth College.

Robin Patel, M.D.(CM), D(ABMM), FIDSA, FACP, F(AAM), graduated from Princeton University with a B.A. in Chemistry and graduated from McGill University with an M.D. She completed a residency in Internal Medicine and fellowships in Infectious Diseases and Microbiology at Mayo Clinic. She is the Elizabeth P. and Robert E. Allen Professor of Individualized

Medicine, Professor of Medicine, Professor of Microbiology, Director of the Infectious Diseases Research Laboratory, and Co-Director of the Clinical Bacteriology Laboratory at Mayo Clinic. Dr. Patel is a Fellow of American Academy of Microbiology, Past President of the American Society for Microbiology, a past associate editor for Clinical Infectious Diseases, and course director for the Mayo Clinic Alix School of Medicine microbiology. She is also the Laboratory Center Director for the NIH's Antibacterial Resistance Leadership Group. Her research focuses on clinical bacteriology diagnostic testing, antimicrobial resistance, and microbial biofilms.

Ribhi Shawar, Ph.D., currently serves as the branch chief at the Division of Microbiology in the Office of In vitro Diagnostic and Radiological Health (OIR) at the Center for Devices and Radiological Health (CDRH) at the FDA where he specializes in the area of antimicrobial susceptibility testing and detection of resistance. Dr. Shawar has a Ph.D. in Medical Microbiology and an M.Sc. in Medical Parasitology. He is a certified diplomate by the American Board of Medical Microbiology (ABMM) for 25 years and was recently elected as a Fellow of the American Academy of Microbiology (F-AAM). Dr. Shawar is a recognized clinical microbiologist with diverse experience in hospital settings, diagnostic and pharmaceutical microbiology, and anti-infective drug development with strong knowledge in regulatory aspects, both in antimicrobial drug products and infectious disease diagnostics. Dr. Shawar has authored multiple publications in peer reviewed journals, served or currently serves as advisor to several CLSI Sub-committees and is the recipient of multiple awards including GSK Gold Award and most recently the FDA's Outstanding Service Award for his pioneering role in the creation of the FDA-CDC AR Isolate Bank. He served for two terms as Chair of the ABMM Standards and Examinations Committee (Parasitology) and as member of the editorial board of the Journal of Clinical Microbiology. Prior to joining FDA, Dr. Shawar served in multiple roles at various institutions including Baylor College of Medicine, VA Medical Center in Houston, PathoGenesis Corporation, Chiron (Novartis) in Seattle, and GlaxoSmithKline in Philadelphia.

Susan Van Meter was named ACLA President in March 2022. She previously served as Executive Director of AdvaMedDx where she directed the policy, advocacy, communications, regulatory, payment and legislative strategy and operations of the association, which represents manufacturers of in vitro diagnostic (IVD) clinical tests in the U.S. and abroad. In this role, she also developed the association's robust response to the COVID-19 pandemic and ongoing advocacy efforts. Prior to her role at AdvaMedDx, Van Meter served as the Senior Vice President of Federal Relations at the Healthcare Association of New York State (HANYS), where she was

responsible for developing their priorities and strategies to further the interests of their hospital and health system members. She also previously worked in the Centers for Medicare & Medicaid Services' (CMS) Office of Legislation. Van Meter holds undergraduate and graduate degrees from Villanova University and Boston University, respectively.

SPEAKER BIOSKETCHES

Phyllis Arthur is Vice President for Infectious Diseases and Emerging Science Policy at the Biotechnology Innovation Organization (BIO). In this role Ms. Arthur is responsible for working with member companies in vaccines, antimicrobial resistance, molecular diagnostics and biodefense on policy, legislative, and regulatory issues. Ms. Arthur joined BIO in July 2009 as the Director of Healthcare Regulatory Affairs. Prior to joining BIO, she worked in numerous marketing and sales positions for Merck & Co. Inc. in their Vaccine Division. Over her 16-year career at Merck, Ms. Arthur launched several exciting new vaccines in the United States and internationally, including the first HPV vaccine, GARDASIL. During her years in Marketing, she worked closely with clinical and academic thought leaders in infectious diseases, oncology, and public health. In addition, Ms. Arthur also led a large vaccine sales organization of more than 75 representatives and managers covering 14 states. Before graduate school, Ms. Arthur worked as a research assistant for two economists at the Brookings Institution in Washington, DC. There she conducted economic analyses related to savings and investment policies for the OECD countries. Ms. Arthur received her B.A. in 1987 in Economics and International Politics from Goucher College and her M.B.A. in 1991 from the Wharton School of Business at the University of Pennsylvania.

Ritu Banerjee, M.D., Ph.D., is professor in the Division of Pediatric Infectious Diseases at Vanderbilt University Medical Center. She is the Director of the Antimicrobial Stewardship Program and Director of Clinical Services for Pediatric Infectious Diseases at Vanderbilt's Children's Hospital. She received her M.D. and Ph.D. degrees from Washington University in St. Louis and then completed Pediatrics residency and Pediatric Infectious Disease fellowship at the University of California, San Francisco. She is a member of many national committees through the Pediatric Infectious Diseases Society, the American Academy of Pediatrics, the Infectious Diseases Society of America, and the Antibacterial Resistance Leadership Group. Dr. Banerjee conducts federally funded clinical research about antibiotic stewardship and implementation and outcomes of rapid diagnostics for infectious diseases.

DANIEL BAUSCH, M.D., MPH&TM, FASTMH, is the Senior Director of Emerging Threats and Global Health Security at FIND, the global alliance for diagnostics (www.FINDdx.org), in Geneva, Switzerland, leading FIND's efforts on pandemic preparedness and response. He is trained in internal medicine, infectious diseases, tropical medicine, and public health. Dr. Bausch specializes in the research and control of emerging tropical viruses, with more than 25 years' experience in sub-Saharan Africa, Latin America, and Asia combating viruses such as Ebola, Lassa, hantavirus, and SARS coronaviruses. Previously, he served as Director of the United Kingdom's Public Health Rapid Support team (2017-2021), a joint effort by Public Health England and the London School of Hygiene & Tropical Medicine to respond and conduct research to prevent and control outbreaks of dangerous infectious diseases around the world. He has also held posts at the World Health Organization in Geneva, Switzerland; U.S. Naval Medical Research Unit No. 6 in Lima, Peru; Tulane School of Public Health and Tropical Medicine in New Orleans, USA; and the U.S. Centers for Disease Control and Prevention in Atlanta, USA. In addition to his role at FIND, Dr. Bausch holds an appointment as a Professor of Tropical Medicine at the London School of Hygiene and Tropical Medicine and is the current President of the American Society of Tropical Medicine and Hygiene (www.ASTMH.org). He places a strong emphasis on capacity development in all his projects and has a keen interest in the role of the scientist in promoting health and human rights. Dr. Bausch is fluent in English, French, and Spanish.

JOHN BILLINGTON, J.D., M.P.H., is Head of Commercial Pipeline and Health Security Policy and Advocacy in the global corporate government affairs department of GSK. In this role, he is responsible for the company's policy and advocacy strategy for infectious diseases at the enterprise level, with a focus on pandemic preparedness and antimicrobial resistance (AMR). Prior to this role, Billington was director of science policy for the global vaccines business and director for U.S. vaccines policy before that. Before joining GSK, he was director of health policy at the Infectious Diseases Society of America (IDSA). At IDSA, he served as lead subject matter expert on vaccines, antibiotics, and medical countermeasures policy. He also launched and coordinated the U.S. Stakeholder Forum on Antimicrobial Resistance (S-FAR), a national stakeholder partnership to advance U.S. and global policies and practices in response to AMR. Earlier in his career, Billington was a manager in the health reform practice at Avalere Health, a health policy advisory firm. He was also a legislative fellow for health policy in the office of U.S. Senator Sherrod Brown of Ohio. Billington received his Juris Doctor and Master of Public Health degree from the Ohio State University in Columbus, Ohio. He received his undergraduate degree from Colgate University in Hamilton, New York.

Bradley Burnam is Founder and CEO of Turn Therapeutics, a biotechnology company addressing critical patient needs across advanced wound care, infectious disease, and dermatology. In an attempt to treat his own recurring, antibiotic-resistant skin infection, Burnam developed the first patented method for permanently and stably fusing polar, water-soluble ingredients in petrolatum without an emulsifier. This process, known commercially as PermaFusion®, enabled Burnam to stably suspend broad-spectrum, liquid antimicrobials into a petrolatum carrier. The initial commercial embodiment, which became Turn's first FDA cleared product, is a non-cytotoxic, petrolatum-based, broad-spectrum antimicrobial ointment with the physical consistency/safety profile of OTC topical antibiotics. PermaFusion® has since enabled Burnam to create Turn's growing product portfolio and therapeutic pipeline, including multiple FDA cleared advanced wound products and a lead therapeutic, non-antibiotic topical candidate intended to be indicated for the treatment of antibiotic resistant skin infections. Burnam is a self-taught regulatory and formulation expert who singlehandedly facilitated Turn's first three FDA clearances. He is a regular guest lecturer at UCLA and was a keynote speaker at the 2019 UCLA commencement. He holds a bachelor's degree from UCLA and a master's degree from Stanford University.

Karen Carroll, M.D., is professor of pathology at the Johns Hopkins University School of Medicine. Her areas of clinical expertise include Medical Microbiology and Infectious Diseases. Dr. Carroll serves as the Director of the Division of Medical Microbiology and the Director of the ACGME-accredited fellowship program in medical microbiology in the Department of Pathology.

Dr. Carroll earned her M.D. from the University of Maryland School of Medicine. She completed her residency at the University of Rochester Medical Center, performed a fellowship in medical microbiology at the University of Utah, and performed another fellowship in infectious disease at the University of Massachusetts Medical School.

Her research interests include the evaluation of novel diagnostic platforms, diagnosis of bloodstream infections/sepsis, and the diagnosis and epidemiology of healthcare-associated infections, such as MRSA and *Clostridium difficile*. More recently Dr. Carroll has collaborated with researchers on novel rapid microfluidics platforms and next generation sequencing technologies for detection of a variety of pathogens. She has participated in programs to foster appropriate test utilization and diagnostic stewardship.

Tracey L. Cohen is a Distinguished Visiting Scholar at the University of Miami Miller School of Medicine Institute for Bioethics & Health Policy.

As a healthcare attorney, Ms. Cohen has represented national and Florida healthcare systems in regulatory compliance, peer-review, transactional and litigation matters. Ms. Cohen also has practiced as an intellectual property attorney, overseeing the intellectual property portfolios of major healthcare institutions, corporations, and individuals.

Ms. Cohen served as an Adjunct Professor of Law at Nova Southeastern University Broad College of Law for six years, where she created curriculum and taught courses in intellectual property law. She is also a legal writer and has published articles for Nolo, a division of Martindale-Hubbell.

Ms. Cohen received her B.A. in Philosophy from Brandeis University and her J.D. from the University of Florida Levin College of Law, where she was the recipient of a Book Award in Legal Research and Writing and sat on the Senior Editorial Board of the *University of Florida Journal of Law and Public Policy*. Ms. Cohen also holds a Master of Science in Bioethics from Columbia University.

Paul Eder, Ph.D., is a Senior Scientific Officer and leads the Concept Acceleration Program for Diagnostics in the Division of Microbiology and Infectious Diseases (DMID) at NIAID. Previously he served for eight years as a Senior Medical Diagnostics Advisor at the Biomedical Advanced Research and Development Authority (BARDA) inside the US DHHS. For seven years prior he served as the Director of Assay Development at Qiagen, where he used a Bill and Melinda Gates Foundation grant to create the first WHO pre-qualified HPV screening test for utility in resource-limited communities worldwide. For that he won the Qiagen Sydney Brenner R&D Award for outstanding accomplishment in global R&D. He completed postdoctoral fellowships in nuclear tRNA transport at the Howard Hughes Medical Institute at the University of Pennsylvania and in catalytic RNA with Nobel laureate Sidney Altman at the Department of Biology at Yale University. His Ph.D. is in biochemistry from the University of Iowa. He holds ten issued patents and has authored 25 publications and reviews.

Nicholas G. Evans, Ph.D., is Associate Professor of Philosophy at the University of Massachusetts Lowell. A 2020-2023 Greenwall Foundation Faculty Scholar, he currently conducts research on the ethics of emerging technologies, with a focus on national security issues. He is best known for his research on "dual-use research" in the life sciences and has recently begun work examining research ethics concerns arising from the performance enhancement of active military personnel, funded by the U.S. Air Force Office of Scientific Research.

In addition to his work on emerging technologies, Evans is a recognized expert in public health ethics, writing on the ethics of social distancing, research ethics during health emergencies, and the use of force in

pandemic response. His 2016 collection, Ebola's Message: Public Health and Medicine in the 21st Century received favorable reviews in *Nature*. In late 2021 he will publish a new, sole-authored work on pandemic preparedness with The MIT Press titled, *War on All Fronts: A Theory of Just Health Security*.

Prior to his appointment at the University of Massachusetts, Evans completed postdoctoral research at the Perelman School of Medicine at the University of Pennsylvania. In 2015, he held an Emerging Leaders in Biosecurity Initiative Fellowship at the UPMC Center for Health Security, Baltimore. He also previously served as a policy officer with the Australian Department of Health and Australian Therapeutic Goods Administration.

Diane Flayhart is the Global Program Leader AMR at the Antimicrobial Resistance Fighter Coalition/BD. She leads efforts for the Antimicrobial Fighter Coalition, a global organization that aspires to change behaviors across the globe that will maintain the effectiveness of antibiotics for future generations. The Coalition seeks to substantially increase awareness of drug-resistant infections and encourage action across a wide range of stakeholders, including policymakers, health agency officials, professional societies, clinicians, patients, and family members. The Coalition is mobilized by BD where Flayhart has served roles of increased responsibility focused on Marketing and Commercial Excellence since 2007. She started her career at Johns Hopkins Medical Institution working as a medical technologist in the Microbiology Laboratory. Flayhart completed her master's degree in Business Administration at the Johns Hopkins University.

Greg Frank, Ph.D., is Director, Global Public Policy with Merck, where he leads Merck's global antimicrobial resistance (AMR) policy. Previously Dr. Frank served as Senior Director, Infectious Disease Policy at the Biotechnology Innovation Organization (BIO), where he led several infectious diseases policy issues, including AMR and vaccine regulatory policy. Prior to BIO, Dr. Frank led science and diagnostics policy as Program Officer for Science and Research Policy at the Infectious Diseases Society of America (IDSA).

Dr. Frank serves on the Leadership Council of the National Institute of Antimicrobial Resistant Research and Education (NIAMRRE) and the expert advisory committee for the Partnership to Fight Infectious Diseases. He is a Board member on the AMR Industry Alliance. Previously, Dr. Frank has served on the U.S. Presidential Advisory Committee on Antibiotic Resistant Bacteria (PACCARB) and joined expert advisory committees of the Access to Medicines Foundation AMR Benchmark, the Global AMR R&D Hub, and the Duke-Margolis Center for Health Policy Antimicrobial Incentives & Payment Reform Project.

Dr. Frank received his doctorate in immunology at the University of Pittsburgh and pursued his postdoctoral training at the Laboratory of Viral Diseases at the National Institute of Allergy & Infectious Diseases.

ALEX GRENINGER, M.D., PH.D., M.S., M.PHIL., is assistant director of the UW Medicine Clinical Virology Laboratory and a UW assistant professor of Laboratory Medicine. Dr. Greninger focuses on genomic and proteomic characterization of a variety of human viruses and bacteria, with a focus on respiratory viruses and human herpesviruses. He has discovered a number of new human and animal viruses. His basic science lab at South Lake Union uses genomically informed approaches to understand human infectious diseases. Dr. Greninger earned his M.D. and Ph.D., from UC San Francisco, his M.S. in Immunology from Stanford, and his M.Phil. in Epidemiology from Cambridge in England. Dr. Greninger has clinical interests in facilitating clinical trial testing for respiratory viruses and human herpesviruses.

JOE LARSEN, PH.D., is Vice President, Clinical Development at Locus Biosciences where he leads development programs for Locus's clinical stage assets. Previously, Dr. Larsen was Vice President, Strategic Portfolio Development at Venatorx Pharmaceuticals, a biotechnology company focused on the development of novel antibiotics. Prior to that, Dr. Larsen spent ten years in the federal government, including serving as Deputy Director of Chemical, Biological, Radiological and Nuclear (CBRN) medical countermeasures at the Biomedical Advanced Research and Development Authority (BARDA), where he oversaw the $2.8B Project Bioshield fund for the late-stage development and procurement of medical countermeasures. Dr. Larsen received his Ph.D. in microbiology and immunology at the Uniformed Services University of the Health Sciences and a B.A. in microbiology from the University of Kansas.

JACLYN LEVY is the Director of U.S. Policy at the AMR Action Fund, where she works to support policy solutions and market reforms related to antimicrobial R&D, pull incentives, stewardship, and access. She joined the Fund from the Infectious Diseases Society of America (IDSA), where she served as Director of Public Policy and advanced a broad portfolio of research, diagnostics, and public health policy issues. Prior to IDSA, Levy worked as a biosecurity analyst for the U.S. Department of Homeland Security and as a scientific editor and consultant. She has over a decade of experience in federal and global policy and advocacy work and has authored numerous publications on pandemic preparedness, antimicrobial resistance, molecular diagnostics, and biomedical R&D. Levy holds an M.S. in Biohazardous Threat Agents & Emerging Infectious Diseases from

Georgetown University and a B.A. from The George Washington University. She was a 2020 Atlantic Council Millennium Fellow.

Joseph Lutgring, M.D., works as a medical officer for the Division of Healthcare Quality Promotion at the Centers for Disease Control and Prevention. He is a graduate of Indiana University School of Medicine. He is board certified in internal medicine, infectious diseases, and medical microbiology. He has interests in diagnostic stewardship, antimicrobial resistance, and working on topics at the intersection of clinical infectious diseases and the microbiology laboratory.

Stanley Martin, MD is a board-certified and fellowship-trained specialist in infectious diseases. His clinical interests include immunocompromised hosts, transplantation, and infections related to mechanical circulatory support. His research interests include antimicrobial stewardship, population health, and optimization of inpatient care. Dr. Martin earned his medical degree from the University of Tennessee. He completed his residency at Mayo Clinic, Rochester, and his fellowship in infectious diseases at Massachusetts General Hospital. Dr. Martin is certified by the American Board of Internal Medicine in infectious diseases. He is Geisinger's director of the Division of Infectious Diseases.

Alita Miller, Ph.D., is the Chief Scientific Officer at Entasis Therapeutics, where she has played a key role in the discovery and development of several novel antibacterial agents, including ETX0462, sulbactam-durlobactam and zoliflodacin. She has more than 20 years of experience in antibacterial research, first at Pfizer, where she led both large and small molecule discovery projects, and then at AstraZeneca, where she was Head of Microbial Genetics and Genomics. Dr. Miller obtained a B.A. in Chemistry from Kalamazoo College and a Ph.D. in Biochemistry & Molecular Biology from the University of Chicago. Her postdoctoral training was in the DiRita lab at the University of Michigan.

Kevin Outterson, J.D., LLM, teaches health care law at Boston University, where he codirects the Health Law Program. He serves as the founding Executive Director and Principal Investigator for CARB-X, an >$800M international public-private partnership to accelerate global antibacterial innovation. Key partners in CARB-X include the US Government (BARDA & NIAID), the Wellcome Trust, the German Federal Ministry of Education and Research (BMBF), the UK Government (GAMRIF), and the Bill & Melinda Gates Foundation. Professor Outterson's research work focuses on the law and economics of antimicrobial resistance, particularly push and pull incentives for antimicrobials. He served as a senior author on many key

research reports on antibiotic innovation, including Chatham House, ERG, DRIVE-AB, and the Lancet Commission. Professor Outterson was given the 2015 Leadership Award by the Alliance for the Prudent Use of Antibiotics for his research and advocacy work. He has testified before Congress, Parliamentary working groups, the WHO, and state legislatures. Since August 2016, he leads CARB-X, the world's most innovative antibiotic accelerator.

Jean Patel, Ph.D., currently serves as the principal scientist, scientific affairs, at Beckman Coulter. Prior to her role at Beckman Coulter, Dr. Patel served as the science team lead, antibiotic resistance coordination and strategy unit, at the Centers for Disease Control (CDC), where she led implementation of its Antibiotic Resistance Laboratory Network and the CDC and FDA Antibiotic Resistance Isolate Bank.

Dr. Patel has served as chair and vice chair of the Clinical and Laboratory Standards Institute Subcommittee for Antimicrobial Susceptibility Testing and works with the World Health Organization (WHO) to develop technical guidance for detecting resistance and strengthening global surveillance of antimicrobial resistance.

Robin Patel, M.D.(CM), D(ABMM), FIDSA, FACP, F(AAM), graduated from Princeton University with a B.A. in Chemistry and from McGill University with an M.D. She completed a residency in Internal Medicine and fellowships in Infectious Diseases and Microbiology at Mayo Clinic. She is the Elizabeth P. and Robert E. Allen Professor of Individualized Medicine, Professor of Medicine, Professor of Microbiology, Director of the Infectious Diseases Research Laboratory, and Co-Director of the Clinical Bacteriology Laboratory at Mayo Clinic. Dr. Patel is a Fellow of American Academy of Microbiology, past President of the American Society for Microbiology, a past associate editor for Clinical Infectious Diseases, and course director for the Mayo Clinic Alix School of Medicine microbiology course. She is also the Laboratory Center Director for the NIH's Antibacterial Resistance Leadership Group. Her research focuses on clinical bacteriology diagnostic testing, antimicrobial resistance, and microbial biofilms.

David (Dave) Persing, M.D., Ph.D., is Executive Vice President and Chief Scientific Officer at Cepheid and in 2017 was appointed Chief Scientific Officer (CSO) for the Danaher Diagnostics Platform. He has spent most of his 30-year career in biomarker discovery, translational medicine, and innovation in the diagnostics space. As CSO, Danaher Diagnostics Platform, he has the responsibility for providing scientific, medical, and strategic input to the Diagnostics' Operating Companies and Platform leadership. He also has the responsibility for development of new clinical processes, technologies, or products that advance patient care, innovation,

and competitive positioning of the Danaher Diagnostics group of operating companies.

Persing joined Cepheid in 2005 and has since focused on the enablement of molecular diagnostic technology to meet global needs in infectious diseases and oncology. He conducted his scientific and medical training with Don Ganem and Nobel laureate Harold Varmus at the University of California, San Francisco. After residency training in Clinical Pathology at Yale University, he held leadership roles in academia and industry starting in the early 1990s with the design, implementation, and scaleup of the first PCR reference laboratory at the Mayo Clinic. His interest in the democratization of molecular diagnostic methods has been longstanding, starting in 1993 with his publication of the first of five widely adopted textbooks to include PCR protocols and guidelines for laboratory operations. He has published more than 300 peer-reviewed articles and reviews, including multiple articles in the *New England Journal of Medicine*, *Science*, and *PNAS*. In 2020, he was named to the Fierce Pharma list of the 22 most influential scientists in the fight against COVID-19. To maintain a connection with the latest trends in translational medicine, Persing also serves as Consulting Professor of Pathology at Stanford University School of Medicine. He obtained his M.D. and Ph.D. degrees from UCSF in 1988.

Melinda Pettigrew, Ph.D., is the Anna M. R. Lauder Professor of Epidemiology and the Interim Dean at the Yale School of Public Health. Pettigrew conducts both laboratory and epidemiologic studies. Her work focuses on how disruptions of homeostasis in the respiratory and gastrointestinal microbiota influence colonization resistance, development of antibiotic resistance, and risk of bacterial infections. Additional research seeks to identify epidemiologic and genetic factors that influence whether opportunistic pathogens asymptomatically colonize or cause diseases such as pneumonia and exacerbations of chronic obstructive pulmonary disease.

Pettigrew is nationally known for her research and leadership in her roles on the steering and executive committees for the Antibiotic Resistance Leadership Group (ARLG). The ARLG is a National Institutes of Health sponsored initiative that supports a national network of scientists to develop, implement, and manage a clinical research agenda to combat the public health crisis of antimicrobial resistance. As the associate director of the Scientific Leadership Core for the ARLG, she leads efforts to implement and integrate principles of diversity, access, equity, and inclusion throughout the network.

A graduate of Grinnell College, Pettigrew received her Ph.D. from Yale University in 1999. She conducted a postdoctoral fellowship at the University of Michigan prior to joining the Yale School of Public Health faculty in 2002. Pettigrew's research has been supported by grants from the

National Institutes of Health, the Centers for Disease Control and Prevention, and private foundations. In addition to her research, she is highly regarded for her teaching. She has received the Yale School of Public Health Distinguished Teaching Award and the Inspiring Yale Award. She also serves on the editorial board of the scientific journal *mBio*.

Valérie Raymond Schwartzmann, PharmD, has been the Director of the Companion Diagnostics Program at bioMérieux since 2014. The objective of this program is to forge close partnerships with healthcare industries (drugs, vaccines, medical and surgical equipment) in order to deliver diagnostic tests with high medical value as well as to support drug prescription and improve patient care in the context of personalized medicine.

Prior to this position, Schwartzmann was Marketing Director "Acute & Critical Care" within the Immunoassay Unit of bioMérieux. She helped develop a marketing strategy centered on the medical value of products, for clinicians, patients, and diagnostic laboratories. She has acquired 14 years of experience in sales and marketing both at local and corporate level, mainly in the field of diagnostics but also in the field of medical devices and pharmaceutical products (Roche Diagnostics—commercial organization, Fresenius HemoCare - Marketing Director and Responsible Pharmacist).

Schwartzmann is a Doctor of Pharmacy and a former intern at the Hospitals of Lyon. She completed her training with a DEA in Analytical Chemistry, an AEU in Toxicology, and a Certificate in Pharmacovigilance.

Diane Shader Smith has had a vibrant career as a writer, speaker, publicist, and fundraiser with an extensive roster of clients that includes products, personalities, services, and celebrities.

In 2017, Shader Smith's daughter Mallory died at the age of 25. This would prove to be the inflection point in her life as this catastrophic loss would lead her on a new path, one that was both unexpected and transformative. Since then, Shader Smith's work has used Mallory's posthumously published memoir, *Salt in My Soul*, and the documentary of the same name to address the following topics: AMR and the urgent global health crisis antimicrobial resistance poses, phage therapy, the power of the patient voice, the opioid epidemic and the need for balance, insurance obstacles and access to healthcare, narrative medicine, storytelling to improve health outcomes, the role of the caregiver, and memoir as medicine.

Shader Smith has given more than 250 talks across the United States—on Capitol Hill, at the White House OSTP, at national and international conferences, Grand Rounds in many hospitals, to lay and medical audiences in Australia, the UK, Paris, and Brussels, NATO, members of the European Union, and a TEDx Talk among others.

Shader Smith has been interviewed by many major media outlets including *The New York Times, Forbes, NPR, The Los Angeles Times, The Today Show,* and *The Hollywood Reporter*, among others. She has raised more than 6 million dollars for basic science research with a focus on phage therapy.

William "Bill" Rodriguez, M.D., is the Chief Executive Officer of FIND, the global alliance for diagnostics. He previously served as Chief Medical Officer between 2015 and 2017. He joined from the Draper Richards Kaplan Foundation, a global venture philanthropy firm supporting early-stage, high-impact social enterprises. As a medical doctor, he has extensive experience across both private and public sectors, founding his own diagnostics company, Daktari Diagnostics—a venture-backed start-up company developing portable diagnostics for HIV, HCV, tuberculosis, typhoid, and maternal health for use in low- and middle-income countries. He is a highly respected figure in the global health community, serving as advisor to the World Health Organization, Bill & Melinda Gates Foundation, national governments on global HIV, tuberculosis, Ebola and COVID-19, as well as numerous established and start-up for-profit and not-for-profit social enterprises focused on global health. He is a graduate of Brown University and the Yale University School of Medicine.

Kristian Roth, Ph.D., is the Deputy Director in the FDA's Division of Microbiology Devices. He received his Ph.D. in analytical chemistry from the University of California Riverside, studying surface bound porphyrin molecules, then completed a postdoc at the University of California Santa Barbara studying the materials synthesis properties of large protein conjugates with Professor Dan Morse. Afterward he moved to the Seattle area to join CombiMatrix, a startup diagnostics company targeting infectious diseases using DNA microarray detection. There, he worked on developing nucleic acid amplification assays for the detection and differentiation of influenza using a novel microfluidic cartridge coupled with electrochemical array detection. Dr. Roth then moved to the Maryland area to join Meso Scale Discovery developing platforms for the detection of influenza, hepatitis, and radiation biodosimetry. In 2011, he started at the FDA as a scientific reviewer and was involved in the writing of guidance documents for assay migration and multiplex infectious disease detection, then later served as Branch Chief in the Multiplex Bacteriology and Medical Countermeasures branch in the Division of Microbiology (DMD). Dr. Roth has also been a stakeholder in DMD's emergency response to the recent Ebola and Zika outbreaks.

Kim Sciarretta, Ph.D., is the Launch Office Branch Chief within the Division of Research Innovation and Ventures (DRIVe), Biomedical Advanced

Research and Development Authority (BARDA), part of the Assistant Secretary for Preparedness and Response (ASPR), within the United States Department of Health and Human Services (HHS). Previously Dr. Sciarretta was a Project Officer within the BARDA CBRN Division, and prior to that, was a technical consultant to multiple U.S. Government Agencies. Dr. Sciarretta was one of the inaugural members of DRIVe and is leading efforts towards improving patient outcomes for sepsis through strategic interagency activities and critical technology investments with external partners. Dr. Sciarretta received her Ph.D. from the University of Chicago in Molecular Genetics and Cell Biology. Her expertise broadly spans medical countermeasure development, biochemistry, synthetic biology, advanced manufacturing, and chemical and biological defense technologies.

Anthony D. So, M.D., M.P.A., is the second professor of the practice and Founding Director of the Innovation+Design Enabling Access (IDEA) Initiative at the Johns Hopkins Bloomberg School of Public Health. The IDEA Initiative fosters innovation and design of new technologies for greater health access and impact. As Director of the Strategic Policy Program of ReAct—Action on Antibiotic Resistance, he works with a global network dedicated to meeting the challenge of antimicrobial resistance, and his program serves as the Secretariat to the Antibiotic Resistance Coalition.

He served as one of the Co-Conveners of the UN Interagency Coordination Group on Antimicrobial Resistance that delivered recommendations to the UN Secretary General in 2019. Most recently, he was Co-Chair of the Technical Working Group aligning pharmaceutical innovation incentives to achieve fair pricing for the 2021 WHO Fair Pricing Forum and currently is a member of the Technical Advisory Group of WHO's COVID-19 Technology Access Pool. He also has served as a member of the Antibiotic Resistance Working Group of the U.S. President's Council of Advisors in Science and Technology and as part of the WHO expert Technical Consultation on In Vitro Diagnostics for Antimicrobial Resistance.

His research and policy work on collaborative R&D models and incentives for innovation has received support under a Robert Wood Johnson Investigator Award in Health Policy Research.

He contributed to the Lancet Infectious Diseases Commission on Antibiotic Resistance, co-edited the Chatham House's Working Group's report, *Towards a New Global Business Model for Antibiotics: Delinking Revenues from Sales,* and co-authored "A Framework for Costing the Lowering of Antimicrobial Use in Food Animal Production" for the UK Review on Antimicrobial Resistance.

Susan Van Meter was named ACLA President in March 2022. She previously served as Executive Director of AdvaMedDx where she directed

the policy, advocacy, communications, regulatory, payment and legislative strategy and operations of the association, which represents manufacturers of in vitro diagnostic (IVD) clinical tests in the U.S. and abroad. In this role, she also developed the association's robust response to the COVID-19 pandemic and ongoing advocacy efforts. Prior to her role at AdvaMedDx, Van Meter served as the Senior Vice President of Federal Relations at the Healthcare Association of New York State (HANYS), where she was responsible for developing their priorities and strategies to further the interests of their hospital and health system members. She also previously worked in the Centers for Medicare & Medicaid Services' (CMS) Office of Legislation. Van Meter holds undergraduate and graduate degrees from Villanova University and Boston University, respectively.

Craig Whiteford, M.S., Ph.D., leads a diverse set of R&D Scientists for BD Integrated Diagnostic Solutions (IDS), who have developed diagnostic tests for blood stream infections, Tuberculosis (ID/DST), bacterial identification & antibiotic susceptibility, enteric diseases, respiratory diseases, sexually transmitted infections, and oncology. Over the past 18 years, Dr. Whiteford has held both R&D and Project Management roles, from which he has driven WW product development from ideation to the launch for the BD MAX Molecular platform as well as various phenotypic platforms inclusive of the BACTEC, MGIT, Phoenix, Phoenix AP as well as Kiestra laboratory automation system, which consist of robotics and artificial intelligence (AI)-driven software that is transforming the way clinical laboratories operate. With his keen interest in infection diseases, he has also led several Technology Sensing and Development Teams. Successfully serving BD in many different roles, his Teams have developed more than a dozen IVD devices. Working closely with Regulatory Affairs, Medical/Clinical Affairs, and Quality Affairs to develop strategies for clinical trials as well as regulatory bodies' submission (FDA, China, Japan, ANVISA, CE regulations). Before coming to BD, he worked as a Lab Manager for a Pediatric oncology lab at the National Cancer institute within the National Institutes of Health, researching, developing, and deploying one of the largest Microarray technologies and research efforts at the National Institutes of Health.

Dr. Whiteford holds a Bachelor of Science in Biology & Microbiology, Master of Science, and a Ph.D. in Microbiology from Kansas State University.