

Changing Diagnostic Paradigms for Microbiology



A report from the

AMERICAN
ACADEMY OF
MICROBIOLOGY
RECOGNIZING SCIENTIFIC EXCELLENCE



Changing Diagnostic Paradigms for Microbiology

Report on an American Academy of Microbiology Colloquium held in Washington, DC, from 17 to 18 October 2016.

Virginia Dolen, *Rapporteur*

The American Academy of Microbiology (Academy) is the honorific branch of the American Society for Microbiology (ASM), a nonprofit scientific society with nearly 48,000 members. Fellows of the Academy have been elected by their peers in recognition of their outstanding contributions to the microbial sciences. Through its colloquium program, the Academy draws on the expertise of these fellows to address critical issues in the microbial sciences.

This report is based on the deliberations of experts who gathered for two full days to discuss a series of questions developed by the steering committee. All participants had the opportunity to

provide feedback, and every effort has been made to ensure that the information is accurate and complete. The contents reflect the views of the participants and are not intended to reflect official positions of the Academy or of ASM.

The Academy acknowledges Margaret Milhous for her assistance in editing this report. In addition, the Academy thanks the efforts of Daniel Peniston for his assistance on this project.

Contents of the report may be distributed further so long as the authorship of the Academy is acknowledged and this disclaimer language is included.

BOARD OF GOVERNORS, AMERICAN ACADEMY OF MICROBIOLOGY

Michele S. Swanson, Ph.D., *Chair*
University of Michigan Medical School

Martin J. Blaser, M.D.
New York University School of Medicine

Donald A. Bryant, Ph.D.
Pennsylvania State University

Arturo Casadevall, M.D., Ph.D., *Chair-Elect*
Johns Hopkins Bloomberg
School of Public Health

Nancy Craig, Ph.D.
The Johns Hopkins University
School of Medicine

Terence S. Dermody, M.D.
Children's Hospital of Pittsburgh
of UPMC

Stanley Fields, Ph.D.
University of Washington

James M. Hughes, M.D.
Emory University School of Medicine

Steven Lindow, Ph.D.
University of California, Berkeley

Margaret McFall-Ngai, Ph.D.
Pacific Biosciences Research Center,
University of Hawaii at Manoa

Mary Ann Moran, Ph.D.
University of Georgia

Graham C. Walker, Ph.D.
Massachusetts Institute of Technology

Alice S. Weissfeld, Ph.D.
Microbiology Specialists

COLLOQUIUM STEERING COMMITTEE

Melissa B. Miller, Ph.D., *Chair*
University of North Carolina
at Chapel Hill

Kenneth Bahk, Ph.D.
Three Lakes Partners

Karen C. Carroll, M.D.
Johns Hopkins University
School of Medicine

Keith Klugman, M.D., Ph.D.
Bill & Melinda Gates Foundation

Nathan A. Ledeboer, Ph.D.
Medical College of Wisconsin

PARTICIPANTS

Edina Avdic, Pharm.D., M.B.A.
The Johns Hopkins Hospital

Tobias Barker, M.D.
CVS Health

Steve Beuchaw, M.B.A.
Morgan Stanley

Carey-Ann Burnham, Ph.D.
Washington University in St. Louis
School of Medicine

Sheldon Campbell, M.D., Ph.D.
Yale School of Medicine

Nancy E. Cornish, M.D.
Centers for Disease Control
and Prevention

Scott Cunningham, M.S., M.T. (ASCP), S.M.
Mayo Clinic

Charlotte A. Gaydos, M.S., M.P.H., Dr.P.H.
Johns Hopkins University

Alberto Gutierrez, Ph.D.
Food and Drug Administration

Alexander J. McAdam, M.D., Ph.D.
Boston Children's Hospital

Jeanne Mumford, M.T. (ASCP)
Johns Hopkins Medicine

Daniel D. Rhoads, M.D.
Case Western Reserve University

Kristian Roth, Ph.D.
Food and Drug Administration

Paul Schreckenberger, M.S., Ph.D.
Loyola University Chicago

Fred C. Tenover, Ph.D.
Cepheid

Dan Wattendorf, M.D.
Bill and Melinda Gates Foundation

ACADEMY STAFF

Marina Moses, M.S., Dr.P.H.
Director

Virginia Dolen
Program Manager

Isabel Hinestrosa
Board of Governors Program Assistant

Daniel Peniston
Colloquium and
Outreach Program Assistant

ASM LEADERSHIP

Stefano Bertuzzi, Ph.D., M.P.H.
Chief Executive Officer

Dedicated to the memory of Paul Schreckenberger.

Recommendations

Implementation	Oversight	Evaluation
<ul style="list-style-type: none">• Redesign clinic workflows to incorporate near-patient and point-of-care (POC) testing.• Promote proper interpretation of tests to avoid adverse outcomes.• Provide resources, such as training videos, to support appropriate self-collection of patient specimens.• Ensure that public health surveillance of infectious diseases is maintained with POC testing.• Link near-patient and POC test results to the patient's electronic medical record (EMR).	<ul style="list-style-type: none">• Maintain clinical microbiology laboratory expertise and oversight of infectious disease tests.• Utilize competent personnel to oversee ordering, testing, and interpretation.• Educate providers and patients on different types of tests.	<ul style="list-style-type: none">• Conduct clinical outcomes and cost-effectiveness studies for near-patient and POC tests.• Evaluate near-patient and POC tests periodically and undertake regulatory action or reclassification for tests that do not meet performance standards.

Introduction

Clinical microbiology laboratories offer specialized expertise to perform diagnostic testing, such as culture and molecular detection of pathogens, for infectious indications (Buchan and Ledebor 2014). Currently, laboratories face increased pressures to perform more testing while reducing turnaround times in the setting of high staff turnover and staff shortages (Bourbeau and Ledebor 2013). Centralized laboratories may need to serve an increasing number of decentralized patients in a system or network affiliated with a hospital, which may include a number of clinics located at a distance from the laboratory. At the same time, economic pressures push healthcare systems to demonstrate cost-effectiveness and high-value care.

While diagnostic tests performed in a central laboratory allow for specialized expertise and high-complexity testing, they may not offer timely results for patient care. The central laboratory may have limited hours of operation and may perform batch testing (versus on-demand testing) in order to optimize use of resources. In addition, delivery mechanisms are changing in healthcare. Some settings (such as rapid or convenient care clinics or clinics in the developing world) do not have a dedicated microbiology laboratory and require

testing methods that require minimal designated space, turnaround times, physical resources, and trained personnel to operate. Patient expectations, advances in medical knowledge and technology, and a desire for targeted treatment are driving the increased availability of on-demand testing for infectious diseases.

Low-complexity, rapid, and accurate diagnostic tests for infectious diseases performed on demand closer to the point of patient care have the potential to deliver timely results to inform diagnosis and treatment. Near-patient and point-of-care (POC) testing increases access to efficient diagnostic testing across many settings; this field is rapidly advancing. Clinical Laboratory Improvement Amendments (CLIA)-waived nucleic acid amplification tests (NAATs) can be performed outside laboratories by nonlaboratorians while producing results essentially equivalent to more-complex, gold standard laboratory assays. To explore the development and implementation of near-patient and POC tests, the American Academy of Microbiology (Academy) convened a colloquium of experts to discuss relevant issues and needs and to provide recommendations.

Statement of Task

The American Academy of Microbiology (Academy) convened a colloquium to examine the role of near-patient testing and its impact on the changing diagnostic paradigms for microbiology. Rapid diagnostic tests have the potential to deliver timely results to enable treatment decisions in both laboratory and nonlaboratory settings. Such tests could, for example, detect the presence of biomarkers, distinguish between viral and bacterial infections, identify causative organisms, determine strain type, or provide information on drug resistance. Automation, simplification, and miniaturization of diagnostic tests allow them to be performed outside clinical microbiology laboratories, such as in physicians' offices, pharmacies, convenient care clinics, or even at home. Innovative developers and the financial community are working to leverage the latest technology to impact patient care, as the information gleaned from rapid diagnostics has the potential to inform individual treatment decisions as well as the public health response when outbreaks are rapidly identified. Expertise in the microbial sciences is needed to guide the development and utilization of new tests, as are oversight and proficiency testing to ensure that the tests are being conducted correctly and that results are reported to the appropriate parties. Additionally, it is crucial to maintain personnel with adequate clinical microbiology laboratory expertise to assist with decision support and perform advanced testing. This colloquium addressed the proliferation of near-patient testing and how diagnostic testing for infectious diseases may be distributed between centralized laboratories and POC locations.



Approach to the Task

The Academy is the honorific leadership group within the American Society for Microbiology (ASM), the world's oldest and largest life science organization. One major role of the Academy is to convene colloquia to deliberate on issues of critical importance in the microbial sciences. On 17 to 18 October 2016, the Academy convened a group of 21 experts at ASM Headquarters to discuss changing diagnostic paradigms in microbiology, including near-patient and POC testing. A steering committee chaired by an Academy fellow was appointed prior to the colloquium and developed a comprehensive and informed agenda, including key discussion questions for the colloquium participants. The distinguished group of participants included representatives from clinical laboratories, academia, government agencies, foundations, and commercial industry with backgrounds in clinical

microbiology, diagnostic and POC testing, pharmacy, medicine, laboratory medicine, public health, informatics, device development, device regulation, and investment. Colloquium participants were assigned 11 main discussion questions (see Appendix), with subquestions that covered the broad topics in the Statement of Task (see the text box). Participants were divided into working groups that consisted of individuals with varied expertise to answer the discussion questions. Groups reconvened for plenary sessions to review all answers. This report summarizes the plenary discussions during the 2-day colloquium.

This report (1) reviews characteristics and applications of near-patient and POC tests for infectious diseases, (2) provides an overview of considerations pertaining to their implementation, oversight, and evaluation, and (3) provides recommendations.

Key Terms

Sensitivity – the proportion of patients with the disease who will have a positive test result. This indicates the ability of the test to correctly identify those patients with the disease.

Specificity – the proportion of patients without the disease who will have a negative test result. This indicates the ability of the test to correctly identify those patients without the disease.

Positive predictive value – the proportion of patients with a positive test result who actually have the disease. The value is dependent on the prevalence of the disease in the patient population.

Negative predictive value – the proportion of patients with a negative test result who do not have the disease. The value is dependent on the prevalence of the disease in the patient population.

Waived testing – an FDA designation that is given to diagnostic assays that are deemed to be simple to perform and have an insignificant risk of an erroneous result and require reduced regulatory oversight. These assays are considered laboratory tests, but they are often performed outside a laboratory (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm393229.htm>).

Nonwaived testing – an FDA designation that is given to laboratory tests that are determined to be of moderate or high complexity and need to be performed in a laboratory that is inspected by a regulatory agency.

Near-patient testing – an imprecise term used to describe laboratory testing (with a waived or nonwaived test) that can be performed in close proximity to the patient, either at the point of care or in a nearby area. Typically, these tests have short turnaround times, and the results often guide the immediate medical management of patients.

Near-Patient and Point-of-Care Tests— Characteristics and Applications

Point-of-Care Testing— Sample Definitions

“Point-of-Care Testing (POCT) is defined as tests designed to be used at or near the site where the patient is located, that do not require permanent dedicated space, and that are performed outside the physical facilities of the clinical laboratories” (<http://www.cap.org/apps/docs/education/OnlineCourseContent/2012/LAP/Resources/Checklists/POC09252012.pdf>).

“POC testing is diagnostic testing that will result in a clear and actionable management decision such as when to start treatment or to require a confirmatory test, within the same clinical encounter” (Pai et al. 2015).

Point-of-care testing and near-patient testing: “testing that is performed near or at the site of a patient with the result leading to possible change in the care of the patient” (<https://www.iso.org/obp/ui/#iso:std:iso:22870:ed-1:vi:en>).

Automation, simplification, and miniaturization of diagnostic tests allow them to be performed outside a clinical microbiology laboratory, either near the patient or at the point of care, including at home. Both terms (“near-patient” and “point-of-care”) can refer to tests performed at or close to the site of patient care, by nonlaboratory personnel, with results available more quickly than with tests performed by a central laboratory. Definitions for these terms vary, as indicated by the sample definitions provided in the side bar. Usage of the terms may also depend on the setting (e.g., academic medical center, convenient care clinic, or clinic in the developing world). As used in this report, POC testing generally refers to the use of waived tests (as defined by CLIA) that are performed by nonlaboratory personnel.

Types of Tests

Near-patient and POC tests currently exist for a number of pathogens, such as tuberculosis (TB), influenza and other respiratory viruses, group A *Streptococcus* (GAS), *Chlamydia*, and gonorrhea. These include antigen tests (most commonly lateral-flow immunochromatographic membrane-based assays) and nucleic acid tests. Due to rapid advances in technology, the field of diagnostic microbiology is shifting from antigen-based testing to nucleic acid amplification-based testing, including multiplex syndromic panels that test for a number of potential pathogens concurrently.

Antigen Tests

Lateral-flow tests detect a microbial antigen present in a clinical sample through binding to a capture antibody and a secondary antibody conjugated to a visible marker (Drancourt et al. 2016). A positive result is indicated visually by the presence of a colored band. While a number of antigen-based tests are currently utilized as near-patient and POC tests, in general, these tests often have lower sensitivity and specificity than nucleic acid-based tests or more-complex laboratory tests.

Nucleic Acid Amplification Tests

Nucleic acid amplification tests (NAATs) can detect RNA or DNA sequences specific to a particular target (which may be present in a specific pathogen or antimicrobial resistance determinant). NAATs include PCR (nucleic acid amplification using thermostable polymerase) or isothermal amplification methods, including transcription-mediated amplification (TMA), strand displacement amplification (SDA), loop-mediated isothermal amplification (LAMP), and helicase-dependent amplification (HDA) (Buchan and Ledebouer 2014). Although NAATs are more sensitive and specific than antigen-based tests, some limitations exist. NAATs demonstrate varied sensitivities when used in practice and may not identify clinically relevant infections in some cases. This may be due to differences between real-world experiences with these

Antigen Test Considerations

Influenza

Severe influenza typically affects 3 to 5 million people globally each year (Chartrand et al. 2012). Although viral culture has high specificity, it has a long turnaround time, which has led to NAATs becoming the gold standard for influenza diagnosis. However, diagnosis by a NAAT is costly and requires specialized equipment. Antigen-based rapid influenza diagnostic tests (RIDTs) are a less expensive and faster option for influenza diagnosis. However, many of these tests exhibit poor sensitivity, particularly in postmarket studies in the United States. A meta-analysis of RIDT studies found a pooled sensitivity of 62.3% and a pooled specificity of 98.2% (Chartrand et al. 2012). In particular, tests that were developed based on the comparator of viral culture may exhibit lower sensitivities. In addition, lower sensitivity may be observed with specific strain types (Ginocchio et al. 2009). The inadequate sensitivity and low negative predictive value necessitates reflex testing, in which a sample from a negative test is sent for laboratory confirmation of results, which might delay patient management. However, due to the high specificity and positive predictive value when used during respiratory season, positive antigen-based tests can be used to guide appropriate therapy for influenza (e.g., antiviral medication).

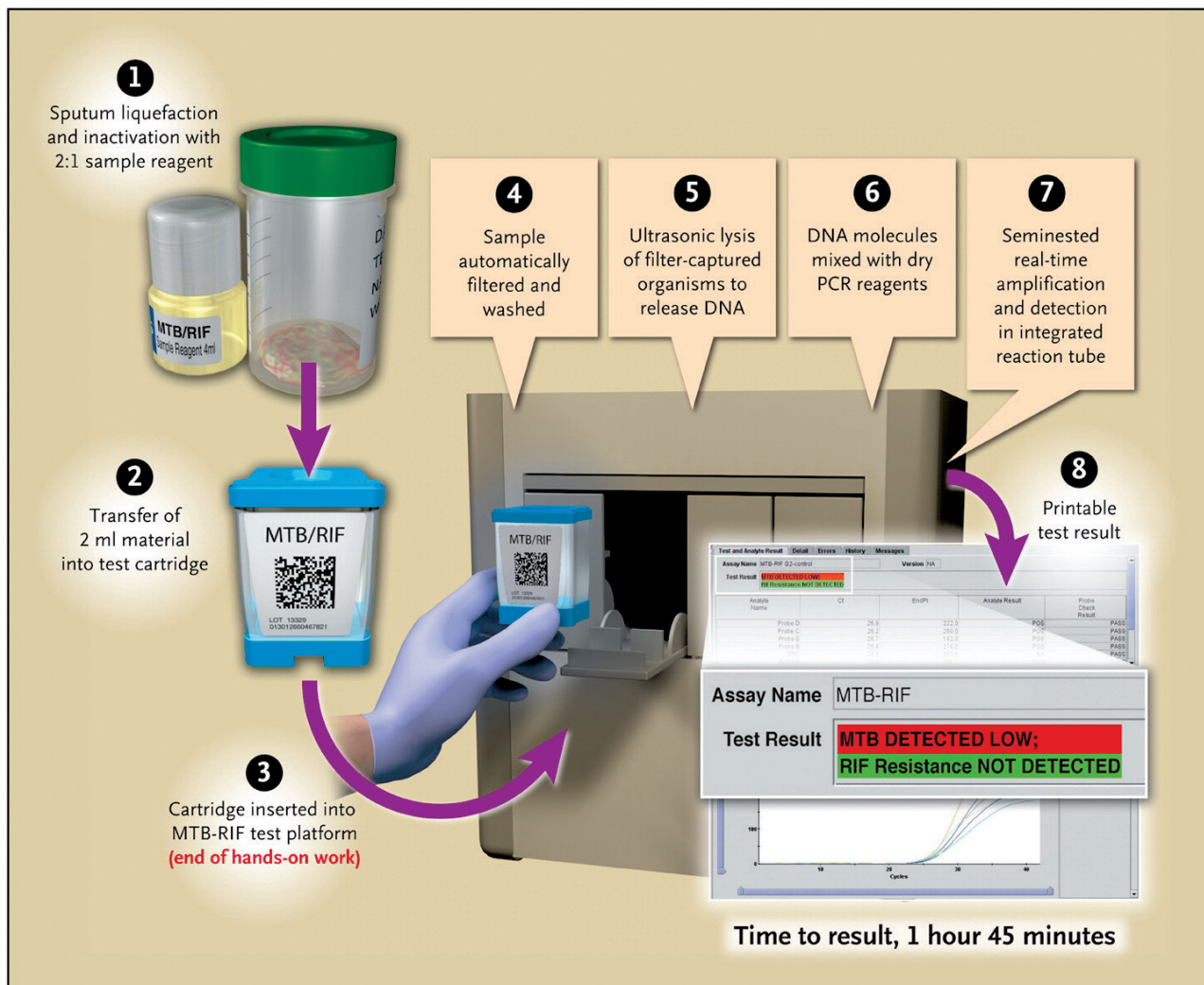
tests in clinical practice versus in controlled clinical trials performed for regulatory review or due to genetic differences in circulating strains. NAATs have a risk of contamination during nucleic acid extraction or from carryover of previously amplified material, including vaccines (Leber 2014; Mohl et al. 2016; Salimnia et al. 2012), or from leakage of test

cartridges, which may affect test results. In addition, performance of NAATs may be impacted by mutations in the RNA or DNA sequences that they are designed to detect and may be falsely negative when mutations are present in the primer/probe binding sites.

Nucleic Acid Amplification Test Considerations Tuberculosis

NAATs have improved the diagnosis of TB, particularly in developing nations with high prevalences of TB. Traditionally, TB is diagnosed through direct microscopy of stained sputum smears, although this method has low sensitivity (~50 to 60%), or through culture, which is a suboptimal gold standard because it takes days or weeks to obtain results (Dheda et al. 2013). Nucleic acid tests for TB have high sensitivity (~98% in smear-positive patients and ~75% in smear-negative patients) and can deliver results within 2 hours, which could allow the physician to initiate treatment for the patient the same day as the healthcare visit (Dheda et al. 2013). POC nucleic acid tests for TB are rapid, sensitive, and specific and have the potential to replace smear microscopy. Nucleic acid tests also have the ability to identify multidrug-resistant TB (resistant to at least isoniazid and rifampin, two of the first-line therapeutic agents).

Figure 1. NAAT procedure.



(Republished from Boehme et al. 2010 with permission.)

Syndromic Panels

With the advent of molecular testing, agent-specific primers included in a particular test detect a single pathogen, but in many cases a clinical presentation may be caused by a number of possible pathogens (Schreckenberger and McAdam 2015). Multiplex NAAT panels (inclusive of pathogens that cause a common syndrome or are commonly found in a specific sample type) have been developed to investigate multiple putative causes of illness simultaneously (Schreckenberger and McAdam 2015). For example, syndromic panels exist for respiratory pathogens, for meningitis/encephalitis, and for gastrointestinal pathogens. Syndromic panels must be thoughtfully developed to provide advantages over single-pathogen tests; the clinical utility of including each pathogen should be considered to ensure that the test results are easily interpretable. Differences in sensitivity and specificity may exist between syndromic panels and the individual molecular tests. For example, one study of a meningitis/encephalitis panel found a significant number of false positives thought to be the result of contamination or some other aspect of

the testing process (Leber et al. 2016). Differences in sensitivity and specificity may also exist between different multiplex assays for the same syndrome (Popowitch et al. 2013).

Concerns exist about indiscriminate deployment of syndromic panels when a nuanced approach to testing is needed. Professional judgment may be required to determine when a panel approach is warranted and to interpret the results of a syndromic panel correctly. For example, a patient's clinical presentation might be the result of a newly recognized pathogen (in which case, it would not be identified with a panel) or an unfamiliar presentation of a known pathogen (in which case, a provider may order an uninformative panel test). If a disease included in a syndromic panel is rare in a particular setting, the number of false positives for that disease may outnumber the number of true positives, requiring further testing to confirm positive test results. In addition, multiple positive results can be obtained with a syndromic test panel, which requires the clinician to interpret which positive results are clinically significant and which might be insignificant.

Syndromic Panel Considerations

Pharyngitis

Pharyngitis (sore throat), which results in an estimated 15 million medical visits annually in the United States, can be caused by viral or bacterial pathogens (Shulman et al. 2012). A nucleic acid syndromic panel could cover key infectious causes of pharyngitis to inform diagnosis and treatment. The most common bacterial cause of acute pharyngitis is group A *Streptococcus* (GAS), accounting for 20 to 30% of cases in children and 5 to 15% of cases in adults (Shulman et al. 2012). Other causes of pharyngitis that could be included in the panel include groups C and G streptococci, *Mycoplasma pneumoniae*, viral agents, and other targeted pathogens (i.e., *Fusobacterium* in Lemierre's syndrome). Antibiotic therapy is recommended for GAS but not for most other causes of pharyngitis, so diagnosis of streptococcal pharyngitis is important to inform treatment. Testing for multiple targets simultaneously could allow providers to more rapidly determine causes of pharyngitis and either initiate antibiotic treatment for GAS or to inform the patient that his/her sore throat is caused by an agent for which antibiotics are not warranted. A syndromic pharyngitis panel deployed in nonlaboratory settings would need to be easily interpretable to nonlaboratorians who may not be familiar with testing for these agents.

Sensitivity and Specificity

With increased testing being performed outside clinical microbiology laboratories, the limitations of each test with respect to sensitivity and specificity must be understood and acknowledged by those ordering and interpreting the tests. Colloquium participants affirmed that near-patient and POC tests should exhibit performance criteria for sensitivity and specificity similar to those of equivalent laboratory-based tests. Even with the best quality tests (whether performed in the laboratory or at the POC), providers need to be wary of adverse outcomes that can arise from improper interpretation of the results. Concerns exist that the results of POC tests may be automatically interpreted as correct results, even though no test

has perfect sensitivity and specificity. False positives and false negatives will occur, and their likelihood needs to be evaluated when making patient care decisions. Particular concerns exist for tests with high analytical sensitivity, which may deliver positive results that are due to contamination or results that should be interpreted as asymptomatic colonization rather than infection. In addition, the pretest probabilities of a particular result and therefore of the positive predictive value of the test in that particular setting for that particular patient population need to be considered. Recommendations to guide oversight of near-patient and POC testing, such as addressing contamination and test interpretation, are provided later in this report.

Sensitivity and Specificity Considerations *Legionella*

Legionella is an important cause of pneumonia, and testing may aid in rapidly identifying outbreaks of Legionnaires' disease (Reller et al. 2003). The available urine antigen tests have good sensitivity and specificity but are designed to detect only *Legionella pneumophila* serogroup I. This test is not designed to detect *Legionella pneumophila* strains other than serotype I and species other than *pneumophila* that can cause disease, so the urine antigen assay alone is not sufficient to rule out Legionnaires' disease. Given these considerations, it would be advantageous to develop a rapid and simple *Legionella* test that reliably detects a broader range of *Legionella* spp. (Benitez and Winchell 2013, Okada et al. 2002).



Regulatory Considerations

In the United States, most *in vitro* diagnostic tests are regulated by the Food and Drug Administration (FDA) (see the text box). CLIA regulates laboratory testing and requires clinical laboratories to be certificated by their state as well as by the Centers for Medicare and Medicaid Services (CMS) before they can accept human samples for diagnostic testing. Laboratories can obtain multiple types of CLIA certificates based on the kinds of diagnostic tests that they conduct (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124105.htm>). Tests that meet certain criteria may be performed in an environment that is exempt from some requirements stated in the CLIA legislation, commonly referred to as a CLIA-waived laboratory. A CLIA waiver may be granted for a test after the clearance or approval process or through a dual pathway in which the clearance and waiver occur simultaneously [known as a Dual 510(k) and CLIA Waiver Application]. Settings that perform only certain tests that are simple to use and have an insignificant risk of an erroneous result are required to obtain a certificate of waiver from the CMS. While the laboratories must follow manufacturers' instructions for the tests, they receive no routine inspections, and the tests are exempt from

most CLIA requirements (https://www.cms.gov/regulations-and-guidance/legislation/clia/certificate_of_waiver_laboratory_project.html, <https://www.cdc.gov/clia/Resources/WaivedTests/default.aspx>).

There are CLIA-waived nucleic acid-based tests for influenza A and B viruses, respiratory syncytial virus, and GAS and a syndromic respiratory panel that tests for *Bordetella pertussis*, coronaviruses, influenza A H1N1 virus, influenza A H3N2 virus, influenza A H1N1-2009 virus, influenza B virus, *Mycoplasma pneumoniae*, parainfluenza viruses, and *Chlamydia pneumoniae* from a single patient sample.

Outside the United States, other regulatory paradigms exist. For example, for the European Union, Directive 98/79/EC pertains to *in vitro* diagnostic medical devices and provides guidance on Conformité Européenne (CE) marking (https://ec.europa.eu/growth/single-market/european-standards/harmonised-standards/iv-diagnostic-medical-devices_en). The approval process and regulatory jurisdiction that apply to POC diagnostic tests must be considered as they are implemented in different settings.

New Tests and Technologies

Innovative developers and the financial community are working to leverage the latest technology to

FDA Regulation of Medical Devices

“Approved medical devices: Approved medical devices are those devices for which FDA has approved a premarket approval (PMA) application prior to marketing. This approval process is generally reserved for high-risk medical devices and involves a more rigorous premarket review than the 510(k) pathway.”

—PMA database: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm>

“Cleared medical devices: These medical devices are ones that FDA has determined to be substantially equivalent to another legally marketed device. A premarket notification, referred to as a 510(k), must be submitted to FDA for clearance. A 510(k) is most often submitted by the medical device manufacturer.”

—510(k) Premarket Notification database: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmnm.cfm>

The above quotes are from <http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194468.htm>.

Waived tests: “Diagnostic tests are categorized as waived based on the premise that they are simple to use, and there is little chance the test will provide wrong information or cause harm if it is done incorrectly. Tests that are cleared by the FDA for home or over-the-counter use are automatically assigned a waived categorization.”

—CLIA database: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCLIA/Search.cfm>

The above quote is from <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVD-RegulatoryAssistance/ucm393229.htm>

develop diagnostic tests that will have a positive impact on patient care. The field is rapidly advancing. Future tests may be able to deliver results with a faster turnaround time than currently available. Ideally, tests would be read by an instrument and electronically interfaced to reduce interpretation errors and to ensure that data are shared. Advances in technology can change the current paradigm in which healthcare systems maintain patient data. As locations of care diversify and patients undergo testing in different settings, patients may gain control of curating their own electronic health record, perhaps with information being stored in the “cloud” and shared across providers (see “Data Connectivity” side bar, page 15).

Colloquium participants discussed targets of interest for developing, improving, and implementing near-patient and POC tests. In the United States, high-priority targets include sexually transmitted infections (STIs), pharyngitis, urinary tract infections (particularly tests that distinguish between infection and noninfection), and community-acquired pneumonia (particularly tests that distinguish between viral and bacterial pneumonia). For STIs and pharyngitis, nucleic acid tests could replace currently available antigen tests. Globally,

targets of highest interest include HIV, malaria (as current tests are very difficult to interpret), and TB, although low-income countries with weak healthcare infrastructures can make particularly effective use of POC diagnostics for a wide range of illnesses.

Future tests may also be able to provide more detailed information than is currently available through POC tests, such as antimicrobial resistance or the ability to quantitate organisms. New tests may be able to identify host biomarkers of infection to guide treatment (even when a test for the etiologic agent is not available), such as biomarkers that distinguish between viral and bacterial infection or between infection and noninfection. For example, approximately 5 to 15% of school-aged children are colonized with GAS (Speert 1998). When GAS is identified, a biomarker test might differentiate between asymptomatic colonization and signs of infection either by examining GAS gene expression or by analyzing the host immune response to GAS. Eventually, rapid tests may even be able to evaluate a patient’s microbiome to monitor health and predict disease risk, leading to “personalized microbial medicine.”

Figure 2. POC laboratory.



POC laboratory implemented in Dielmo village in rural Senegal, showing the DNA extraction and mix preparation materials. (Republished from Sokhna et al. 2013 with permission.)

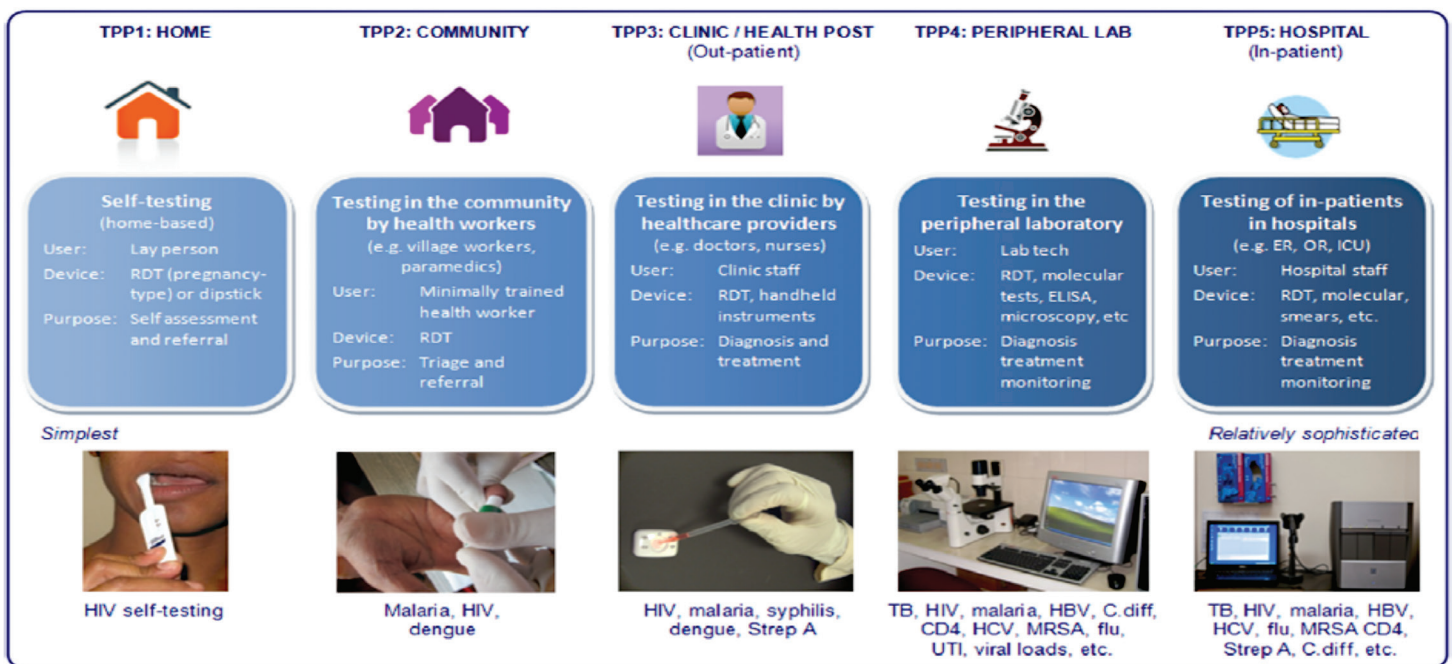
Due to their expertise and experience with diagnostic tests for infectious agents, clinical microbiology laboratory personnel can complete clinical needs assessments to guide future directions for test development (Weigl et al. 2012). For example, a survey of STD clinic clinicians regarding POC tests for STIs found that respondents valued sensitivity the most, followed by cost, specificity, and time to result (Hsieh et al. 2010; Hsieh et al. 2011; Hsieh et al. 2012). However, different practice settings can have different values because of the practice environment. The results of needs assessments can be used to inform manufacturers as to what technology they should pursue, as well as be shared with business incubators and investors who will work to develop and fund new technologies.

Regardless of the technology, it is vital to ensure that POC tests will perform accurately and reproducibly when used according to the manufacturer's instructions. Removing the test from the laboratory removes the ability for analysis and "troubleshooting" by experienced personnel. Given the potential for limited monitoring of POC tests, engineering controls must be included when tests are developed. Some colloquium participants expressed concern that controls might not be ade-

quate in their current format and that tests should be able to employ simple checks, such as inhibition controls to ensure that, for example, a negative result truly indicates the absence of the pathogen in question. The technological needs for enabling appropriate controls for tests that will routinely be used by nonlaboratorians must be identified. For example, colloquium participants suggested that contamination should be auto-monitored for NAATs. One way this might be accomplished is if the software accompanying the test device alerts the user when a positive threshold (as established by the user) is exceeded within a period of time, indicating the potential for false positives due to contamination. Periodic environmental monitoring to assess contamination could also be recommended.

Colloquium participants asserted that developing countries should have access to the same high-quality testing as is available in developed countries. A recent Perspective in the *New England Journal of Medicine* called for a model list of essential diagnostics, similar to the Model List of Essential Medicines maintained by the WHO, which could include POC tests (Schroeder et al. 2016).

Figure 3. Diversity of target product profiles, users, and settings within the spectrum of POC testing.



HBV, hepatitis B virus; HCV, hepatitis C virus; UTI, urinary tract infection; MRSA, methicillin-resistant *Staphylococcus aureus*; C. diff, *Clostridium difficile*; RDT, rapid diagnostic test; Strep A, group A *Streptococcus*. (Republished from Pai et al. 2012 with permission.)

Implementation of Near-Patient and Point-of-Care Tests

The information gleaned from rapid diagnostics has the potential to inform individual treatment decisions as well as the public health response when outbreaks are rapidly identified. With changing paradigms for diagnostic testing both within and external to traditional hospital and healthcare facilities, near-patient and POC testing will likely become increasingly common and extend to additional settings. Near-patient and POC tests may provide an attractive option to provide diagnostic testing in medical settings that do not maintain or cannot support central microbiology laboratories (such as small physician practices or long-term care facilities) or are outside traditional medical settings (such as convenient care clinics or pharmacies or even at home in conjunction with the practice of telemedicine).

Incorporating near-patient and POC testing for infectious disease indications may induce changes in workflow and necessitate electronic linkages to share information among providers. As healthcare becomes increasingly patient centered (designed around patients' needs, preferences, circumstances, and well-being [Cosgrove et al. 2013]), near-patient and POC tests provide an opportunity to improve patient care and increase patient satisfaction.

Effects on Clinical Practice

Near-patient and POC tests provide rapid diagnostic results outside central clinical microbiology laboratories. However, to recognize this benefit, clinical workflow needs to allow for the test to be performed and for results to be reported in a short turnaround time. This is especially true in convenient care or retail clinics, which provide services for simple acute conditions (the most common reasons for visits include upper respiratory tract infections, sinusitis, and bronchitis [27.4% of all visits] and pharyngitis [21.2%]) (Mehrotra et al. 2008). For encounters in convenient care clinics as they are currently run, diagnostic tests for infectious diseases would need to exhibit a turnaround time under 20 minutes to have an impact on clinical care decision-making during the encounter. However, redesigning workflow can allow settings to realize the benefits of rapid diagnostic tests even if the test requires 60 to 90 minutes to complete. Shifting patient flow and reorienting specimen collection may provide a way to integrate POC tests into a brief clinical encounter at a physician's office or convenient care clinic. The workflow could begin with specimen collection ordered through a triage mechanism based on patient symptoms and accomplished through nurse-initiated provider orders. A potential model

Shifting patient flow and reorienting specimen collection may provide a way to integrate POC tests.



for a “flipped” patient encounter is the Dean Street clinic in London (<http://dean.st/>). Specimen collection might also be performed at home and testing performed at either a clinic, an emergency department (Gaydos et al. 2013), or an off-site diagnostic laboratory. Through a telemedicine approach, the testing may also be performed at home, with results sent electronically for secure interpretation and linkage to care (Gaydos et al. 2016). Reorienting timing of specimen collection and testing would allow the result to be available before the healthcare provider sees the patient. The decreased time to reliable results granted by the utilization of rapid NAATs can enable optimal therapeutic management to occur more quickly and can foster better adherence to clinical treatment guidelines (Gialamas et al. 2009, May et al. 2015, May et al. 2016).

One particular area in which near-patient and POC tests might impact appropriate treatment is the prescription of antibiotics. Having a test result readily available to the provider prior to providing antibiotics to a patient may allow for more-directed therapy and improve antimicrobial stewardship. Further studies are needed to examine the impact of POC testing on antibiotic prescribing. Colloquium participants observed that patients do not necessarily want an antibiotic when they come in with an illness, but they do want an answer. The results of rapid diagnostic tests could provide a basis for the provider to explain the recommended therapy (or lack thereof) to the patient. Near-patient and POC tests contributing to antimicrobial stewardship might also support requirements under Joint Commission accreditation

(Joint Commission 2016) or CMS Conditions of Participation (<https://www.cms.gov/Newsroom/MediaReleaseDatabase/Fact-sheets/2016-Fact-sheets-items/2016-06-13.html>).

As near-patient and POC testing increases, and if workflows begin to shift in response, potential caveats must be considered. If the provider will need data from additional laboratory tests to inform diagnosis and treatment, then the time savings from performing the POC tests is lost, and the test may be performed in the laboratory to allow for greater-complexity testing and to gain benefits from batch testing, including lower costs. Some POC systems may be able to test only a limited number of samples concurrently, so scaling up test volume might be problematic for a high-volume setting. In some situations in the developing world, such as for multidrug-resistant TB, appropriate treatment may not be available even if test results are known, which provides little incentive for incurring the cost of the test. These issues must be considered when ordering diagnostic tests for a particular patient.

Effects on Patient Care

Rapid diagnostic tests have the potential to deliver timely results to make better treatment decisions. Depending on the current standard of care in the context of the patient, near-patient or POC testing may provide information more quickly than current practice, allowing a provider to make a treatment decision at the time that the patient is seen rather than to require a follow-up visit. In regions where infectious disease testing is currently unavailable, especially in developing countries, POC



tests can provide critical information to inform both diagnosis and treatment.

With expansion of near-patient and POC testing, driven by provider uptake and/or patient demand, guidelines or criteria need to be available for the clinicians ordering the tests to ensure that the tests will have a positive impact on patient care. First, it is important that appropriate tests are ordered, and whether a POC test is preferable to a laboratory-based assay for the particular patient encounter should be considered. Providers must also consider how the test results will be interpreted. The practice of medicine has been described as “a science and an art,” and POC test results are only one piece of information out of many in the clinical picture that providers should consider when assessing a particular patient. It is vital that the results of POC tests are entered into the laboratory results section of the electronic medical record (EMR) of the patient, so that the laboratorian has access to the data to aid the physician in interpreting results when necessary and so that other care providers can easily identify the results upon future patient encounters.

As with all laboratory tests, providers need to be wary of adverse outcomes that can arise from improper interpretation of the results of near-patient and POC tests. Overreliance on POC test results may lead a clinician to miss a diagnosis if the test returns a false-negative result, which can lead to adverse outcomes, either in terms of progression of illness in the patient or continued spread of the

untreated disease. False positives, due to contamination, colonization, or incorrect interpretation, may result in inappropriate treatment.

If near-patient and POC tests are utilized wisely as part of the clinical decision-making process, they have the potential to reduce the spread of disease by reducing the time to treatment. Their use can improve a healthcare facility use by reducing the amount of time that a patient waits in the facility and by reducing the resources needed to follow up on laboratory-based test results. Reducing the time that a patient spends in a doctor’s office or emergency room can decrease the exposure to other patients who may be contagious. Specimens for testing could even be collected at home and sent for testing to a reference laboratory, obviating the need to visit the physician’s office or emergency department altogether; if results can be returned rapidly, POC test results may also reduce the spread of disease by optimizing antimicrobial therapy earlier in the course of infection. Appropriately treating only patients with infections improves patient outcomes and improves judicious use of antimicrobial agents, which decreases adverse events and the development of antimicrobial-resistant organisms.

Examples of near-patient and POC tests that may improve patient care include those for HIV, STIs, TB (especially in high-burden developing countries), sepsis, and GAS infections. A review of POC tests for HIV mentions clinical benefits, such as earlier treatment initiation, reduced loss to follow-up, and



POC tests will enable much more in-home testing for infectious diseases in the future.

improved linkage to care and treatment (Drain and Rousseau 2017). A review of POC tests for STIs reports findings from a mathematical model that molecular POC tests with high sensitivity can reduce the prevalence of chlamydia and gonorrhea in high-prevalence settings; even POC tests with lower sensitivity can result in additional patients being treated (Gaydos and Hardick 2014).

Utilization of near-patient and POC testing will likely impact (besides clinical outcomes) patient satisfaction, which is becoming increasingly important to providers and healthcare systems. Receiving a diagnosis and appropriate treatment at the time of service might increase patient satisfaction by decreasing diagnostic delays due to reflex testing that requires patient follow-up. More-efficient workflows as a result of increased POC testing may result in healthcare providers spending more time with their patients and addressing their questions, thus increasing satisfaction scores.

POC tests will enable much more in-home testing for infectious diseases in the future. In-home tests may lead to increased patient satisfaction due to convenience, may be an attractive option for indications for which privacy is an issue, and may reduce the spread of disease (from a mildly ill patient with a positive test who self-isolates or to a well patient with a negative test who does not present to healthcare). Currently, in-home antibody tests for HIV in saliva specimens can provide results in 20 minutes (<http://www.oraquick.com/>). FDA-cleared in-home sample collection kits for HIV and hepatitis C from fingerstick blood samples allow the patient to mail their specimen to a laboratory for testing. Additional kits for GAS, gonorrhea, chlamydia, and influenza will likely be available soon. Patients could collect their own samples at home and either bring the specimen into a laboratory or run the test at home.

The use of in-home tests will bring specific challenges. Clear and concise sample collection instructions will be critical for in-home testing. To ensure correct sample collection, instructions could be accompanied by QR codes that link to training videos. These videos might also be useful for nonlaboratorian staff in convenient care clinics or pharmacies who may not have extensive experience with specimen collection. Instructions should be provided in multiple languages to expand adoption of the technology. Additionally, specific in-home collection kits could be developed with specialized equipment to make sample collection easier for the public.

Effects on Public Health Response

Public health surveillance is important for monitoring the epidemiology of infectious diseases, identifying outbreaks or epidemics, and informing strategies to address the spread of disease. It is also an important way to get “feedback” on how diagnostic tests perform for the most contemporary version of a particular infection. Reporting to public health agencies, ideally automatically, should be part of a system that utilizes POC testing.

Because of the nature of near-patient and POC testing, care must be taken to ensure that public health surveillance of infectious diseases can be maintained. Pathogen characterization, such as strain typing, may be needed for public health agencies to link cases to an outbreak. Public health agencies have traditionally needed isolates in pure culture for pathogen characterization and analysis, but near-patient and POC tests are culture independent. Some near-patient and POC collection devices inactivate any pathogens present or deplete the entire specimen, making follow-up testing impossible. Thus, POC test users would need to collect another specimen to submit to public health laboratories. In some cases, strain typing is the standard of care (e.g., *Salmonella* typing), but in cases in which it is not, it is unclear who will pay for the additional specimen collection (if needed) and the typing necessary for public health purposes but not for the immediate care of the patient. In anticipation of increased near-patient and POC culture-independent testing, test users, clinical microbiology laboratories, and public health agencies need to develop methods to allow for continued public health surveillance (Langley et al. 2015).

With an increase in culture-independent testing and decentralized data sets, it might be more difficult to recognize outbreaks quickly, especially if testing is performed in small independent physician offices not connected to healthcare or public health systems. However, if test results are sent to a central repository for surveillance, the increase in data flow may allow outbreaks to be identified more quickly. To harness that benefit, systems that allow for data sharing, with outbreak monitoring and alert systems built in, must be implemented to enable a coordinated public health response. When relevant surveillance information is shared with public health authorities, it is important that patient confidentiality be maintained.

Data Connectivity

With near-patient and POC tests being performed in an increasing number of settings and with the possibility for increased numbers of home-based testing platforms, it is important that all test results be linked to a patient's EMR if possible or be made accessible at least to the patient's provider(s). The fragmentation of laboratory testing may necessitate a paradigm shift in the collation of results. In the future, patients may gain increased ownership of their healthcare data; for example, in 2014 the Department of Health and Human Services amended CLIA regulations to give patients direct access to their completed laboratory test reports (<https://www.hhs.gov/hipaa/for-professionals/special-topics/clia/index.html>). Rather than each healthcare system or provider individually holding a patient's data and granting access of the data to the patient, in the future, patients may have a singular EMR database or a personal health record that contains all of their EMR data, and patients might grant access of the data to their providers (<https://www.healthit.gov/providers-professionals/faqs/what-personal-health-record>).

Information technology (IT) solutions to link databases are needed to allow portability of POC test results so that the results of tests can be submitted back to the patient's medical record. For example, sharing data could be achieved through a test device that is electronically interfaced with the patient's EMR, which would forward results automatically. Alternatively, if that is not available, patients could load test results into their smartphone or a Web portal and upload to their EMR. Informatics support and IT security measures are needed to encrypt data and ensure data protection and confidentiality.

While connectivity and sharing of test results are not currently routine practice in all settings, test manufacturers should include clear wording on the test package regarding the importance of sending test results to the patient's EMR so that they are readily available to all of their healthcare providers. Applicable methods for sharing results from the particular test should be developed. In the future, there may be mandates to share data with the patient's EMR or to link with public health surveillance reporting. Test users can provide feedback to industry regarding how best to incorporate connectivity features into future tests.



Oversight of Near-Patient and Point-of-Care Tests

Clinical microbiology laboratories traditionally ensure that diagnostic testing is accurate and safe. With the changing paradigms for infectious disease diagnostics, personnel without specific laboratory medicine training, who may not be accustomed or required to perform proficiency testing or quality assurance, will perform testing. There is a strong potential for misuse, incorrect performance, and misinterpretation of tests, especially as tests extend to nontraditional settings. In addition, chemical and biological safety standards need to be maintained when implementing near-patient and POC tests. Clinical laboratory expertise will still remain an important component of oversight of such near-patient and POC tests as they move to being performed by nonlaboratorians.

Clinical Microbiology Laboratory Oversight

Colloquium participants noted that when clinical microbiology expertise is available in a healthcare setting, the laboratory should retain oversight of the quality assurance of infectious disease diagnostic tests, even those that are performed outside the laboratory.

However, lack of staffing is currently a challenge for clinical microbiology laboratories. With increased diagnostic testing for infectious diseases performed outside central laboratories, additional staffing

models or support may be needed to oversee competency, proficiency, and quality assurance. New staffing models may result in laboratory technologists transitioning from performing testing to overseeing tests performed outside the laboratory. Alternatively, a new type of healthcare worker certified in POC testing may be needed to fulfill the oversight functions. Most large facilities currently employ clinical laboratory scientists as POC coordinators to manage POC tests (including those for infectious indications and others). The American Association for Clinical Chemistry offers a Point-of-Care Specialist certificate program (<https://www.aacc.org/store/certificate-programs/9600/point-of-care-specialist-certificate-program>), and there are postbaccalaureate programs in clinical laboratory science that can provide advanced training. Specific training could be developed, with input from clinical microbiology laboratory experts, regarding competency and proficiency for infectious disease tests.

Colloquium participants felt strongly that the central laboratory should remain responsible for monitoring for environmental contamination when NAATs are used to decrease problems with false-positive results. Laboratory or site personnel can conduct “swipe testing,” in which swabs or pledgets are used to sample various areas of the test setting and then subjected to NAATs to detect any contaminating nucleic acid that may be



present (Mohl et al. 2016). Clinical microbiology laboratory technicians possess expertise that can guide the procedures and schedules for swipe testing and other forms of contamination risk management and that can assist with interpretation of results or necessary decontamination.

Oversight in Other Settings

Near-patient and POC testing will also be performed in small physician-run laboratories as well as nonmedical settings. In those settings, the routine oversight afforded by regular contact with the clinical microbiology laboratory is unavailable. Voluntary frameworks for ensuring oversight and seeking relevant expertise may be useful. Clinical microbiology laboratory expertise may be obtained in these settings through employing consultants or part-time staff to review POC testing, similar to how infection control expertise may be obtained in nursing home facilities. Another option for oversight is a “self-monitoring” electronic system that assesses results from POC tests and alerts when results fall outside normal baselines, for example, when there is a strong increase in influenza-positive tests in summer, which may indicate erroneous test results. It is imperative that competent personnel review results on a regular basis to ensure that rapid action is initiated if any anomalies are identified. Site personnel would also need to monitor contamination, with consultant staff aiding with interpretation and decontamination as needed.

As the healthcare landscape changes, accreditation and state oversight may provide additional avenues for oversight of POC testing. The Joint Commission accredits hospitals, laboratories, and ambulatory healthcare settings, among others, including convenient care clinics (<https://www.jointcommission.org/>). COLA (an organization that “accredits almost 8,000 medical laboratories and provides the clinical laboratory with a program of education, consultation, and accreditation” [<http://www.cola.org/>]) is an option for reaching small physician-run laboratories. State-mandated oversight is also an option for monitoring testing, although requirements vary by state and only a small percentage of locations may be reviewed each year. In addition, the current requirement for a prescription for infectious disease diagnostic tests will provide some level of control and oversight over POC testing.

With increased infectious disease testing using more-powerful and -complex methods occurring outside clinical microbiology laboratories and in new settings, mandatory oversight of CLIA-waived tests may be considered. Colloquium participants discussed whether CLIA, as it currently exists, fits the changing paradigm of POC testing or whether it needs to be updated to conform to expanding testing and emerging technologies. Oversight would meaningfully alter what a certificate of waiver entails, but it may be beneficial, as increased testing leads to increased potential for and consequences of error. Oversight of CLIA-waived testing could be initiated through regulations or rule making but would have to balance the intended goals of quality and access.

Ordering and Interpretation

Quality assurance of test performance must be coupled with assurance that tests are properly ordered and interpreted. No test has perfect sensitivity and specificity, resulting in false positives and false negatives; the pretest probability of a particular result can vary by setting and by season, affecting where and when the test may be appropriate, and contamination or colonization may return positive results that should not result in patient treatment. Clinical microbiology laboratories are able to provide feedback regarding the tests physicians order or amend comments to the patient report to document issues that may affect interpretation, but the ability to do so is lost for near-patient and POC testing. Educated or trained personnel serving as “learned intermediaries” might be appropriate for settings without dedicated clinical microbiology laboratory expertise to inform test ordering and interpretation. As with the personnel for test oversight, this may be a position that is filled on a consultant or part-time basis.

Regardless of which methods a setting enacts to ensure proper oversight and interpretation of near-patient and POC tests, an outreach program with training and education is needed as this testing is rolled out. Both providers and patients need to be educated on the tests that are available and the appropriateness of each for a particular setting and patient population. Clinical laboratory professionals will need to acquire new skills and expand the concept of a “laboratory” to encompass and contribute to a complex network of centralized and distributed testing capabilities.

Evaluation of Near-Patient and Point-of-Care Tests

With the potential for near-patient and POC tests to expand in use and to additional settings, solid data regarding outcomes and cost-effectiveness are needed to make informed decisions regarding the use and further development of these tests. In addition, appropriate evaluation and regulation of tests can ensure that tests function as intended and identify tests that do not perform to specifications.

Clinical Outcome Studies

While the potential benefit to patient care of near-patient and POC tests would be rapid diagnostic results to guide treatment, there is a need for high-quality clinical outcome studies to demonstrate the actual value of these tests to patient care. Colloquium participants expressed concern that few outcome studies have been published. Published clinical trials and multicenter studies are needed to determine whether near-patient and POC tests improve patient care and clinical outcomes.

Outcome studies should examine one syndrome at a time and consider the setting, which influences the pretest probability of a particular pathogen. Clinical microbiologists can collaborate with other stakeholders, such as hospital administrators, laboratory administrators, statisticians, and mathematical modelers, to assist with study design and analysis. In particular, the U.S. Preventive Services Task Force, which grades recommendations for clinical preventive services based on the strength of the evidence and the balance of benefits and harms, might provide a model for structuring and analyzing outcome studies (<https://www.uspreven->

[tiveservicestaskforce.org](https://www.uspreventiveservicestaskforce.org)). Along with impacts on patient care, studies can also examine benefits to society, such as reduced disease transmission or more-judicious antibiotic use.

Funding will be needed to complete the outcome studies. Potential sources include funding related to the National Action Plan for Combating Antibiotic-Resistant Bacteria, funding from the Agency for Healthcare Research and Quality, or funding from philanthropy and foundations, such as the CDC Foundation.

Along with outcome studies by syndrome to show the benefit of near-patient and POC testing generally, there is a need to evaluate particular tests. Tests need to be accurate and safe to be FDA cleared, but not all FDA-cleared tests are the best available test for their stated indication. Colloquium participants suggested large-group evaluations of all POC tests for a particular agent as an information source to analyze tests, similar to the evaluation of rapid influenza diagnostic tests for the detection of H1N1 virus in 2009 (Balish et al. 2009). An impartial evaluator could review the tests and award a “quality seal” to tests that perform according to certain specifications. Another option is to alter practice guidelines to recommend the exclusive use of POC tests that meet a minimum threshold of sensitivity and specificity. Alternatively, data from outcomes studies could be fed into a central repository and assessed by an ongoing algorithm to determine test quality. Federal agencies, such as the CDC, FDA, NIH, or CMS, might be involved in developing criteria for such evaluations.

POC Tests for Group A *Streptococcus* (GAS)

Several lateral-flow antigen tests exist for GAS. At best, these are approximately 85% sensitive. Specimens from children and adolescents that are negative by the rapid test are recommended to be cultured as a backup, as the antigen test misses a number of infected patients who may go on to develop complications or spread the infection (Shulman et al. 2012). Nucleic acid tests for GAS, which demonstrate higher sensitivity than antigen tests, have eliminated the need for reflex culture (Wang et al. 2016). A quality seal or practice guidelines could inform providers that the nucleic acid tests perform on par with gold standard laboratory testing and encourage their use.

Cost-Effectiveness Studies

Insufficient data on the cost of implementing POC testing compared to the cost of laboratory-based diagnostic testing exist. Considering the cost of the test itself, it is almost always more expensive to do a test at the point of care than in the laboratory. The labor cost for personnel who are performing the test significantly contributes to POC testing expenses. With increased emphasis on value-based healthcare driving reimbursement decisions, facilities need to be able to demonstrate the return on investment of near-patient and POC tests.

Justification for these increasingly expensive tests may come from downstream metrics, such as improved clinical outcomes, reduction in disease transmission, better utilization of costly in-hospital testing (e.g., magnetic resonance imaging or computed tomography scans), expedited patient healthcare encounters, reduction in unnecessary or inappropriate antibiotic prescriptions, and increased patient satisfaction. Early diagnosis and treatment may avert the cost of repeat visits to the clinician, emergency room visits, or hospital admission if the disease progresses. Cost-effectiveness research is needed to determine whether the cost of a POC test is justified based on downstream effects (Hsieh et al. 2014, Hsieh et al. 2016, Soto et al. 2016).

Evaluating the true value of near-patient and POC tests may involve new methods to determine cost savings. Due to slowed and decreased budgets in healthcare systems, the cost savings (or additional reimbursement) afforded by a POC test may be realized in a department other than the one ordering or performing the test. A test performed in an emergency department may be accounted under different billing algorithms than a test performed in a laboratory. POC tests might even shift the burden of payment away from the medical system and increase the amount that patients are billed if the tests are not covered by insurance or are purchased over the counter. Healthcare economics expertise is needed to study the true costs and value of POC tests in relation to those ordering the tests, those performing the tests, the patient being tested, and the public's health.

With the development and implementation of new technologies, the cost of each near-patient

and POC test is predicted to decrease, but the overall volume and total expense of POC testing is expected to increase. Market drivers, including healthcare competition and patient expectations, may lead to increased adoption of POC testing.

Test Regulation

While a number of tests that can be utilized in near-patient and POC settings have been cleared or approved by the FDA, some may be of higher quality than others. Once a test is on the market and substantially equivalent tests are able to be cleared through the 510(k) process, it is very difficult to remove those tests from the market, even if they are no longer the best test for the stated indication. With the current regulatory paradigm, colloquium participants discussed options for reviewing tests on the market and possible regulatory considerations.

Mechanisms for tracking and identifying contamination events, such as a high frequency of test failures, including leaking test cartridges or tubes, should be developed. For example, test users could report postmarketing adverse events to the FDA. The FDA's MedWatch website (<https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting,home>) explains what constitutes an "adverse event." Some issues, however, may be mischaracterized as local problems when in fact they are more widespread. Based on the information received through adverse-event reporting, the FDA further investigates issues and takes any appropriate regulatory actions.

It is also possible to reclassify some devices when issues arise. For example, the FDA recently reclassified rapid influenza detection tests from class I to class II devices and has issued special controls for these tests (Federal Register 2014). Issues with current tests include an advance in the predicate technology (PCR, not viral culture) since approval and the poor sensitivity of some assays, especially for newly emerged influenza viruses. Special controls necessitate clinical performance criteria, annual analytical reactivity testing, and testing with newly emergent influenza viruses to ensure that the tests deliver meaningful results.

Outcome studies should examine one syndrome at a time and consider the setting...

Recommendations

Automation, simplification, and miniaturization of diagnostic tests, including CLIA-waived NAATs, are bringing about a new paradigm for diagnostic testing for infectious diseases in which tests are performed outside traditional clinical microbiology laboratory settings. Innovative developers and the financial community continue to advance the technology, enabling tests to improve in sensitivity and specificity while decreasing turnaround time and complexity. Clinical practice is responding by developing new workflows to incorporate rapid testing and by introducing near-patient and POC tests to new settings, such as convenient care clinics. Near-patient and POC tests

can improve patient care and public health by reducing the progression and spread of disease and optimizing treatment.

While these rapid diagnostic tests have the potential to deliver timely results to make treatment decisions, thoughtful expertise is needed to guide the development, utilization, and interpretation of tests to ensure maximum benefits. If tests are not used and interpreted correctly, or if inadequate tests are used, adverse outcomes may occur. Colloquium participants developed a number of recommendations to guide the implementation, oversight, and evaluation of near-patient and POC testing.

Implementation

Redesign clinic workflows to incorporate near-patient and POC testing.

Shifting patient flow to collect the specimen at the beginning of a clinical encounter will allow test results to be available before a provider sees the patient.

Promote proper interpretation of tests to avoid adverse outcomes.

Even the best-quality tests are subject to false-positive and false-negative results. Clinicians must consider test characteristics and the patient's clinical presentation when making treatment decisions informed by near-patient and POC tests.

Provide resources, such as training videos, to support appropriate self-collection of patient specimens.

In-home tests for infectious indications may lead to increased patient satisfaction and reduced spread of disease. Training videos available online, accompanied by clearly written instructions in multiple languages, can help to ensure correct sample collection.

Ensure that public health surveillance of infectious diseases is maintained with POC testing.

If possible, near-patient and POC test providers should continue the traditional elements of public health surveillance (strain typing, specimen or isolate submission). At a minimum, near-patient and POC test results for reportable diseases must be shared with public health agencies to allow for a coordinated response.

Link near-patient and POC test results to the patient's EMR.

Results of near-patient and POC tests should be automatically linked with a patient's EMR, with results available to the patient and all necessary healthcare providers.

Oversight

Maintain clinical microbiology laboratory expertise and oversight of infectious disease tests.

The clinical microbiology laboratory should retain oversight of quality assurance, competency, and proficiency testing related to infectious disease tests performed outside laboratories, as well as of detection of contamination. Settings lacking clinical microbiology laboratory expertise may employ consultants or part-time personnel.

Utilize competent personnel to oversee ordering, testing, and interpretation.

Personnel could be certified in clinical laboratory science or POC testing with specific training in infectious disease tests. "Learned intermediaries" can use clinical microbiology laboratory expertise to inform appropriate test ordering and interpretation.

Educate providers and patients on different types of tests.

Providers and patients should understand the tests that are available, including differences in sensitivity and specificity and the appropriateness of each test for a particular setting and patient population.

Evaluation

Conduct clinical outcomes and cost-effectiveness studies for near-patient and POC tests.

Near-patient and POC tests can allow for early diagnosis and treatment, which may reduce disease progression and spread of disease, but studies are needed to confirm clinically relevant outcomes. Utilization of these tests may avert the cost of additional diagnostic tests, repeat visits to the clinician, emergency department visits, hospital admission, or lengthy hospital stays. Funding, whether from philanthropy, foundations, or other sources, will be needed to complete the studies.

Evaluate near-patient and POC tests periodically and undertake regulatory action or reclassification for tests that do not meet performance standards.

Studies could determine performance characteristics for tests that are already on the market and whether any regulatory action is warranted. In cases where tests of varying quality exist on the market, an impartial evaluator could award a "quality seal" for high-performing tests, and/or professional societies which represent clinical stakeholders could recommend against the use of specific assays that are known to perform poorly.

Conclusion

Near-patient and POC testing for infectious disease diagnostics is rapidly evolving. CLIA-waived NAATs have performance characteristics similar to those of more-complex, gold standard laboratory assays. The impact that these new assays will have on patient outcomes, healthcare delivery models, public health, and healthcare costs is still not clear. The role that clinical microbiology laboratories will play in advanced POC tests for infectious diseases is changing. As near-patient and POC testing is increasingly implemented in new settings and by nonlaboratorians, clinical microbiology laboratory expertise is needed to ensure proper oversight of quality assurance, competency, and proficiency testing. Integration of POC tests into electronic systems, along with automated quality monitoring, can greatly improve their contribution to diagnostic microbiology. Utilization of trained personnel and evaluation of tests will ensure that the best-quality tests are ordered and interpreted correctly to benefit patient care.



References

- Balish A, Warnes CM, Wu K, Barnes N, Emery S, Berman L, Shu B, Lindstrom S, Xu X, Uyeki T, Shaw M, Klimov A, Villanueva J. 2009. Evaluation of rapid influenza diagnostic tests for detection of novel influenza A (H1N1) virus—United States, 2009. *MMWR Morb Mortal Wkly Rep* 58(30):826–829.
- Benitez AJ, Winchell JM. 2013. Clinical application of a multiplex real-time PCR assay for simultaneous detection of *Legionella* species, *Legionella pneumophila*, and *Legionella pneumophila* serogroup 1. *J Clin Microbiol* 51:348–351. doi:10.1128/JCM.02510-12.
- Boehme CC, Nabeta P, Hilleman D, Nicol MP, Shenai S, Krapp F, Allen J, Tahirli R, Blakemore R, Rustomjee R, Milovic A, Jones M, O'Brien SM, Persing DH, Ruesch-Gerdes S, Gotuzzo E, Rodrigues C, Alland D, Perkins MD. 2010. Rapid Molecular Detection of Tuberculosis and Rifampin Resistance. *N Engl J Med* 363:1005–1015 doi: 10.1056/NEJMoa0907847
- Bourbeau PP, Ledebouer NA. 2013. Automation in clinical microbiology. *J Clin Microbiol* 51:1658–1665. doi:10.1128/JCM.00301-13.
- Buchan BW, Ledebouer NA. 2014. Emerging technologies for the clinical microbiology laboratory. *Clin Microbiol Rev* 27:783–822. doi:10.1128/CMR.00003-14.
- Chartrand C, Leeflang MGM, Minion J, Brewer T, Pai M. 2012. Accuracy of rapid influenza diagnostic tests: a meta-analysis. *Ann Intern Med* 156:500–511. doi:10.7326/0003-4819-156-7-201204030-00403.
- Cosgrove DM, Fisher M, Gabow P, Gottlieb G, Halvorson GC, James BC, Kaplan GS, Perlin JB, Petzel R, Steele GD, Toussaint JS. 2013. Ten strategies to lower costs, improve quality, and engage patients: the view from leading health system CEOs. *Health Aff* 32:321–327. doi:10.1377/hlthaff.2012.1074.
- Dheda K, Ruhwald M, Theron G, Peter J, Yam WC. 2013. Point-of-care diagnosis of tuberculosis: past, present and future. *Respirology* 18:217–232. doi:10.1111/resp.12022.
- Drain PK, Rousseau C. 2017. Point-of-care diagnostics: extending the laboratory network to reach the last mile. *Curr Opin HIV AIDS* 12:175–181. doi:10.1097/COH.0000000000000351.
- Drancourt M, Michel-Lepage A, Boyer S, Raoult D. 2016. The point-of-care laboratory in clinical microbiology. *Clin Microbiol Rev* 29:429–447. doi:10.1128/CMR.00090-15.
- Federal Register. 2014. Microbiology devices: reclassification of influenza virus antigen detection test systems intended for use directly with clinical specimens. *Fed Regist* 79:29387–29392. <https://www.gpo.gov/fdsys/pkg/FR-2014-05-22/pdf/2014-11635.pdf>.
- Gaydos CA, Hardick J. 2014. Point of care diagnostics for sexually transmitted infections: perspectives and advances. *Expert Rev Anti Infect Ther* 12:657–672.
- Gaydos CA, Jett-Goheen M, Barnes M, Dize L, Hsieh Y-H. 5 August 2016. Self-testing for *Trichomonas vaginalis* at home using a point-of-care test by women who request kits via the Internet. *Sex Health* doi:10.1071/SH16049.
- Gaydos CA, Solis M, Hsieh Y-H, Jett-Goheen M, Nour S, Rothman R. 2013. Use of tablet-based kiosks in the emergency department to guide patient HIV self-testing with a point-of-care oral fluid test. *Int J STD AIDS* 24:716–721. doi:10.1177/0956462413487321.
- Gialamas A, Yelland LN, Ryan P, Willson K, Laurence CO, Bubner TK, Tideman P, Beilby JJ. 2009. Does point-of-care testing lead to the same or better adherence to medication? A randomised controlled trial: the PoCT in General Practice Trial. *Med J Aust* 191:487–491.
- Ginocchio CC, Zhang F, Manji R, Arora S, Bornfreund M, Falk L, Lotlikar M, Kowerska M, Becker G, Korologos D, de Geronimo M, Crawford JM. 2009. Evaluation of multiple test methods for the detection of the novel 2009 influenza A (H1N1) during the New York City outbreak. *J Clin Virol* 45:191–195. doi:10.1016/j.jcv.2009.06.005.
- Hsieh Y-H, Gauvey-Kern M, Peterson S, Woodfield A, Deruggiero K, Gaydos CA, Rothman RE. 2014. An emergency department registration kiosk can increase HIV screening in high risk patients. *J Telemed Telecare* 20:454–459. doi:10.1177/1357633X14555637.
- Hsieh Y-H, Gaydos CA, Hogan MT, Jackman J, Jett-Goheen M, Uy OM, Rompalo AM. 2012. Perceptions on point-of-care tests for sexually transmitted infections—comparison between frontline clinicians and professionals in industry. *Point Care* 11:126–129. doi:10.1097/POC.0b013e-31825a25e8.
- Hsieh Y-H, Gaydos CA, Hogan MT, Uy OM, Jackman J, Jett-Goheen M, Albertie A, Dangerfield DT, Neustadt CR, Wiener ZS, Rompalo AM. 2011. What qualities are most important to making a point of care test desirable for clinicians and others offering sexually transmitted infection testing? *PLoS One* 6:e19263. doi: 10.1371/journal.pone.0019263.
- Hsieh Y-H, Hogan MT, Barnes M, Jett-Goheen M, Huppert J, Rompalo AM, Gaydos CA. 2010. Perception of an ideal point-of-care test for sexually transmitted infections—a qualitative study of eight structured group discussions. *PLoS One* 5:e14144. doi:10.1371/journal.pone.0014144.
- Hsieh Y-H, Holtgrave DR, Peterson S, Gaydos CA, Rothman RE. 2016. Novel emergency department registration kiosk for HIV screening is cost-effective. *AIDS Care* 28:483–486. doi:10.1080/09540121.2015.1099603.
- The Joint Commission. 2016. Approved: new antimicrobial stewardship standard. *Joint Comm Perspect* 36:1–8. https://www.jointcommission.org/assets/1/6/New_Antimicrobial_Stewardship_Standard.pdf.
- Langley G, Besser J, Iwamoto M, Lessa FC, Cronquist A, Skoff TH, Chaves S, Boxrud D, Pinner RW, Harrison LH. 2015. Effect of culture-independent diagnostic tests on future emerging infections program surveillance. *Emerg Infect Dis* 21:1582–1588. doi:10.3201/eid2109.150570.
- Leber AL. 2014. Pertussis: relevant species and diagnostic update. *Clinics Lab Med* 34:237–255. doi:10.1016/j.cl.2014.02.003.
- Leber AL, Everhart K, Balada-Llasat J-M, Cullison J, Daly J, Holt S, Lephart P, Salimnia H, Schreckenberger PC, Desjarlais S, Reed SL, Chapin KC, LeBlanc L, Johnson JK, Soliven NL, Carroll KC, Miller J-A, Dien Bard J, Mestas J, Bankowski M, Enomoto T, Hemmert AC, Bourzac KM. 2016. Multicenter evaluation of the BioFire FilmArray Meningitis/Encephalitis Panel for the detection of bacteria, viruses, and yeast in cerebrospinal fluid specimens. *J Clin Microbiol* 54:2251–2261. doi:10.1128/JCM.00730-16.
- May L, Ware CE, Jordan JA, Zocchi M, Zatorski C, Ajabnoor Y, Pines JM. 2016. A randomized controlled trial comparing the treatment of patients tested for chlamydia and gonorrhea after a rapid polymerase chain reaction test versus standard of care testing. *Sex Transm Dis* 43:290–295. doi:10.1097/OLQ.0000000000000438.

- May LS, Rothman RE, Miller LG, Brooks G, Zocchi M, Zatorski C, Dugas AF, Ware CE, Jordan JA. 2015. A randomized clinical trial comparing use of rapid molecular testing for *Staphylococcus aureus* for patients with cutaneous abscesses in the emergency department with standard of care. *Infect Control Hosp Epidemiol* 36:1423–1430. doi:10.1017/ice.2015.202.
- Mehrotra A, Wang MC, Lave JR, Adams JL, McGlynn EA. 2008. A comparison of patient visits to retail clinics, primary care physicians, and emergency departments. *Health Aff (Millwood)* 27:1272–1282. doi:10.1377/hlthaff.27.5.1272.
- Mohl D, Stevenson JB, Binnicker MJ, Contezac JM. 2016. General aspects of molecular diagnostics, p 12.2.1–12.2.3.6. *In* Leber AL (ed), *Clinical microbiology procedures handbook*, 4th ed, vol 3. ASM Press, Washington, DC.
- Okada C, Kura F, Wada A, Inagawa H, Lee GH, Matsushita H. 2002. Cross-reactivity and sensitivity of two *Legionella* urinary antigen kits, Biotest EIA and Binax NOW, to extracted antigens from various serogroups of *L. pneumophila* and other *Legionella* species. *Microbiol Immunol* 46:51–54. doi:10.1111/j.1348-0421.2002.tb02676.x
- Pai M, Ghiasi M, Pai NP. 2015. Point-of-care diagnostic testing in global health: what is the point? *Microbe (Wash, DC)* 10:103–107.
- Pai NP, Vadnais C, Denkinger C, Engel N, Pai M. 2012. Point-of-care testing for infectious diseases: diversity, complexity, and barriers in low- and middle-income countries. *PLoS Med* 9:e1001306. doi:10.1371/journal.pmed.1001306.
- Popowitch EB, O'Neill SS, Miller MB. 2013. Comparison of the BioFire FilmArray RP, GenMark eSensor RVP, Luminex xTAG RVPv1, and Luminex xTAG RVP Fast multiplex assays for detection of respiratory viruses. *J Clin Microbiol* 51:1528–1533. doi:10.1128/JCM.03368-12.
- Reller LB, Weinstein MP, Murdoch DR. 2003. Diagnosis of *Legionella* infection. *Clin Infect Dis* 36:64–69. doi:10.1086/345529.
- Salimnia H, Lephart PR, Asmar BI, Prebelich D, Paulson E, Fairfax MR. 2012. Aerosolized vaccine as an unexpected source of false-positive *Bordetella pertussis* PCR results. *J Clin Microbiol* 50:472–474. doi:10.1128/JCM.01250-11.
- Schreckenberger PC, McAdam AJ. 2015. Point-Counterpoint: Large multiplex PCR panels should be first-line tests for detection of respiratory and intestinal pathogens. *J Clin Microbiol* 53:3110–3115. doi:10.1128/JCM.00382-15.
- Schroeder LF, Guarner J, Elbireer A, Castle PE, Amukele TK. 2016. Time for a model list of essential diagnostics. *N Engl J Med* 374:2511–2514. doi:10.1056/NEJMp1602825.
- Shulman ST, Bisno AL, Clegg HW, Gerber MA, Kaplan EL, Lee G, Martin JM, Van Beneden C. 2012. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. *Clin Infect Dis* 55:e86–e102. doi:10.1093/cid/cis629.
- Sokhna C, Mediannikov O, Fenollar F, Bassene H, Diatta G, Tall A, Trape JF, Drancourt M, Raoult D. 2013. Point-of-care laboratory of pathogen diagnosis in rural Senegal. *PLOS Neglected Tropical Diseases* 7:e1999. doi:10.1371/journal.pntd.0001999.
- Soto M, Sampietro-Colom L, Vilella A, Pantoja E, Asenjo M, Arjona R, Hurtado JC, Trilla A, Alvarez-Martínez MJ, Mira A, Vila J, Marcos MA. 2016. Economic impact of a new rapid PCR assay for detecting influenza virus in an emergency department and hospitalized patients. *PLoS One* 11:e0146620. doi:10.1371/journal.pone.0146620.
- Speert DP. 1998. Group A streptococcal carriage: can the troll be tamed? *Paediatr Child Health* 3:229–230.
- Wang F, Tian Y, Chen L, Luo R, Sickler J, Liesenfeld O, Chen S. 2016. Accurate detection of *Streptococcus pyogenes* at the point of care using the cobas Liat Strep A nucleic acid test. *Clin Pediatr (Phila)* 1:9922816684602. doi:10.1177/0009922816684602.
- Weigl BH, Gaydos CA, Kost G, Beyette FR, Jr, Sabourin S, Rompalo A, de los Santos T, McMullan JT, Haller J. 2012. The value of clinical needs assessments for point-of-care diagnostics. *Point Care* 11:108–113. doi:10.1097/POC.0b013e31825a241e.

Appendix

Changing Diagnostic Paradigms for Microbiology Colloquium Discussion Questions

- 1. How are pressures on clinical microbiology laboratories changing as a result of changing paradigms in medicine?**
[e.g., need for 24/7 labs; rapid tests are no longer “rapid” if they are batched or sit around; economic pressures; shrinking trained work force]
- 2. What are characteristics and applications of currently available rapid diagnostic tests?**
 - Distinguish between rapid diagnostics performed in clinical laboratories and those performed at the point of service
 - Distinguish between NAT based vs. other technologies in terms of potential for contamination, accuracy, patient safety, etc.
- 3. What are characteristics and applications of future or needed rapid diagnostic tests?**
 - What targets (infectious agents) are useful for developing POCTs?
 - Will targets of interest be variable based on type of clinic/health care system?
 - Will POC tests be in a single analyte format or in syndromic panels?
 - Is currently available methodology sufficient for future testing development of POCTs?
- 4. How do the sensitivity and specificity of rapid diagnostics and POCTs compare to standard laboratory-based assays?**
 - Will there be special concerns for syndromic panels, when a CLIA waiver is sought for a broader panel?
 - How will contamination events be identified and investigated, and who will be responsible?
 - Are there minimal acceptable performance criteria?
 - Distinguish between current performance and desired/necessary
- 5. How will rapid diagnostic tests affect clinical practice?**
 - How will POCTs alter clinic flow? Getting patients through the clinic and freeing up exam room space is critical. TAT longer than ~20 minutes could significantly delay the flow of patients through the clinic.
 - There is a perception among laboratorians that POC testing can be a threat to the lab and lab volume. As testing may shift to the clinic, requiring less skilled staff, what effect will be observed on laboratory staff?
- 6. How will rapid diagnostic tests affect public health response?**
 - How will diseases of public health concern be reported?
 - How will specimens/isolates be transferred to public health when necessary?
 - How will rapid diagnostics impact outbreak response?
- 7. How can rapid diagnostics and POCTs be utilized to improve patient care?**
 - Do POCTs change patient outcomes?
 - Do POCTs contribute to positive or negative patient satisfaction?
 - How can they support antimicrobial stewardship?
 - How do you measure an improvement in patient care? (this will be important to define and studies will need to be done to assess this)
- 8. What is the cost of implementing POC testing compared to laboratory-based diagnostics?**
 - Will POC testing positively or negatively affect cost of care?
- 9. Which approach (near patient or POCT) provides the optimal solution for healthcare? (in this case, defined as optimal clinical value/dollar)**
- 10. What are considerations for POCTs performed in different settings (physicians’ offices, convenient care clinics, homes)?**
[e.g., in cases where persons see a doctor regularly, is a POCT needed, or can they come back for follow-up?; performance needs to be independent of operator; esp. in non-healthcare settings; safety concerns for staff performing tests]
 - Who will be responsible for performing POC testing? Will tests account for the different skill level operators?
 - Who is responsible for competency and proficiency?
 - How will data be placed into a centralized electronic information system? [e.g., use of WIFI; use of cloud computing]
 - How will off-label testing be controlled/monitored?
 - What is the potential role for at-home testing?
- 11. Are there regulatory or clinical practice considerations for the future development/implementation of POCTs?**
[e.g., reporting strategies, reflexive testing, confirmatory testing]
 - Rapid flu tests have often been criticized for poor performance, which can partially be attributed to poor antibody/antigen match. An example might be a mutation in a virus that may impact assay performance. Should manufacturers be required to reevaluate POC tests after a defined period and update the tests as a condition of approval?

MICROBIOLOGY

SEX. M / F

American Academy of Microbiology
1752 N Street, NW
Washington, DC 20036

www.asm.org/academy

SOURCE

BLOOD

FLUID

THROAT

SPUTUM

CSF

NA

UR.

STOOL