AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology®

COMMENTARY

Advances Afoot in Microbiology

Robin Patel,[a,b] **Brad S. Karon**[c,d]

Division of Clinical Microbiology, Department of Laboratory Medicine and Pathology,[a] Division of Infectious Diseases, Department of Medicine,[b] Division of Clinical Core Laboratory Services, Department of Laboratory Medicine and Pathology,[c] and Point-of-Care Testing,[d] Mayo Clinic, Rochester, Minnesota, USA

ABSTRACT In 2016, the American Academy of Microbiology convened a colloquium to examine point-of-care (POC) microbiology testing and to evaluate its effects on clinical microbiology. Colloquium participants included representatives from clinical microbiology laboratories, industry, and the government, who together made recommendations regarding the implementation, oversight, and evaluation of POC microbiology testing. The colloquium report is timely and well written (V. Dolen et al., *Changing Diagnostic Paradigms for Microbiology*, 2017, https://www.asm.org/index.php/colloquium-reports/item/6421-changing-diagnostic-paradigms-for-microbiology?utm_source=Commentary&utm_medium=referral&utm_campaign=diagnostics). Emerging POC microbiology tests, especially nucleic acid amplification tests, have the potential to advance medical care.

KEYWORDS American Academy of Microbiology

Accepted manuscript posted online 24 May 2017

Citation Patel R, Karon BS. 2017. Advances afoot in microbiology. J Clin Microbiol 55:1984–1988. https://doi.org/10.1128/JCM.00664-17.

Editor Andrew B. Onderdonk, Brigham and Women's Hospital

Address correspondence to Robin Patel, patel.robin@mayo.edu.

The views expressed in this Commentary do not necessarily reflect the views of the journal or of ASM.

It would be impossible to argue that our lives have not changed because of technology. We grew up with land lines but rapidly adopted cell phones in the last century and then smart phones in recent years. Similarly, we left for college with typewriters, wrote our theses on university mainframes, and then migrated to desktop and laptop computers in the years that followed. Smartphones in our pockets today have as much computing power as the mainframes we started out with. Technology revolutions have been rapid and their adoption quick because technology has enabled improvements in our lives; we could not go back, and we have spent and continue to spend a surprising amount of money, sometimes seemingly without limits, on technology; we just have to have the latest and greatest.

As physicians, we were carefully trained to hand write our notes, manage our patients face to face (and sometimes over the phone), and evaluate printed laboratory results. As laboratorians, we saw rudimentary laboratory information systems in place during our training, but much of the work-up—the "microbiology work card," for example—was hand written. Today, this has changed, and for the better. Medicine, including laboratory medicine, has become electronic; this includes medical records, laboratory information systems, and even communications to and from the most important component of the system—our patients. Clinical microbiology testing is currently undergoing a parallel revolution, and an area poised to rapidly advance practice is point-of-care (POC) microbiology testing, especially POC NAATs (nucleic acid amplification tests).

POC tests are not new, of course; it is hard to imagine a world without them. Consider home pregnancy tests, for example. Interestingly, these tests were initially disfavored because they might render physicians less needed and cause "hysterical women" to harm themselves upon privately viewing their results; there was also concern that those using the tests would be unable to do so properly and that they might not seek prenatal care (1). These tests have now been available in the United States for more than 4 decades, and these concerns seem irrelevant today, when most women learn they are pregnant from a home pregnancy test (1). At just a few dollars

per test, the "…home-testing wand has become a bit of everyday magic" (1). The drivers of the current state are arguably the women who use these tests.

Although POC microbiology tests have not been around as long as home pregnancy tests, they are not new. POC tests for HIV evolved alongside other diagnostics for HIV, and home HIV tests have been available for over 2 decades—though they initially generated concerns similar to those raised about pregnancy tests (1). The American Academy of Microbiology colloquium report on POC microbiology tests is timely and well written (2). These tests will advance medical care; clinical microbiologists should embrace and be part of these developments.

POC microbiology tests have not always enjoyed great repute. As mentioned in the Academy's report, POC antigen-based testing for group A *Streptococcus* (GAS) is widely used because of its ease of performance, low cost, and short turnaround time; however, as a result of relatively low sensitivity, it is common to confirm negative results with culture, compromising the advantages of otherwise rapid testing (3). A similar situation exists with influenza virus antigen-based POC tests, which are also well covered in the report. NAATs for GAS, influenza virus, and an increasing number of other organisms and clinical syndromes overcome sensitivity limitations associated with GAS and influenza virus antigen-based testing (3). As a result, we adopted NAAT for the diagnosis of GAS pharyngitis a decade and a half ago (4), when no POC NAAT was available, with the test performed in the laboratory and a previously described system in place to expeditiously perform the test and fill the patient's antibiotic prescription if the test was found to be positive (3). Today, however, Clinical Laboratory Improvement Amendments-waived rapid NAATs are available for GAS (and influenza virus) detection (5, 6). These assays are not only advantageous in their ease of use and short turnaround time (≤15 min) but notably provide results commensurate with those of NAATs performed in the clinical laboratory (3). The low sensitivity of POC GAS and influenza virus antigen-based tests may have tainted the reputation of POC microbiology tests, but today, there is no reason why POC NAATs cannot recapitulate the results of NAATs performed in clinical laboratories, provided, of course, that they are developed and maintained to meet this standard.

Colloquium participants were appropriately concerned that POC microbiology tests would not be immune to some challenges of conventional microbiology NAATs, including contamination, changes in assay performance postmarketing, detection of organisms not causing patients' symptoms (e.g., colonizing organisms), etc. Several strategies to address these concerns are outlined in the report, including regulatory and accreditation suggestions, as well as postmarketing evaluations. We agree that, like all microbiology tests, POC tests should be periodically reevaluated because disease epidemiology changes over time as a result of changing vaccination practices, emerging infections, evolving antimicrobial resistance, new medical and surgical interventions, etc., alongside the rapid evolution of microorganisms in general. There should be a mechanism for postapproval surveillance of waived devices and removal of poorly performing POC tests from the market. Groups such as the Diabetes Technology Society are beginning to address the issue of postapproval surveillance of glucose meters, but the issue has received too little attention for other commonly used waived tests. Also, in our opinion, POC microbiology NAATs should be designed to be very rapid (≤20 min and even faster as technology improves)—it remains unclear whether devices with longer turnaround times will lead to more efficient care in the hospital or clinic environment.

Participants in the Academy's colloquium recommended that clinical microbiologists "retain oversight of the quality assurance of infectious disease diagnostic tests." This may not be possible in all instances; however, health care systems should ideally involve microbiologists knowledgeable about microbiology POC tests in the development, implementation, and maintenance of processes associated with the use of such tests. While we agree that clinical workflow redesign is needed, this may not be sufficient and instead, patient care processes may need to be redesigned (from scratch, in some instances) to incorporate this new type of testing. Consideration and approval

of new POC microbiology tests within health care systems should rely upon established groups with expertise in POC program management and oversight, including M.D. and Ph.D. laboratory directors, clinicians from patient care areas proposing to use POC tests, medical technologists, and POC coordinators. These groups may or may not now include microbiologists; however, input from microbiologists on the implementation of new infectious disease POC tests and systems for quality control will be essential. The basic principles of POC management and implementation are, however, unlikely to differ between infectious disease tests and any others.

If proponents of POC testing cannot define how patient care will be expedited or improved by receiving laboratory information faster, then outcomes are not likely to improve by implementing testing at the POC. All tests, not just POC tests, should be actionable, with the action(s) to be taken, whether the test is positive or negative, defined prior to test ordering. Systems need to be built to ensure that results seamlessly effect the appropriate action(s), including antibiotic prescription, which could be linked directly with test results in certain scenarios, especially if metadata, such as patient symptoms, comorbidities, and allergies, are incorporated into the determination, or the equally important action of no antibiotic prescription; furlough from school or work; isolation in health care settings; performance of follow-on testing, etc. Systems to automate these processes using informatics should be strongly considered; there are opportunities for clinical microbiologists to play a role in this. POC tests should enable less use of empirical antibiotic therapy, which will be advantageous in decreasing antibacterial resistance, cost, and anxiety associated with stopping a drug that was already started. It is estimated that 30% of antibiotics are inappropriately prescribed in outpatient settings (7); POC microbiology tests have the potential to improve this sobering statistic. However, it is important to realize that POC testing alone, without redesigned clinical protocols and practice models predicated on more rapid pathogen detection/identification, is unlikely to improve outcomes such as antibiotic use.

The Academy's colloquium report also recommends that training videos be provided to "to support appropriate self-collection of patient specimens." Although we agree that proper training videos might support self-collection of patient specimens, we note that patients can appropriately collect their own specimens with simple instructions in the absence of videos (8, 9) and suggest that care must be taken not to make processes of self-collection too complex.

Potential downsides to the increasing availability of POC tests, nicely emphasized in the report, include addressing newly recognized pathogens, and unfamiliar presentations of known pathogens. The report also highlights effects on public health practice; potential advantages for public health include rapid access to data, including numbers of tests being performed and results thereof (and therefore more rapid recognition of outbreaks), and the opportunity to monitor infectious diseases not traditionally tracked by public health workers and about which there is clearly more to learn. Similar to other POC implementation decisions, data management, connectivity, and features such as electronic lockout for failed quality control or unapproved users are essential to consider before implementing a new test. Advantages related to public health monitoring (and patient care) may be unrealized if data management and connectivity are not addressed during implementation.

We agree with colloquium participants that premiere issues to address are cost and lack of outcome studies. Cost will be a key driver, but it is not clear what will be acceptable. For home tests, the payer may, as with over-the-counter medications, be the patient, who will personally assess whether the test is worth it. In health care settings, downstream cost savings may compensate for costs of expensive POC microbiology NAATs. In this regard, the lack of outcome studies makes it difficult to define the value of POC testing to health care systems. We hope that industry will work to drive down costs of POC microbiology NAATs as technology advances make this possible, because we suspect that this will motivate increased use of POC tests, which will facilitate improvements in medical care.

Outcome studies, which are just now becoming common in microbiology (10), will

be important. Unfortunately, in many instances, these tests are simply "too new" for us to know exactly how to use them most effectively. For POC microbiology tests deployed within health care facilities (e.g., emergency departments, intensive care units), studies are needed to inform the appropriate utilization of these tests if they are more expensive than those performed in laboratories. Even sophisticated testing, such as spinal fluid testing for meningitis and encephalitis pathogens, may become available for POC use, for example, in emergency departments, as a tool to decide whether or not to admit a patient who may have enteroviral meningitis. Likewise, intensivists may benefit from POC microbiology testing of respiratory secretions. POC microbiology testing will ideally be performed algorithmically, with follow-on testing for positive and negative results (e.g., culture for antimicrobial susceptibility testing in the case of bacterial detection or additional testing in the case of a negative result) thoughtfully defined ahead of time. As pointed out, sequencing of patient evaluation and testing will need to be optimized to maximize the value of POC tests, but data to define what is ideal are lacking and details may vary, depending on the specifics of individual settings. Outcomes to be measured are myriad, including patient outcomes, patient and provider satisfaction, test and treatment (especially antibiotic) avoidance, infection transmission, etc. Patient satisfaction will be an important driver; many patients today are quite knowledgeable about medicine (thanks, in part, to other technologies) and are increasingly making decisions about their health care. Workflow efficiencies realized by using microbiology POC tests, including preempting the need for additional testing, procedures, hospitalization, etc., will likely further enhance patient satisfaction. Results of yet-to-be-performed outcome studies will need to be used to inform the development of practice guidelines for use of POC microbiology tests and also to inform ideal compositions of panels deployed by POC microbiology diagnostics companies. This will not be trivial, as, given the rapid evolution of microbiology technology, current guidelines often do not yet even address how to incorporate some NAATs performed in laboratories into clinical practice. Notably, some testing that we take for granted is controversial when the evidence is examined and will need to be reexamined in light of these new diagnostics. There is debate, for example, about whether or not diagnostic testing for GAS should be performed, and there has not been an evaluation of the role of POC NAATs for GAS in clinical medicine. Further, as pointed out by the colloquium authors, there are other causes of pharyngitis, including *Fusobacterium necrophorum*, group C and G streptococci, *Mycoplasma pneumoniae*, *Arcanobacterium haemophilum*, etc. that could be targeted by POC diagnostics, but if this is done, technology will be ahead of practice guidelines and additional data will be needed to determine how to manage patients testing positive for these organisms, and indeed, whether or not such testing is even needed. It is an exciting time, with opportunities for new studies to determine how best to use these new technologies in patient care.

Physicians take an oath to "first do no harm," a dictum that must be remembered as microbiology POC tests make their way into clinical practice. As highlighted in the report, panels with missing, medically unnecessary or underperforming, or extraneous targets may cause clinical confusion and even compromise patient safety. Ideally, industry, working with regulatory agencies, should be tasked with configuring and reconfiguring panels to maximally benefit patients and not to cause harm; clinical microbiologists can help in these deliberations. Panels should focus on necessary and sufficient analytes. Unfortunately, in many cases, the tail is wagging the dog here, since sophisticated tests are providing results the likes of which have never been available clinically. Therefore, assessing outcomes will need to be addressed iteratively—technology first, then outcome assessments, then revisions to technology, and so forth. This assessment is not easy, but it is exciting and provides new opportunities for clinical microbiologists to define the use of microbiology diagnostics in patient care, even if such testing is not actually performed in their laboratory.

Microbiology testing is more complex than pregnancy testing, as a result of the numerous and ever-expanding list of clinically relevant microorganisms, some of which have public health implications; changing epidemiology; evolving biodiversity; emerg-

ing antimicrobial resistance; and the evolution of pharmacotherapy and knowledge about how best to use it. However, with the arrival of POC infectious disease tests, especially NAATs, new opportunities exist to advance patient care. These tests will have distinct benefits in smaller health care settings, including in the rural United States, developing nations, and convenience clinics, and for home testing but overall will be an advance for all. There will be an evolving role of clinical microbiologists in POC testing for infectious diseases. Clinical microbiologists must become familiar with and continue to be knowledgeable about available POC diagnostics for infectious diseases and work within their health care systems to ensure their ideal use. At the same time, it is envisioned that, especially as the price of these tests falls (hopefully, this will happen), the nature of clinical microbiology laboratory testing will also evolve, focusing on complex testing and evaluation of challenging clinical cases. One may argue about whether POC microbiology tests are needed or are a convenience, but it does not matter, in our view. POC microbiology testing is here to stay and is what patients and many providers will want, if they do not already do so today.

ACKNOWLEDGMENTS

R.P. reports grants from BioFire, Check-Points, Curetis, 3M, Merck, Hutchison Biofilm Medical Solutions, Accelerate Diagnostics, Allergan, and The Medicines Company. R.P. is a consultant to Curetis. In addition, R.P. has a patent on a *Bordetella pertussis/B. parapertussis* PCR assay with royalties paid by TIB, a patent on a device/method for sonication with royalties paid by Samsung to the Mayo Clinic, and a patent on an antibiofilm substance issued. R.P. serves on an Actelion data-monitoring board. R.P. receives travel reimbursement and an editor's stipend from ASM and IDSA and honoraria from the USMLE, Up-to-Date, and the Infectious Diseases Board Review Course.

REFERENCES

1. Kennedy P. 29 July 2016. Could women be trusted with their own pregnancy tests? New York Times, New York, NY. https://www.nytimes.com/2016/07/31/opinion/sunday/could-women-be-trusted-with-their-own-pregnancy-tests.html?_r=0.
2. Dolen V, Bahk K, Carroll KC, Klugman K, Ledeboer NA, Miller MB. 2017. Changing diagnostic paradigms for microbiology. Report on an American Academy of Microbiology colloquium held in Washington, DC, from 17 to 18 October 2016. American Society for Microbiology, Washington, DC. https://www.asm.org/index.php/colloquium-reports/item/6421-changing-diagnostic-paradigms-for-microbiology?utm_source=Commentary&utm_medium=referral&utm_campaign=diagnostics.
3. Pritt BS, Patel R, Kirn TJ, Thomson RB, Jr. 2016. Point-counterpoint: a nucleic acid amplification test for *Streptococcus pyogenes* should replace antigen detection and culture for detection of bacterial pharyngitis. J Clin Microbiol 54:2413–2419. https://doi.org/10.1128/JCM.01472-16.
4. Uhl JR, Adamson SC, Vetter EA, Schleck CD, Harmsen WS, Iverson LK, Santrach PJ, Henry NK, Cockerill FR. 2003. Comparison of LightCycler PCR, rapid antigen immunoassay, and culture for detection of group A streptococci from throat swabs. J Clin Microbiol 41:242–249. https://doi.org/10.1128/JCM.41.1.242-249.2003.
5. Uhl JR, Patel R. 2016. Fifteen-minute detection of *Streptococcus pyogenes* in throat swabs by use of a commercially available point-of-care PCR assay. J Clin Microbiol 54:815. https://doi.org/10.1128/JCM.03387-15.
6. Cohen DM, Russo ME, Jaggi P, Kline J, Gluckman W, Parekh A. 2015. Multicenter clinical evaluation of the novel Alere i Strep A isothermal nucleic acid amplification test. J Clin Microbiol 53:2258–2261. https://doi.org/10.1128/JCM.00490-15.
7. Fleming-Dutra KE, Hersh AL, Shapiro DJ, Bartoces M, Enns EA, File TM, Jr, Finkelstein JA, Gerber JS, Hyun DY, Linder JA, Lynfield R, Margolis DJ, May LS, Merenstein D, Metlay JP, Newland JG, Piccirillo JF, Roberts RM, Sanchez GV, Suda KJ, Thomas A, Woo TM, Zetts RM, Hicks LA. 2016. Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010–2011. JAMA 315:1864–1873. https://doi.org/10.1001/jama.2016.4151.
8. Murray MA, Schulz LA, Furst JW, Homme JH, Jenkins SM, Uhl JR, Patel R, Cockerill FC, Myers JF, Pritt BS. 2015. Equal performance of self-collected and health care worker-collected pharyngeal swabs for group A *Streptococcus* testing by PCR. J Clin Microbiol 53:573–578. https://doi.org/10.1128/JCM.02500-14.
9. Dhiman N, Miller RM, Finley JL, Sztajnkrycer MD, Nestler DM, Boggust AJ, Jenkins SM, Smith TF, Wilson JW, Cockerill FR, III, Pritt BS. 2012. Effectiveness of patient-collected swabs for influenza testing. Mayo Clin Proc 87:548–554. https://doi.org/10.1016/j.mayocp.2012.02.011.
10. Banerjee R, Teng CB, Cunningham SA, Ihde SM, Steckelberg JM, Moriarty JP, Shah ND, Mandrekar JN, Patel R. 2015. Randomized trial of rapid multiplex polymerase chain reaction-based blood culture identification and susceptibility testing. Clin Infect Dis 61:1071–1080. https://doi.org/10.1093/cid/civ447.