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Right-Sizing Technology in the Era of Consumer-Driven Health Care

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Abstract

Technology for modern clinical and public health microbiology laboratories has evolved at an impressive rate over the last two decades. Contemporary diagnostics can rapidly provide powerful data that can impact patient lives and support infectious disease outbreak investigations. At the same time, dramatic changes to health care delivery are putting new pressures on a system that is now focusing on patient-centric, value-driven, convenient care. For laboratories, balancing all these demands in a cost-contained environment remains a challenge. This article explores the current and future directions of diagnostics in our dynamic health care environment.

Introduction

The Affordable Care Act (ACA) in the United States was enacted by President Obama in March 2010. The goal of the ACA was to improve the quality of and access to health care by transforming insurance coverage and lowering health care costs. We have seen shifts in health care plans (i.e., account-based health plans) that have the consumers of the health care opting for lower monthly premiums with higher deductibles. These deductibles are often paid for by personal health savings accounts, thus pushing the costs of health care onto the individual consumer. Couple this with an unprecedented boom in technology, which in some cases can offer on-demand diagnostics within the time of an office visit, and the result is consumer-driven health care, particularly for those who can afford it. Despite recent administrative changes in Washington and the uncertainty of “repeal and replace” in the Republican agenda for the current ACA, the trend toward consumer-driven health care, with an emphasis on pre-budgeted spending, is likely to continue.

For consumers of a product who will continue to pay more of the bill, the bright side of this trend is a movement to value-based care delivery from

the perspective of the affluent consumer. Value-based care is defined as safe, appropriate, and effective care at a reasonable cost, which is predicated on evidence-based medicine and proven outcomes. Patients are looking for more pricing transparency and more options for efficient care delivery (i.e., telemedicine, retail care providers, and mobile health solutions). Health care providers are trying to better understand consumer wants and needs, measure performance, and improve the patient experience; this is a distinct change from the historical fee-for-service system that did little to incentivize providers to produce value.

From the laboratory's perspective, there continue to be operational challenges to lead these changes. Emerging and re-emerging pathogens demand rapid responses at an unprecedented level. The skilled workforce continues to shrink, while the work demands go up. There are legislative influences on testing. At the same time, reimbursement and budgets are contracting. Yet still, at the end of the day, the laboratory is expected to produce quality results for improved patient care. Initiatives like antibiotic stewardship are helping to drive better outcomes with laboratory results, but many of these programs

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are dependent on post-analytical variables for the optimal impact on patient care to be realized [1,2].

Another key laboratory issue is the breath and scope of the technology that is now available. Today, we have molecular point-of-care (mPOC) devices that can provide a rapid diagnostic answer within 20 minutes in a clinic, multiplex PCR sample-to-answer devices that can screen for >20 analytes in a single specimen in about an hour, high-volume automation that can enhance throughput and efficiency in the clinical microbiology laboratory with digital imaging, and next-generation sequencing (NGS) that can reveal a treasure trove of information in a single test. Combined, the changes in health care and technology have left many laboratories asking how to “right-size technology” for routine care while transforming practice. Ultimately, change will depend on the goals that are driving the conversion and utilization of the technology into daily laboratory practice. Factors may include syndrome-specific diagnostic needs, ease of use, the need for rapid results, improved sensitivity and specificity, operational needs (such as staffing and expertise), laboratory design (such as centralized versus decentralized models), cost, consumer demand, and the potential for improved patient outcomes. The laboratory must weigh all these factors while trying to make a business case to improve service despite the fact that there are few or no outcome data available to support the use of new technology.

Technology comes at a cost that is often shifted to the consumer, the patient. While consumer choice can help push innovation, one also has to wonder to what extent the market will allow the significant increases in testing costs that can come with technology. For example, in the case of acute gastroenteritis which is typically a self-limiting infection with the majority of specimens coming from an outpatient setting, traditionally a stool culture would be ordered that would cost a patient less than \$100. The newer multiplex stool PCR panels can result in a charge that can cost a patient over \$1,000. Will patients be willing to bear paying this increased cost for such a diagnostic test long term? While one can agree that there is improved turnaround time, sensitivity and pathogen coverage in a sophisticated multiplex diagnostic assay, it must be used in conjunction with diagnostic algorithms that prevent needless additional downstream testing as well as excess costs. Clearly, there is a need for diagnostic stewardship alongside antibiotic stewardship to improve quality and the prudent use of health care dollars. This article explores the impact of technology on the clinical and public health microbiology laboratory in the age of consumer-driven health care.

POC Testing

Testing considerations

“Right-sizing technology” means that the right test is offered at the right time for the right patient with maximal operational efficiency and cost-effectiveness. The outcome of right-sizing is to provide results with the potential to inform therapeutic and infection control decisions for improved care and, ultimately, reduced downstream costs. The diagnostic testing needs of a medical institution such as Kaiser Permanente in Northern California,

which is comprised of 21 hospitals and over 200 medical offices spread out over a wide geographical area with over 3.5 million members and serviced by a central laboratory, are significantly different than those of a 500-bed county hospital with an on-site laboratory. Advances in technology have provided flexibility in diagnostic testing to address the differing needs of health care systems and the laboratories that serve them. For any given analyte, there are a number of highly sensitive and specific tests available from which to choose. Considerations that go into the selection of a test or instrument platform for implementation include perceived turnaround time needs for improved patient care, sample volume requirements, number of tests expected, suitability for the intended laboratory based on available expertise and desired workflow, as well as cost.

Implementation and oversight

In the past decade, manufacturers have targeted their research toward development of more sensitive and specific mPOC diagnostic infectious disease platforms and tests. Such mPOC tests have evolved for more practical use at the bedside. Manufacturers have appreciably simplified tests by removing the need for sample manipulation and handling. Instrumentation has become more automated and/or involves fully integrated systems that are portable or significantly smaller and more modular. Instruments have also incorporated mechanisms for recording and transmitting results. All the while, tests have become faster while demonstrating improved sensitivity and specificity [3]. These modifications in technology have enabled molecular testing to migrate from large central laboratories. Most POC tests are still moderately complex, which is defined by the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as one requiring basic laboratory knowledge and training for personnel performing the test. Users of these tests must adhere to CLIA regulatory requirements, which includes quality assurance, along with appropriate documentation, validation of analytical performance, proficiency testing, and ongoing competency training. CLIA director oversight is still required [4].

Increasingly, diagnostic molecular tests are being designed and submitted for CLIA-waived status. CLIA-waived tests are defined by the Food and Drug Administration (FDA) as being “so simple and accurate as to render the likelihood of erroneous results negligible; or pose no reasonable risk of harm to the patient if the test is performed incorrectly” [4,5]. Based on this definition, non-laboratorians can perform the test without CLIA director oversight if they are following the manufacturer’s instructions [4]. The first CLIA-waived mPOC test to receive FDA approval was the Alere i Influenza A&B in 2015. To better ensure quality results are being reported, some of the new mPOC tests have incorporated internal electronic and reagent quality control (QC) and have built in a shut-down mechanism in the event of failed QC. Since the waived testing program began in 1992, the number of approved CLIA-waived diagnostics has increased from 9 to over 100, with more than 20 analytes approved for infectious disease testing [6]. There are over 200,000 laboratories in the United States that now hold a certificate of waiver, which enables them to perform any CLIA-waived test [4].

However, just because anyone can perform the test does not mean they should. There must be an understanding of test limitations by all testing personnel. Few non-laboratorians realize that the central laboratory filters out many inappropriate specimens, and non-laboratorians require extensive training to understand the testing complexities of even waived tests. Laboratories frequently receive incorrectly collected specimens and are asked to test them because there is a lack of appreciation of why these specimens would not be tested. For example, *Clostridium difficile* testing is not performed on a formed stool specimen or for patients less than 1 year old due to the confounding issues of potential colonization, and as in a central laboratory, pre-analytical knowledge and conditions would need to exist to prevent misuse of testing. One question is whether we would be needlessly treating people in these cases if left to the facility performing the waived testing. Also, testing a specimen type that is not included in the intended use of an FDA cleared test will result in an off-label use of an assay.

Turnaround time and patient impact

Application of diagnostics in medicine is a balancing act between what we can do, what we need, and what we can afford. Diagnostics will continue to evolve. It will become faster, cheaper, and easier to perform, but technology comes at a price, and implementing new technologies with faster turnaround times nearer the patient requires careful thought about placement within the flow of the patients. Moving a rapid molecular test closer to the patient has the potential to have an immediate impact on therapeutic decisions.

A prospective cohort study examined the potential cost benefit of near-patient mPOC testing for *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) in a clinic based on reduction of contact attempts [7]. As part of the study, 1,356 patients who had CT/NG nucleic acid amplification tests (NAAT) also completed a questionnaire to ascertain the maximum time patients were willing to wait after consultation for CT/NG test results and thus the potential for immediate treatment of individuals testing positive while preventing unnecessary treatment of patients who tested negative. The study determined that of the 1,356 patients, 26.2% were unwilling to wait even 20 minutes for the results of an mPOC test. Based on the results from a questionnaire, of 129 patients who tested positive by a NAAT, use of a 20-minute mPOC test would have resulted in immediate treatment of 71.9% of the individuals, whereas a 90-minute test would have influenced the immediate treatment time of only 3.1% of these positive patients. Of 1,227 patients who tested negative for CT/NG by NAAT, use of a 20-minute mPOC test would have prevented 3.2% of empirical treatments, while a 90-minute mPOC test would have prevented 0.3% of the empirical treatments.

Another study looked at the impact of the 90-minute Xpert CT/NG test when sample collection was performed on arrival of the patient, with the intention being that the patients receive their results and treatment as needed during the appointment [8]. Actual wait times were evaluated. Only 21.4% of the patients received their results before leaving the clinic with the 90-minute Xpert test. It was determined that a test turnaround time greater than 30 minutes would likely not be effective, given that it took 48 minutes

from the time of sample collection to the clinical consultation. For such mPOC tests to affect patient management, results will need to be available at the time of consultation to maintain patient flow. There are limited studies examining the clinical impact of mPOC tests for other infectious diseases [9].

The Infectious Disease Society of America's practice guidelines for group A *Streptococcus* (GAS) currently recommends two-tiered testing for pediatric patients [10]. It is recommended that rapid antigen detection tests (RADTs) be performed on throat swabs due to the rapid turnaround time of the test (<10 minutes). However, due to the low sensitivity, bacterial cultures are recommended for confirmatory testing of negative RADTs. CLIA-waived mPOC GAS diagnostic tests with turnaround times comparable to those of the RADTs are becoming more readily available. These PCR tests do not detect group C or group G streptococci. However, they have been shown to have improved sensitivity for detection of GAS, even compared to culture [3,11]. Additional studies are needed to assess the clinical value of these tests and the potential for detection of low-level colonization.

In a retrospective study, Blaschke et al. [12] examined visits to U.S. emergency departments (EDs) using data from the National Hospital Ambulatory Medical Care Survey. They found that rapid influenza diagnostic tests (RIDT) were performed during 4.2 million visits and that 42% of influenza diagnoses were made in association with RIDT. Test results did suggest that some influence on physician behavior occurred, as patients diagnosed with influenza had fewer ancillary tests ordered (45% versus 53% of visits), fewer antibiotic prescriptions (11% versus 23%), and increased antiviral use (56% versus 19%) when the diagnosis was made in association with RIDT. Thus, diagnosis of influenza made in conjunction with RIDT resulted in fewer tests and antibiotic prescriptions and more frequent use of antivirals.

Early influenza virus antigen-based POC tests lacked sensitivity [13,14]. The newer mPOC tests are significantly more reliable and have the potential for improved outcomes in the POC environment [15]. However, as more mPOC options become available, it will be important for laboratories to continue to assess their performance, as not all mPOC tests may demonstrate the same sensitivity and specificity [16]. A recently published open-label, randomized, controlled trial looking at the routine use of mPOC testing of respiratory viruses in adults presenting to hospital with acute respiratory illness enrolled 720 patients (362 assigned to POC testing and 358 to routine care). The authors found that routine use of mPOC for respiratory viruses did not reduce antibiotic usage. However, many patients in the study were already started on antibiotics before the mPOC results were available. mPOC was also associated with a reduced length of stay and improved antiviral use [17].

The Clinical Laboratory and Diagnostic Effectiveness (CLADE) study was a prospective observational cohort study undertaken to assess the impact of a highly sensitive (97%) 20-minute CLIA-waived mPOC influenza test on patient management in the emergency department (ED) and associated economic benefit [18].

The study indicated that 57% of the ED physicians changed their management of patients, primarily of patients who tested influenza virus negative. The influenza test results impacted decisions about hospital admissions and discharges, ordering of additional medical procedures, and laboratory tests, as well as antimicrobial and antiviral usage. This model, applied to 2,000 ED visits, revealed a cost savings of nearly \$800,000 [19]. The study reiterated that getting the right information to the right people at the right time has the ability to impact clinical care.

The role of pharmacies

Community pharmacies have also become effective players in infectious disease management through provision of vaccinations and are increasingly offering POC tests. Over 5% of the laboratories with a certificate of waiver are in pharmacies [20]. A physician-pharmacist collaborative practice agreement (CPA) can be set up to delegate prescriptive authority to pharmacists for treatment of infectious diseases based on CLIA-waived POC test results. The use of this model has been shown to be effective for influenza virus and GAS [21,22].

In a pilot study conducted at 55 pharmacies in 3 states using the CPA model, pharmacists performed a CLIA-waived POC influenza test to screen individuals presenting with influenza-like symptoms [22]. Pharmacists provided oseltamivir to all individuals who tested positive for influenza virus by the POC test within an hour of the initial encounter. Meanwhile, individuals who tested negative for influenza virus did not receive inappropriate antiviral therapy.

In a similar pilot study, pharmacists performed a CLIA-waived POC GAS diagnostic test to screen individuals coming into the pharmacies with symptoms of pharyngitis [22]. About 13 million physician office visits are due to acute pharyngitis every year. Rates of antimicrobial use as high as 80% have been reported in the literature to treat pharyngitis, although GAS has been shown to be associated with only 10% to 30% of pharyngitis cases. Of the individuals screened in the study, about 18% tested positive for GAS and were thus treated with an antimicrobial consistent with prevalence studies. This study indicates a significant potential of POC tests in pharmacies to decrease inappropriate antibiotic usage in the outpatient setting, although it must be emphasized that moving testing from a central laboratory to a medical unit or more accessible location does not guarantee improved outcomes without systematic changes in management. Additionally, when POC testing is performed by clinical staff, errors can arise from a lack of understanding of the importance of QC and quality assurance [23].

Future directions

The American Academy of Microbiology recently convened a colloquium of industry thought leaders and subject matter experts to evaluate the role of “near-patient testing,” as well as the impact of this diagnostic “paradigm shift” for microbiology [24]. The report from this colloquium was recently published, with thoughtful recommendations. These recommendations were divided into three categories: (i) implementation, (ii) oversight, and (iii) evaluation.

Key recommendations included (i) rethinking patient flow in the clinical setting to optimize POC utilization, (ii) retaining proper oversight by the microbiology laboratory, and (iii) the need for better outcome data which includes health economics data [24,25].

Multiplex versus Flex Testing

Syndromic testing

Syndromic testing has gained popularity in recent years. These multiplex tests detect most common and some uncommon pathogens associated with a syndrome based on similar signs and symptoms. In 2008, the Luminex xTAG Respiratory Viral Panel was the first multiplex molecular panel to receive FDA clearance in the United States. Since then, a number of large syndromic multiplex panels have been FDA cleared for use in clinical diagnostics. Multiplex panels currently exist for gastroenteritis (gastrointestinal [GI]), bloodstream infections, and meningitis/encephalitis. Although some instrument platforms still require offline extraction, many platforms have evolved into sample-to-result assays requiring less than 5 minutes of hands-on time with a turnaround time of 1 to 2 hours. For the most part, the sensitivity and specificity of these multiplex tests are comparable; however, sensitivity and specificity of the individual targets can vary by platform. Multiplexed molecular panels that can target up to 27 pathogens have the potential to simplify ordering for the physician, as well as workflow in the laboratory, and require less expertise on both ends as a single automated test. As new faster and simpler technologies are introduced for multiplexed platforms, there has been continued growth in adoption of these tests for clinical diagnosis. However, there are limitations to this shotgun approach that are associated with high financial costs as reimbursements continue to decrease, as well as test interpretation dilemmas, especially in the context of low prevalence rates.

A point-counterpoint paper was recently published on large multiplex panels as first-line tests for respiratory and GI pathogens [26]. A proposed advantage was the potential to provide timely results for targeted therapy. However, detecting more pathogens might not impact treatment at all, as low sensitivity for certain targets can result in missed diagnoses with additional consequences. Also, low prevalence rates for many of the targets may lead to false positives followed by unnecessary treatment and potentially delayed diagnosis. Diagnostic errors caused by inappropriate ordering can cause delays in care or harm patients [27].

Pre-test probability is important with sensitive molecular assays. A tuberculosis meningitis case that was misdiagnosed as herpes simplex virus 1 (HSV-1) infection presented by Gomez et al. [28] underscored the risk of using syndromic multiplex assays without fully understanding the limitations associated with them. The patient’s true diagnosis was delayed because of an initial HSV-1-positive FilmArray Meningitis/Encephalitis (ME) panel result, which ultimately contributed to severe neurological sequelae. On the other end of the spectrum, another recent article reported that the meningitis panel demonstrated reduced sensitivity for HSV detection from pediatric cerebrospinal fluid specimens [29]. Positive results due to panel detection of colonization in a

gastrointestinal panel with *C. difficile* and long-term shedding of organisms such as norovirus or rotavirus can also lead to inappropriate therapeutic decision making [26,30,31].

Testing impact

The selection of the platforms that laboratories implement is usually based on accuracy, cost, hands-on time, level of complexity, staffing, throughput, and convenience. However, we also need to think about how we are going to use the test once we implement it, whether to restrict ordering of these tests to only the sickest patients or to offer them to everyone as a first-line test. For a high-volume laboratory, using a costly multiplex platform as a first-line test is not feasible. Patient outcome data based on large multiplex tests has been slow to evolve [9,32]. Additional data are needed to determine which patients will benefit from this type of testing.

For respiratory infections, testing needs may vary by season and geography. During flu season, it may be more cost effective to perform a targeted Influenza/RSV panel on patients presenting with respiratory symptoms before testing for a broad panel of organisms. Panels may be better suited to the critically ill or immunocompromised populations. Implementation of a testing algorithm for laboratory utilization of molecular multiplex panels with decision support built into ordering may be needed to avoid substituting one set of unintended consequences for another. Education and mandated improved test utilization will hopefully improve economic outcomes for the laboratory and decrease the financial burden on the patient.

CLIA-waived status is being obtained for multiplex platforms, with a number of implications. In October 2016, BioFire Diagnostics received FDA clearance and CLIA waiver for the FilmArray Respiratory Panel EZ, which requires only 2 minutes of hands-on time and has a run time of 1 hour. The EZ panel is the CLIA-waived version of the FDA-cleared respiratory panel, which tests for 14 viral and bacterial pathogens, adenovirus, coronavirus, human metapneumovirus, human rhinovirus/enterovirus, the influenza viruses, parainfluenza virus, respiratory syncytial virus (RSV), *Bordetella pertussis*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*. There are numerous questions that arise from the availability of these expensive multiplex tests for placement outside the central laboratory without required oversight by technical experts. It will be necessary to determine what algorithms will be used by physicians to decide which patients to test and how results will be interpreted, particularly if multiple targets are positive.

Flex testing

Until recently, multiplexed molecular panels have been one size fits all. Panels with fixed prices based on fixed targets may be excessive and may not necessarily include all the pathogens being considered by the physician. Multiple platforms may be required in order to address the needs of the physician in such cases. This scenario becomes a very expensive approach to diagnostic testing. Testing needs to fit the medical center and be tailored to the population that the laboratory services. The diagnostic needs of a children's hospital can be very different from those of a medical center that

caters to a large elderly population. Likewise, a cancer center or a transplant center may have very specific diagnostic needs.

Nanosphere has FDA clearance for its Verigene Respiratory Pathogens *Flex* Nucleic Acid Test (RP *Flex*) on the automated, sample-to-result Verigene system, which allows flexibility in testing and is the first multiplex test that is scalable. Each RP *Flex* cartridge contains 16 viral and bacterial targets. The physician can order any combination of targets for testing. Laboratories pay for only the targets that are ordered. Results for other targets not initially ordered on the panel can be reflexed at an additional cost without having to re-run the test. For example, one possible scenario during influenza season is to first order only influenza virus targets or influenza virus plus RSV from the panel. If the result is negative, adenovirus, human metapneumovirus, rhinovirus, and parainfluenza virus can be ordered and the results released. *Bordetella* sp. targets can be ordered separately based on clinical suspicion.

Reimbursement challenges

Medicare recently proposed universal non-coverage for respiratory multiplex panels, which will make it even more challenging for laboratories to utilize the technology. There has been a lot of discussion surrounding multiplex GI panels and whether this is clinically meaningful testing. In May 2017, Medicare Administrative Contractor Palmetto GBA posted draft local coverage determinations (LCD) for two types of multiplex infectious disease tests [33]. This decision would provide limited coverage for nucleic acid amplification-based GI pathogen panels and a non-coverage decision for multiplex PCR respiratory viral panels. The LCD proposed coverage for molecular panels to detect GI pathogens would be limited to 5 targets (*Salmonella*, *Campylobacter*, *Shigella*, *Cryptosporidium*, and Shiga toxin-producing *Escherichia coli*), which represent the majority of foodborne pathogens. Current Infectious Diseases Society of America guidelines for infectious diarrhea suggest a selective approach to workup based on whether the patient has traveler's diarrhea with fever or blood, hospital-acquired diarrhea, or persistent diarrhea [34]. A *Flex* platform may be more suitable for testing of diarrheal illnesses. Regardless of the number of analytes on a GI panel, the cost when reimbursement is limited to a maximum of 5 targets, may be affected only by the actual cost of the panel itself.

The different approach for multiplex PCR testing for respiratory viruses, apart from influenza A/B viruses, with or without inclusion of RSV, is being applied. The reasoning for non-coverage included the fact that the pathogen targets in such panels do not represent a common syndrome and that targets can be very rare. The notice said that a "one size fits all testing approach is screening and not a Medicare benefit" and went on to say that "one size fits all panels contribute to test over-utilization, and increased cost to health care without specific benefit to a given patient. Testing should be limited to organisms with the greatest likelihood of occurrence in a given patient population, and if results are negative, with a reflexive testing to more exotic organisms." Examples are *C. pneumoniae* or *B. pertussis* in combination with rhinovirus, influenza viruses, and RSV [33].

Telemedicine

Telemedicine and remote diagnostics can take on several roles. Today with total laboratory automation (TLA) and digital microbiology, laboratories have the capability to read and review slides and plates from facilities that are miles or oceans away. A recent *Clinical Microbiology Newsletter* article highlighted the impact of telemedicine on Gram stains in the health care system in Arizona [35]. Telemedicine companies like VSee (www.VSee.com) have set up field kits with multiple devices that enable remote diagnosis. Through the use of software like eHealth Opinion, rural patients and physician experts in the U.S. and China are connected through the Virtual Doctor Project [36]. Such projects are expanding in many parts of the developing world [37]. Telemedicine companies like Doctor on Demand (www.doctorondemand.com) offer virtual doctor's visits through tablet computers or smartphones.

Other areas of remote diagnostics being explored are Internet-based programs and self-collected specimens for mail-in testing. There are currently FDA-approved CT/NG NAAT assays for self-collected specimens in clinical settings. Internet-based mail-in programs for sexually transmitted infection (STI) screening has been successfully implemented in a public health system (www.iwantthekit.com), as well as through private companies (mylab-box.com) [38]. Public Health England in 2015 published a guidance document on commissioning an Internet-based *Chlamydia* screening program [39]. Such strategies are aimed at diagnostic testing and improving access over the continuum of care. With this new way of delivering care comes the question of validating at-home self-collected specimens and the stability of a specimen mailed through the post. While STI programs may be a starting point for specimen self-collection, it begins a conversation that would expand the realm of consumerism in health care to a new level. One could argue that no one is better able to properly collect a specimen than the person with the greatest interest in the results, the patient. Clinical studies comparing clinician-collected and self-collected specimens in a clinical setting for CT/NG have demonstrated that self-collected vaginal specimens have equivalent performance with acceptable patient satisfaction [40,41]. For a recent review of self-collected specimens for infectious disease testing, see Tenover et al. [42].

Internet-based programs have the potential to triage non-critical medical needs while reducing visits to traditional brick-and-mortar clinics. At Kaiser Permanente, virtual visits have been used for several years through secure e-mails, telephone calls, and some video encounters. In the Northern California Kaiser Permanente region, which has over 8,000 physicians and over 3.5 million members, virtual visits grew from 4.1 million in 2008 to 10.5 million in 2013, with projections that virtual visits will soon exceed physical visits [37]. Near-patient testing for STI programs, such as the Dean Street Clinic in London, offering walk-in STI testing and treatment with an short message service or SMS Text on a cell phone to let patients know their results (www.dean.st/testing), are also available. Investment in such programs is evolving, yet what is lacking is the return on investment (ROI) analysis, which is needed

to further policies that could help provide financial support for the evolution of technology in daily practice.

Next-Generation Sequencing

NGS has had one of the most significant impacts on microbial sciences since the advent of PCR. Through initiatives like the CDC's Advanced Molecular Diagnostics (AMD) and response to infectious disease outbreaks, public health microbiology has started to transform into the next generation of thinking for the investigation, prevention, and control of infectious diseases. NGS has provided insight into questions that just was not possible through previous technology. For a review of NGS technologies and AMD see MacCannell [43].

NGS platforms like the MinION (Oxford Nanopore) can provide portable real-time NGS analysis. The system is miniature in size, plugs into the USB port of a laptop, and offers minimal sample preparation at a low cost (<https://nanoporetech.com/products/minion>). The potential of such technology is just beginning to be realized. Applications such as the direct detection of *Mycobacterium tuberculosis* from sputum for identification and antimicrobial susceptibility prediction available the same day have been described [44]. Barriers are bioinformatics, interoperability of results, and building a workforce with a new skill set and infrastructure to support it. Given the debate around reimbursement and multiple panels, it will be interesting to see where the conversation leads with NGS. NGS will provide much more information than a 20-plex respiratory or stool panel. The technology is already changing practice in the public health laboratory, and the clinical microbiology laboratory is following [45,46].

Outcome Data and Building a Business Case

Twenty years ago, the CDC created PulseNet, a molecular-subtyping network of federal, state, and local public health laboratories designed to facilitate the identification of and response to outbreaks caused by bacterial foodborne pathogens. The specific objectives of PulseNet are to detect foodborne disease case clusters through comparison of pulsed field gel electrophoresis (PFGE) "fingerprint" patterns, to facilitate early identification of common-source outbreaks, and to help food regulatory agencies identify areas where implementation of new measures is likely to improve the safety of the food supply. At the time, PFGE was considered cutting-edge technology. To celebrate the 20th anniversary of PulseNET, the economic impact of the program was recently published [47]. PulseNet costs roughly \$7.3 million to operate but saves more than \$500 million annually in medical and productivity costs avoided [47]. This ROI is impressive, but the fact that it was 20 years before this economic analysis was published is surprising given the program's success. With federal budget cuts to critical programs that support national infrastructure, evaluating and communicating the value of technology to the health economics of the nation should be part of the national strategy. Looking ahead, it is clear that it is only a matter of time before PFGE will be replaced by NGS for such foodborne outbreak investigations in the PulseNET system. The economic impact of NGS should be analyzed in a timely manner so that the ROI of

this powerful technology can be communicated to the appropriate funding agencies.

The same is true for the clinical microbiology laboratory. While it sounds very appealing to place an mPOC influenza virus platform nearer to the patient in the ED or in urgent care, the initial investment to place and maintain that testing may be a daunting sell to administrators. The question around this ROI is where the cost avoidance is over the continuum of care. For patients coming through the ED during influenza season the greatest impact to patient management would be avoiding a hospital admission. The average cost of a hospital admission due to pneumonia is \$14,143, according to the Agency for Healthcare Research and Quality (Rockville, MD) [48]. Compared to the cost of a Tamiflu prescription, which is roughly \$100, the avoidance of hospital admission would clearly have the greatest financial impact. When one adds the implementation costs of the mPOC instrument and reagents over the course of a flu season, the ROI can become a more comprehensive sell to the C-suite or the corporation's senior executives. Tables 1 to 3 demonstrate the estimated cost of implementing an mPOC influenza assay in a hospital system with 14 medical centers, each with an ED. The total cost of implementation for instrument and reagents over 3 months of the respiratory disease season adds up to \$420,00 (Table 1). The number of admissions that would need to be avoided to break even on the cost of implementation is 30, or roughly 2 per ED (Table 2). This number is equal to 0.5% of the estimated 6,000 tested patients over the course of the respiratory disease season, which would equate to an ROI of <3 months (Table 3). Another factor to consider when thinking about a rapid mPOC test is that placing testing correctly in the system may actually be cost neutral, because testing is being shifted without the need to bring

on any additional testing. Outcome studies looking at technology placement are forthcoming [9].

Summary

In 1987, the original patent for PCR was issued, with Kary Mullis listed as the inventor. In 1993, he was awarded the Nobel Prize for PCR. These accolades came only after the article reporting the invention was rejected by both *Nature* and *Science*. It was finally published in *Methods in Enzymology* [49]. As one reflects on the impact of technology like PCR, it is easy to lose sight of how far technology has come. The conversation is now focused on where we need to go. In the world of instant gratification that we have become so accustomed to living in, it is important to remember that changes in medicine take time and require data built on evidence. Shifting practice also requires buy-in by stakeholders that the laboratory may not be considering. During the lifespan of technology, the stakeholders will range from biotechnology companies to laboratories, physicians, regulators, policymakers, guideline committees (steered by industry thought leaders), payers, and patients. These stakeholders will influence the maturity of technology application over time.

Thus, the laboratory community must assess and factor in key drivers that address need, satisfy administration, and influence health economics. Properly designed pilot studies remain an important step in assessment. Publishing these results is key to moving the field forward. Sharing information that may be initially considered only for internal quality improvement projects is essential. Laboratories could benefit from more coordinated collaboration from stakeholders, who have a vested interest in such data and the impact on patient care and health economics. At the end of the day, we are all consumers of health care. We should all be looking

Table 1. Cost of mPOC implementation across 14 emergency departments

Expenditure	Cost ^a	No. needed	Estimated cost of implementation
Instrument	\$15,000	14	\$210,000
Tests	\$35	6,000 ^b	\$210,000
Total			\$420,000

^aHypothetical costs; not reflective of a specific platform.

^b6,000 tests = 4.76 tests/day/ED over the 3-month flu season; does not include cost of controls, validation, or training materials.

Table 2. Cost of implementation and estimated cost avoidance to break even

Reagent costs	Instrument costs	Total cost of implementation	Estimated cost of avoidance of admission ^a	No. of admissions avoided required to break even
\$210,000	\$210,000	\$420,000	\$14,143	30 (2.12/ED)

^aAverage published cost per stay with a diagnosis of pneumonia. Healthcare Cost and Utilization Project (HCUP) Nationwide Emergency Department Sample (NEDS), HCUP, 2007, 2008, 2009. Agency for Healthcare Research and Quality, Rockville, MD (www.hcup-us.ahrq.gov/nedsoverview.jsp). The actual budget impact, depending on the payment schedule, is a saving of \$6,715 due to \$7,428 reimbursement if admitted, based on a blended rate of top diagnosis related group (DRG) associated with an influenza diagnosis.

Table 3. Estimated ROI based on hospital cost avoidance

Estimated no. of admissions avoided required to break even (0.5% over 3-month flu season)	Total estimated hospital cost avoidance	ROI ^a
30	\$424,290	<3 months

^aROI, return on investment.

around asking, “What are our expectations?” With the ACA, we have more patients to take care of and fewer health care dollars to do it with in an imperfect health care system. We have improved and expanded technology that allows us to ask how we improve access, overcome barriers, and provide smarter care. Technology can help get us there, but thoughtful approaches to technology placement and health care delivery will make it a reality.

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