BRINGING THE LAB TO THE PATIENT

developing point-of-care diagnostics for resource limited settings
BRINGING THE LAB TO THE PATIENT
developing point-of-care diagnostics
for resource limited settings
by Ann Reid

This report is based on a colloquium convened by the American Academy of Microbiology on September 15-16, 2011 in Annecy France.

The American Academy of Microbiology is the honorific leadership group of the American Society for Microbiology. The mission of the American Academy of Microbiology is to recognize scientific excellence and foster knowledge and understanding in the microbiological sciences.

The American Academy of Microbiology is grateful for the generosity of the Gates Foundation and the Foundation Merieux for their generosity and support for this project.

The opinions expressed in this report are those solely of the colloquium participants and do not necessarily reflect the official positions of the sponsors or the American Society for Microbiology.

Copyright ©2012
American Academy of Microbiology
1752 N Street, NW
Washington, DC 20036
www.asm.org
Every day in laboratories around the world, microbiologists are studying the intimate interactions between infectious microbes and the human immune system.

Some are examining how the immune system tailors its responses to viruses versus bacteria versus parasites. Others are trying to figure out how the pathogen that causes tuberculosis hides itself from the immune system, and why it re-emerges in some people and not others. Still others study patterns and mechanisms of antibiotic resistance. At the same time, week after week, scientists and engineers report the development of new and more capable technologies — enabling such possibilities as sequencing individual genomes and visualizing individual molecules. Every once in a while, one of these researchers has an ‘a-ha’ moment: “this discovery could be used to make a great diagnostic test!”

Meanwhile, in clinics around the world, local health care workers are forced to make treatment decisions with inadequate information. Is this patient’s TB drug resistant? Is that child’s dehydration due to a parasite, or cholera? Asked what would help them in their jobs, rapid diagnostic tests to answer such questions would be high on local practitioners’ wish lists. And both national and international public health officials know that inexpensive, accurate diagnostic tests can make a tremendous difference in the cost and quality of health care services.

This report is about how to bring these different communities together. How can we capitalize on researchers’ “a-ha” moments? And how do we make sure that researchers know which are the most pressing needs of local practitioners and international public health authorities? The answer is complicated. But there have already been many successes leading to the availability of crucially important diagnostic tests in places where few patients have access to sophisticated microbiological laboratories. Many lessons have been learned, and one of the most important is that even the greatest idea will need a lot of different supporters to make it all the way through this complicated process. As a result, this report has several audiences: first, it aims to provide guidance and context to researchers interested in developing point-of-care tests for limited resource settings: which tests are most needed and what characteristics do they have to have to succeed? Second, it speaks to research funders: what are the most promising areas of basic research and technology development that would contribute most to creating the transformative diagnostic tests of the future? Finally, the report addresses the larger international community devoted to improving health care in limited resource settings: what could be put in place at the level of the overall system that would ease the development of all kinds of diagnostic tests? The answers to these questions are provided in the form of recommendations, but perhaps the more important goal of this report is to contribute to greater communication and understanding among the many communities that need to work together to reach their common goal of increasing the availability and use of inexpensive, reliable diagnostics wherever they are needed.
BACKGROUND: AN AMERICAN ACADEMY COLLOQUIUM ON POINT-OF-CARE DIAGNOSTICS

Accurate diagnostics have the potential to affect health care decisions to a degree well out of proportion to their cost. It has been estimated that diagnostics account for only 2% of the cost of health care, but affect 60-70% of treatment decisions.\(^1\) In resource-limited settings, the impact of diagnostic tests that can be provided at the immediate point-of-care (a point-of-care test, or POCT) is potentially even greater, because the alternative to a POCT may be no diagnostic support at all.

Determining the agent responsible for a patient’s illness remains fundamental to evidence based treatment and care decisions, but in the parts of the world where the burden of infectious disease is highest, microbiology laboratory capacity is often limited and inaccessible to most patients. Point-of-care diagnostic tests (POCT) can provide access to state of the art diagnostic support even in settings where health care infrastructure is minimal. Advances in science and technology in areas as diverse as microbiology, immunology, molecular biology, materials science, computer science, and wireless communications are enabling the automation, simplification, and miniaturization of highly dependable and multi-capable tests. The potential for inexpensive, effective tests has never been higher. However, setting priorities and ensuring that the tests are developed and implemented in the most efficient way possible remains a challenge. In September 2011, as part of its Critical Issues in Microbiology Colloquium series, the American Academy of Microbiology convened a diverse group of experts to consider three broad questions related to developing new point-of-care diagnostics for resource-limited settings:

- Which diseases or medical conditions would benefit most from inexpensive, rapid, point-of-care diagnostics?
- What scientific and technological advances could be brought to bear on developing point-of-care diagnostics for these conditions?
- What are the challenges to developing and deploying the identified diagnostics approaches?

---


The goal of the colloquium was to identify those situations in which diagnostics would have an especially big “bang for the buck”. Participants at the colloquium were drawn from many different areas of expertise, including clinical microbiology, public health, molecular and computational biology, bioengineering, and others. The group met in small groups and in plenary sessions for 1-1/2 days. The steering committee, participants, and outside experts were asked to review the resulting report to ensure that it reflected the consensus reached at the meeting. Travel and report preparation costs were supported by a grant from the Gates Foundation.

The Academy was fortunate to hold the colloquium in conjunction with a forum organized by the Fondation Merieux, which also generously covered all local costs of the colloquium. The forum Moving Forward in the Diagnosis of Infectious Diseases in Resource Limited Countries: Diagnostic Technology Advances, held on September 12-14, at the Les Pensieres Conference Center in Annecy, France, presented 24 speakers with direct experience in the development, deployment, and evaluation of point-of-care diagnostics in resource limited settings. Some colloquium participants spoke at the Forum, and all benefited from an intensive introduction to recent advances in diagnostics for many different diseases in diverse settings. The Forum talks established a common foundation for the subsequent colloquium discussions, and many of the “lessons learned” discussed by Forum speakers were referenced repeatedly during colloquium discussions.

1. **Success requires a long-term commitment:**
   POCTs do not exist in a vacuum, and their successful deployment requires navigating many hurdles: successful innovations require a rock-solid rationale, significant resources, and one or more groups committed to supporting the idea as it progresses through the development and deployment process.

2. **An ideal POCT must have many different characteristics simultaneously:**
   it is not enough for a test to be inexpensive, it must also perform impeccably in a challenging setting. One Forum speaker introduced the following acronym to delineate the characteristics of an ideal test:

   **ASSURED**:
   - Affordable
   - Sensitive
   - Specific
   - User-friendly
   - Robust and Rapid
   - Equipment-free
   - Deliverable

3. **A POCT may create new health care responsibilities — and the need for additional tests:**
   The deployment of near-universal testing for HIV, a critical first step in halting the spread of the virus, also identified a huge cohort of patients requiring antiviral therapy. HIV/AIDS treatment is lifelong, and requires regular monitoring, both of the individual patient’s response to medication, and to guard against the emergence of resistant strains.
4. **Incorporating POCTs into an overall health care strategy and system can be challenging — and expensive:**

Just because a POCT test can be developed doesn’t necessarily mean that it is the best approach. Public health authorities in South Africa have proceeded with decentralizing TB testing from central laboratories to local clinics, but this strategy has been estimated to increase the cost of testing by 70% and introduces important public health challenges. Incorporating and monitoring quality control, and ensuring that results are accurately reported and maintained are significantly more difficult when the number of testing sites is multiplied. At the same time, POCTs can create competition for a lab-based “gold standard” test, and can therefore be seen as taking away revenue from a stakeholder, slowing acceptance.

5. **POCTs can have unintended consequences:**

Introduction of a test for malaria reduced the number of patients inappropriately prescribed anti-malaria medication. But patients who tested negative were almost universally given antibiotics — probably inappropriately in many cases.

The information provided by point-of-care tests (POCTs), whether the identification of a disease-causing agent or some other diagnostically relevant information, is of paramount interest, of course, to the patient and healthcare provider, but pathogen identification may also have public health relevance that goes beyond an individual patient. POCTs can also support preventive health care decisions or gauge treatment effectiveness, or even play a role in environmental testing and monitoring, or surveillance and diagnostics in animals. With such a multitude of potential benefits, the number of potentially valuable POCTs is large. In reality, though, it will not be possible to provide all POCTs everywhere, all the time, so the first order of business is rigorous evaluation of the overall cost-benefit ratio for any proposed POCT. Resources are limited, and as this report will detail, the road from brilliant idea through development to successful implementation for any POCT is long and expensive. Without a convincing, and preferably quantitative, argument for how the proposed test will contribute to improved individual or public health, the necessary resources and political will to navigate that road will not be forthcoming.
PART I: SETTING PRIORITIES: WHICH DIAGNOSTIC TESTS WOULD HAVE THE BIGGEST IMPACT?

Determining which, out of a multitude of possible POCTs, would be most useful, was the first topic addressed by the participants of the colloquium.

Demonstrating that a POCT will meet a concrete need is the first step in building support for its development, so the group first delineated some criteria that suggest that a POCT could have an important impact:

- **When the cost of an incorrect or late diagnosis is high**
  Diseases that are rapidly fatal, or that respond to treatment only early in their course, are prime candidates for POCTs because the difference to the outcome for the individual patient is so large. Misdiagnoses can also have public health implications (for example, if detection of an emerging epidemic is delayed) or economic implications (for example, if the source of a food borne illness is mis-identified).

- **When the wrong treatment could harm the patient**
  Failure to administer antibiotics promptly could be life threatening in some situations — in others, antibiotics could make the disease worse. Good POCTs to differentiate conditions where treatments have substantial side effects would minimize the chances of subjecting the patient to unnecessary harm. Giving the wrong drug, by delaying resolution of the infection, can also increase the risk of transmission.

- **When the current sample collection technique is risky**
  Diagnostic tests that currently require cerebral-spinal fluid (CSF) or material obtained through invasive biopsies are prime candidates for new POCTs that use easily obtained samples like saliva, urine or blood from a simple finger or heel stick.

- **When the current test requires expensive equipment or advanced training to administer**
  State of the art rapid test platforms and multiple target screening techniques can test for the presence of more than one target in a specimen. These investigational tests tend to involve complex equipment, are expensive to deploy, and have not proven to be robust in field situations where power sources are spotty and regular maintenance is a challenge.
When the current test has poor sensitivity or specificity, or is slow
Growing and characterizing a pathogen in laboratory culture is the traditional gold standard of microbiology diagnosis. However, identification by culture can take days for bacteria and weeks for viruses, compared to hours or minutes for molecularly-based tests, which are also often more sensitive — all important qualities where follow-up after several days or weeks may be difficult.

When there is a high likelihood of overtreatment
When the cause of a disease is unknown, there may be little choice but to treat with whatever is available — especially if the treatment poses a low risk to the individual patient. Antibiotic treatment for fever is the classic example; a POCT that provided an alternative to such a scenario would have a substantial impact. Overuse of antibiotics not only fails to help the patient, but also wastes scarce resources and contributes to the emergence of resistance in the community.

When failure to detect has a high public health cost
Not all POCTs have their greatest impact on the individual patient. POCTs can play a critical role in detecting the outbreak of an infectious disease, the emergence of treatment resistance, an infection requiring a public health intervention, or other events that call for prompt action to prevent harm to the community.

When early detection could play an important preventive role
Early detection of transmissible diseases can help prevent spread, and many chronic, non-infectious diseases like diabetes and heart disease are more easily treated or managed when early screening identifies patients at risk.

In prioritizing POCTs in terms of their potential impact, it is also helpful to recognize that the tests can serve multiple purposes. Supporting immediate patient care decision-making is important, but the impact of the POCTs on preventive care (e.g. screening for human papilloma virus (HPV), interrupting secondary transmission of infections), treatment monitoring (viral load, evolution of resistance), and public health surveillance, should also be taken into account.

Discussions at the colloquium then turned to identifying conditions that met as many of these criteria as possible. While recognizing that priorities would differ from place to place, and that input from local providers and rigorous quantitative assessments of prevalence and current treatment options would be necessary to validate these suggestions, the group felt that the following conditions would be promising ones to pursue:

■ Determination of whether an infection is bacterial or viral
Some disease symptoms, like fevers or upper respiratory infections, can be caused by many different pathogens. A problem not only in resource limited settings but universally, no simple test is available to determine whether a virus, a bacterium, a fungus, or a parasite is responsible for such syndromes, but this information is fundamental to making the appropriate treatment decision. Ideally, such a test would also be able to determine the resistance profile of the causative agent, but even a simple differentiation among causes would be helpful. Where laboratory services are available, a white blood cell differential test is used to differentiate between bacterial
and viral infection, but this requires drawing blood and the sensitivity and specificity of the test is problematic. Analysis can be automated, but requires expensive equipment, or can be done manually, but this requires highly trained technical personnel. A robust POCT for this purpose would contribute to more rapid initiation of appropriate treatment for individual patients, reduce overuse of antibiotics, help slow the emergence of resistance, and provide important epidemiological information for public health authorities.

- **Strain determination**
  A syndromic POCT like the preceding example, with the goal of determining the cause of an infection, could be customized according to the diseases prevalent in a given area. For example, in areas where malaria is widespread, a test that identified not only malaria, but also the specific malaria type, would be very useful because some types cause more severe disease.

- **Determination of drug resistance**
  The emergence of resistance to drugs is an inevitable, evolutionary phenomenon and will never be completely eliminated. However, being able to determine the drug-resistance status of a pathogen can guide initial treatment decisions, and allow monitoring of treatment efficacy. Drug resistance can develop during the course of treatment of infections like HIV and TB that require long-term drug therapy; continuing treatment after resistance has developed not only fails to help the patient, but increases the risk that a resistant strain will spread to others. An agent’s resistance profile can be determined in a microbiology laboratory equipped to culture pathogens and directly test their susceptibility to different drugs. More recently, tests have been developed that rely on detecting known genetic mutations that confer resistance. The latter approach is amenable to adaptation to a POC setting, but it should be noted that such tests only find “what they’re looking for” — that is, known patterns of resistance. New mutations or resistance mechanisms would not be detected.

- **Diagnosis of central nervous system infections**
  With the exception of cryptococcal meningitis, which can be diagnosed by means of an antigen test performed on serum or plasma, meningitis can only be diagnosed by examination of cerebral spinal fluid obtained through lumbar puncture — an invasive procedure requiring highly skilled practitioners. Eliminating the need for lumbar puncture would be helpful as it may be dangerous if performed in unskilled hands. A test that could differentiate bacterial and viral meningitis and, ideally, the pathogens responsible for encephalitis and meningitis, would be extremely useful for guiding appropriate treatment, including justification for rapid transportation to a regional health center. Development of such a test will require the discovery of specific biomarkers for different meningitis pathogens in blood, saliva, urine or some other readily obtainable patient sample. Alternatively, a multiplex test that could screen clinical samples for broad pathogen categories responsible for encephalitis and meningitis would be useful.

- **Monitoring HIV treatment: viral load and CD4 count**
  With over one million people on anti-retroviral (ARV) treatment in South Africa alone, the need for ongoing monitoring of treatment efficacy is enormous. Rapid diagnostic tests for HIV status have proven to be a critical tool for
monitoring and controlling the spread of AIDS. However, monitoring treatment response is a far more complicated proposition than a straightforward “yes” or “no” test of HIV status. Falling numbers of CD4 cells (the white blood cells targeted by HIV) is currently used to determine when ARV should be started, or to indicate when the risk of opportunistic infection indicates the need for prophylactic treatment or further diagnostic testing. Recent studies suggest that starting HIV-positive patients on ARV much earlier could be an important strategy to prevent spread of the virus, meaning that there may soon be even more people on anti-retrovirals for longer times. Viral load should ideally be tested every 3-4 months; resurgence of the virus can indicate either non-compliance with therapy, or the emergence of resistant clones. Either result has public health implications because of the renewed risk of transmission, especially in the case of emerging resistant strains. Monitoring, by definition, implies ongoing access to testing. That characteristic makes these tests especially appropriate for a POC setting. However, tests are only one part of successful management of a chronic disease. The ability of the local health care infrastructure to respond to the tests’ results must be considered.

- **Sexually-transmitted disease panel**
  Because sexually-transmitted diseases affect not only the individual patient, but sexual partners and, often, fetuses, it would be useful to have a multiplex test that could detect and differentiate syphilis, herpes simplex, trichomonas, chlamydia and HPV. Another possibility would be a rapid POCT for HPV, which could be used as a marker for risk of other STDs and also have implications for patient management.

- **Rapid diagnosis of viral hemorrhagic fevers**
  Rapid POCT for hemorrhagic fevers like Ebola and Lassa would likely have little impact on treatment decisions, but would have a major impact on the ability to respond to and contain outbreaks of these lethal and highly transmissible diseases. Local availability of such tests would be extremely useful for surveillance, infection control, and emergency response. In some instance, like Lassa fever, patients who are suspected to be infected are shunned, thus creating social disruptions that can be devastating to the community.

- **“State of health” diagnostic panel**
  The focus of the colloquium was on diagnostic tests for infectious diseases, but the group recognized that many of the same opportunities and challenges apply to other kinds of POCTs, including those that measure health indicators related to chronic or non-infectious diseases like diabetes, heart disease, and others. A panel that provided similar information to that currently gathered through a standard blood panel — white cell count, lipid profile, etc. — could also have a significant individual patient and public health benefit.
There are a number of technological and scientific advances that would contribute broadly to the effort to develop effective, inexpensive tests.

In some cases, these are areas where public or private investment would have impact across the field. Others may require political or regulatory action in the form of developing and then requiring the use of standard interfaces or formats.

Scientifically, the group identified advances in the identification of biomarkers as having the most potential to contribute to the development of successful new POCTs. A biomarker is any entity that can stand as an indicator of a biological condition. For example, fever and high white blood cell count have long been used as biomarkers of infection.

Traditionally, infectious disease diagnosis has depended on identifying, usually by laboratory culture, the causative organism. More recently, many kinds of biomarkers have been brought into clinical practice to allow differentiation among potential pathogens without the need for culture. It is now often possible to detect a pathogen’s nucleic acid (DNA or RNA), antigens unique to a pathogen, or antibodies specific for a certain pathogen, thus bypassing the need for culture. Such tests are generally binary; one pathogen is tested for and the test is either positive or negative. Increasingly, though, we understand disease less as an “on-off” condition governed by the presence or absence of a specific pathogen. Instead it is becoming clear that disease is the result of complex interactions that involve the immune system — which reflects both the patient’s genetics and also historical exposures — the pathogen, and the other microbes that live in or on the patient, permanently or transiently. Progress on a number of scientific fronts is rapidly expanding the potential range of biomarkers that can provide insight into this more complex view of disease. From specific gene sequences and surface markers, to ratios of expressed genes, to quantitative measures of antibody or pathogen levels, to detection of specific metabolites, proteins, and lipids, the universe of potential biomarkers is expanding rapidly. Our understanding of disease processes at the molecular level is becoming more sophisticated, opening the door to tests that measure not only the presence or absence of a pathogen, but also probe the interaction between the pathogen and the host and, thus, the actual impact on health and implications for treatment.

There is currently tremendous scope for the discovery and development of new biomarkers. In particular, the ‘one biomarker/one disease’ model may no longer be optimal. High-throughput techniques like proteomics, metabolomics, and microarrays open up the possibility of characterizing various disease states by examining
a panel of makers. Developing such panels will require a great deal of new science (to discover and verify panels of markers that reliably identify various agents or disease states) and new technology (e.g., chip-based devices that can read multiple biomarkers simultaneously).

With particular relevance to the field of POCT development, the following areas are ripe for biomarker discovery:

- Antibiotic resistance
- Immune status
- Inflammation
- Virulence factors
- Disease stage
- Disease progression
- Response to treatment

Specific biomarkers and technologies that would contribute to the development of more powerful POCTs are clearly important, but there are a number of enabling technologies that could potentially have an across-the-board effect, making many POCTs more useful, inexpensive, or robust. For example:

- **Connectivity — making it possible to capture all POCT results permanently and in real-time**

  Discussions at the colloquium returned repeatedly to the importance of ensuring that POCT results were not lost to the overall health system. While deployment of a POCT in isolation can provide a diagnosis and have an important immediate impact on treatment, the ability to capture the results of the test would multiply this impact by allowing follow-up with the patient, quality control and monitoring, and public health surveillance, among other goals. Such forward-thinking design would be greatly facilitated by the adoption of a set of universal operability standards for result recording and reporting. Similar standards for wireless and satellite inter-connectivity are important for devices that are not hard-wired. Finally, a simple, sturdy, standardized camera would be extremely useful for transmitting test data. Simple colorimetric tests are increasingly cost-effective options for diagnostics, especially if sophisticated equipment to ‘read’ results can be centrally located and remotely accessed. The ability to submit test results by sending a photograph taken by cell phone is currently hampered by the many different camera standards used in different phones. Agreed standards, dedicated phones or the ability to interconvert images from different phones would all be possible ways to overcome this technical barrier. Making this kind of connectivity and standardization a reality will require building reporting capability into the earliest design stages for each individual test. This effort is partly a technical one, but it also requires an investment in and commitment to the development of agreed standards and in their enforcement.
**Batteries and sustainable power**
Better battery technology, and solar chargers and generators would help reduce the problem of inconsistent or non-existent local electrical sources.

**Refrigeration and heat tolerance**
Many tests rely on heat-sensitive reagents. Improvements in packaging, monitors or indicators of temperature history, improved supply chain management, and development of substitutes for heat-sensitive reagents are all possible means of reducing losses and failed tests because of problems with the cold chain.

**Microfabrication**
Micro- and nano-arrays have the potential to allow multiplexing of tests, incorporation of quality control, reductions in sample size, and decreased reagent costs.

**Microfluidics**
Microfluidic devices allow the automation and miniaturization of multi-step tests.

**Machine-learning/artificial intelligence**
As tests move beyond simple one-agent-one disease approaches, software and apps that help providers interpret results and support decision-making will be increasingly important.

**Non-invasive sampling technologies, nanotechnologies that require minimal sample volume, sample concentration technologies**
A successful test begins with an appropriate sample, so technologies that allow samples to be smaller, more easily obtained, or more consistently processed could have an impact on many different POCTs.
PART III: STARTING WITH THE ENDS IN MIND: DESIGNING EFFECTIVENESS INTO POCTS

Many conditions could benefit from diagnosis at the point-of-care, and both scientific understanding and technological capabilities are advancing rapidly. But whatever the condition being diagnosed, and whatever technical approach is taken, there are some characteristics that any POCT should have.

Designing these characteristics into the POCT from the beginning will ease their deployment and acceptance, and enhance their eventual utility. Many of the characteristics that would make POCTs especially valuable would also contribute to a more efficient and effective health care system overall. Incorporating these characteristics will require advance planning and coordination among users, test developers, health care providers, and others, but the pay-off could be substantial. In discussing what information would be provided by the “ideal” POCT, colloquium participants had suggestions that fell into the following four categories:

- Results and decision support
- Quality control
- Training of field staff
- Medical records interface

Results and decision support

Of course the first order of business for a POCT is to deliver test results, but consideration of how those results are delivered and how they will be interpreted and acted upon should be included in the early design stage. In some cases, test results would be a simple yes/no answer to a question like: “is pathogen A present or not?” making result delivery straightforward. For many of the conditions described in the first section, however, POCTs would be providing more complex information, including distinguishing among several possible pathogens, determining a pathogen’s resistance profile, measuring viral load, or differentiating between natural and acquired immunity. In such cases, it is critical to consider how and by whom the test results will be evaluated, and ensure that test results are reported in a form that the end-user will be able to interpret. Clear and unambiguous results are especially important in a point-of-care setting where little decision support is available. Other possibilities would be to build decision support into the device itself, or incorporate the capability of remote monitoring and decision support.
Quality control

Even the simplest test can give the wrong answer and there is an extended history and literature concerning the science of quality control. For a POCT, quality control is critical, and it must be delivered — like the test itself — at the point-of-care. Practically speaking, this means that quality control must be built into the test to the greatest degree possible. An incorrect result can lead to any number of bad outcomes, from incorrect or delayed treatment, to stigma, to failure to detect or control a disease outbreak. Thus, any new POCT must come with a comprehensive quality assurance plan.

Quality control built into the device should take into account common mistakes or problems. For example, if any component of the test is heat sensitive, there should be a control for that component’s viability. Similarly, if inadequate sample is frequently a source of error, there should be a control for sample quality or amount. To reduce operator error, manual handling of tests and samples should be kept to a minimum. Human error is inevitable, so a primary design goal should be simplicity — as few steps as possible, and built-in quality control to detect errors. The cost of quality control also must be taken into account. If operators are expected to devote a percentage of their test inventory to quality control, both time and cost considerations are going to work against consistent quality control because end-users will be in the difficult position of choosing between testing more patients and fulfilling quality control requirements. The concept that test results are meaningless if quality control is neglected should be a core component of user training. There should be an absolute requirement for a quality control ‘gatekeeper’ — that if any control steps are skipped or fail, the result should not even be reported. No matter how effective the internal controls, however, compliance with quality control will require some kind of external oversight. Building in some kind of automatic reporting, perhaps via cellular telephone, would allow external monitoring so that trends in test usage and results could be tracked. The urgent need for affordable proficiency testing panels should also be kept in mind.

Training

Training materials must be developed with the non-laboratory healthcare worker in mind. Tests must be designed in such a way that training can be simple and based to the greatest degree possible on clear, visual graphics. No prior level of experience should be assumed, so good laboratory practice training, including safety training, should be included in the test training process. Ideally, the user should be trained to understand and interpret the results, understand what the test can and cannot do, and be convinced of the value of the test. Proficiency testing should be built into the training process and it is important that trainers be familiar and experienced with common problems of the region — which may require “training the trainers.”
Medical Records Interface

Automated reporting serves another important purpose — in addition to quality control monitoring, it allows the integration of POCT results into an electronic patient record and public health surveillance. Linking the test result accurately and permanently to the individual patient is critical. Like all other aspects of quality control, integrating collection and recording of the appropriate ‘metadata’ — patient name, location, time, etc. — directly into the sample collection step would be ideal. Ultimately, the goal is to provide medical tracking to the bulk of the population so that medical records would be accessible from any clinic. Given how difficult it is proving to transition to electronic medical records even in wealthy countries, the goal of a fully electronic medical record may be unrealistic. However, investment in the design and deployment of an inexpensive device that could be used to link individuals to their medical records — a fingerprint scanner, for example — might be an ingredient in allowing resource-limited countries to leapfrog over record-keeping inefficiencies that plague more developed health care systems. Using an open-source approach to the design of such a device would provide an incentive for the development of ‘apps’ that could be added as new tests and capabilities become available.
One theme emerged again and again throughout the colloquium — the development of a POCT is not a single discovery or event, but a process with many steps and many stakeholders.

The first two sections of this report focused on what types of tests would be useful and what scientific and technological advances have the potential to contribute to cheaper and more capable tests. The third section addressed design considerations that could improve test performance and adoption success. In this section, we turn to systemic issues that affect all point-of-care tests and have the potential to make or break the success of any individual test. Addressing some of these challenges at the system level would help to create an environment in which the efforts of scientists, engineers, and information technology specialists to develop innovative, inexpensive and effective POCTs would have a higher likelihood of success.

Point-of-care tests are just one small part of the effort to provide effective and efficient healthcare, and decisions about which tests to develop and how they should be used have medical, economic, political, and social considerations. Given that there are dozens of possible diagnostic targets, an ever-expanding menu of technological approaches, and scores of different countries where the test would be useful, who decides which tests should be developed? What — in addition to appropriate design — increases the odds that the development process will lead to a viable product, and that the test will be successfully adopted? Experience with diagnostics development efforts for TB, malaria, and AIDS provide some answers to these difficult questions (see FIND box).

Participants at the colloquium emphasized the need for a long-term commitment involving stakeholders at multiple levels. Success requires more than an innovative and inexpensive test. It requires a systematic approach and identification of a champion to take responsibility for each step. As a result, development and deployment of new diagnostics is most likely to be successful if it takes place within a larger framework. Such a framework has been successfully constructed for diagnostic tests for some of the most important disease threats — HIV, TB, malaria — but it exists only in part for other applications. An important message that emerged from colloquium discussions is that finding a way for all interested parties to communicate and cooperate would make it dramatically easier to develop and deploy new tests. The following suggestions address these system challenges.

■ **Develop new communications channels**

No single accomplishment would contribute more to the development of new POCTs than finding new ways for the many stakeholders in the field of point-

---

3 http://pubs.rsc.org/en/journals/journalissues/lc
FIND: The Foundation for Innovative New Diagnostics

FIND is a nonprofit foundation dedicated to the development of innovative and affordable point-of-care diagnostic tests for resource limited countries. Founded in 2003 by a grant by the Bill and Melinda Gates foundation, FIND emphasizes diagnostics development as a way to shorten the time between disease incidence and treatment, halt disease transmission, and minimize overall disease impact. Initially FIND specialized in diagnostic tests for tuberculosis, but has branched out to work on diagnostic tests for malaria and human African trypanosomiasis (sleeping sickness).

FIND forms partnerships with commercial companies, academic researchers, international health organizations, charitable donors, and ministries of health. The Foundation works with these partners to accelerate development of new diagnostic products along a “value chain” (see below) that extends from the initial design of a diagnostic to the implementation in a resource limited setting.

FIND’s partnerships have contributed significantly to diagnostic test development and implementation, including the development of a cartridge-based automated test for tuberculosis that can accurately diagnose disease in less than 90 minutes. Three years of FIND sponsored research identified a set of markers to accurately diagnose sleeping sickness. FIND also teamed up with the World Health Organization to evaluate 41 rapid diagnostic tests for the detection of malaria — the largest independent evaluation of malaria point-of-care diagnostic tests.
of-care diagnostics to communicate with each other. For example, the journal “Lab on a Chip” has been a great source of information that is freely accessible. Each step of the process — from determining quantitative measures of various tests’ impacts and setting priorities, to assessing whether a test will meet local needs, to managing the approval process, to carrying out post-introduction quality control — requires that a robust chain of communication exist from the test developer right through to the end-user, including national and international regulatory and public health authorities. Both internet-based and face-to-face approaches could be explored, but the value of creating an open, flexible, and inclusive set of communications channels cannot be over-emphasized.

- Integrate point-of-care tests into overall health care systems

Just because the test is being provided at the point-of-care does not mean that it is isolated from the broader health care system — like any other innovation, people and networks are critical to encourage adoption. Effort is required at all levels — global, regional, national, state, county, province or district, and village — and stakeholders must be identified and formed into a constituency that takes ownership of the success of the deployment and, ultimately, the sustainability of the test. It is important to establish a series of layers between the manufacturer or national health service, including professional and business societies, local charities, associations of laboratory workers, nurses, or physicians, that can bring people together to introduce the new tests and advocate for them. Local health care workers must be convinced of the value of the test, and this is made more likely by involving this constituency from the beginning. This interconnecting network will also help with the ongoing need for training, monitoring, and supply management, and with ensuring that results are reported and integrated into the overall health care system.

Another consideration that underlines the need to consider new POCTs within the context of national health systems is that more sophisticated and inexpensive POCTs create a risk that diagnostic capabilities can get ahead of local healthcare systems’ ability to care for patients. If a POCT provides a specific diagnosis, the expectation is raised that specific treatment will also be available. Whether that means prescribing a specific antibiotic in response to resistance profiling, or referring a patient for treatment at a regional level when local resources are inadequate, the risk is that both healthcare workers and patients will be frustrated if the test results cannot be acted upon.

The risk of frustrating local stakeholders is heightened when one considers that the results of tests may be useful for public health surveillance and monitoring, even where capacity to care for individual patients is limited. For example, detecting an Ebola virus or cholera outbreak, or monitoring the number of multi-drug-resistant TB cases, would have considerable public health value. Achieving the very important goal of connectivity — that is, ensuring that test results are captured by the overall health care system — increases the potential disconnect between use of the test and benefit to the individual patient.

One final consideration that arises with the widespread adoption of non-culture based POCTs, is that the opportunity to study the actual pathogen is lost. The benefits of disseminating diagnostic capability to the local level are many, but microbiology pathogenesis dictates that an
isolate is critical if scientists want to study the pathogen and thereby gain insight into how to develop appropriate POCTs and therapeutics. Indeed, for public health purposes, maintaining adequate laboratory capacity for microbiological study and diagnostics is important, and potentially problematic if most of the diagnostic case load is moved out to the local level.

- **Address the inefficiencies of the test approval process**

  In the United States and other developed countries, diagnostic tests are regulated by government agencies that evaluate evidence of the test’s accuracy. Manufacturers invest considerable time and resources into clinical trials that demonstrate test performance. What is an expensive and time-consuming task in the developed world becomes a nearly insurmountable obstacle in resource-limited settings. Clinical trials to show effectiveness are difficult and costly in places where laboratory capacity and trained personnel are in limited supply. Approval must be obtained one country at a time, and most poor countries have little capacity to evaluate performance data provided by manufacturers, leading to long delays. In developed countries, laboratory accreditation and oversight provide strong incentives to use only licensed tests. Poor countries often do not have the resources to keep a close eye on every clinic — much less every private laboratory — so counterfeit and non-approved tests find easy markets. In turn, the abundance of inexpensive knock-offs act as powerful disincentives to investing the resources needed to navigate the complex approval pathway. In yet another example of the many ways that POCTs do not exist in a vacuum, their success will be more likely if countries are supported in their efforts toward achieving laboratory accreditation through development of external quality assurance (EQA) and proficiency testing capacity and overall laboratory system development.

  Fulfilling regulatory requirements is expensive both for the test developer and for the regulators, and in resource limited settings, the approval and subsequent regulatory process is often anything but clear. Participants at the colloquium described a patchwork of rules and processes from country to country, many of them expensive and slow to navigate, made even worse by a lack of enforcement. In the case of tuberculosis, the Gates Foundation and the Foundation for Innovative New Diagnostics (FIND) funded large trials; in the case of HIV, the World Health Organization (WHO) and U.S. Centers for Disease Control and Prevention (CDC) funded the development of a large test panel. Tests can be evaluated in different ways, but the main suggestion of colloquium participants is the need to remove the need for each country to evaluate the quality of a proposed test.

It seemed clear to colloquium participants that this is an area where
international cooperation could have a significant across-the-board impact. The implementation of a standardized process for pre-qualification of diagnostic tests — perhaps through WHO in partnership with such regional organizations as the new African Society for Laboratory Medicine — would benefit POCT developers and manufacturers who would not have to undergo numerous regulatory processes, and user countries, which would not have to devote resources to evaluating tests. Especially as tests become more sophisticated and capable of multiple simultaneous tests, reducing the costs of demonstrating test performance will become even more important.

**Develop more efficient means of quality oversight**

Moving the approval process to the international level does not, unfortunately, eliminate the need for oversight to ensure that the tests that actually reach the end-user are authentic and operative. A regional or in-country system for quality control may be necessary, although as discussed above, it is possible to build many aspects of quality control directly into the test. Quality control is inextricably linked to training: the more the end-user knows about a test, the more likely that counterfeit or defective tests will be detected. Just as putting in place a regional or international system for approving tests removes a serious obstacle to test deployment, it has also proven useful to develop quality control test panels and sample materials at the international, regional or national level. However achieved, the cost of regulation, quality control, inventory management and testing, must be considered in the overall evaluation of whether a test will be economically viable.
CONCLUSION

Developing a new point-of-care test for use in a resource limited setting is not a trivial endeavor. It requires an auspicious blend of an unmet need, a ripe technology, a receptive health care system and a persistent effort to engage all of the necessary stakeholders. Despite the hurdles, there are many reasons why now is a good time to rise to the challenge.

Technological and scientific progress, combined with experience gained from the development and deployment of diagnostic tests for HIV, TB, and malaria, actually make this a promising time to invest in additional POCTs that could have a dramatic impact on the quality and cost of health care in remote areas. The day when a clinic anywhere in the world could have the capacity to provide all of its patients with accurate diagnoses for virtually any infectious disease, along with appropriate treatment and timely follow-up, need not be too distant. Some policy changes are needed to incentivize development of POCTs and it is important to figure out how to reduce the cost of bringing a high-quality POCT to market, for example by reducing the cost of oversight regulations. Participants at the American Academy of Microbiology colloquium agreed that the colloquium, and opportunities like it for the many different communities involved in diagnostic test development and deployment to meet, discuss needs and opportunities, and set priorities are crucial. It is our hope that the communication channels opened at the AAM colloquium will lead to more opportunities for easing the path from a researcher’s “a-ha” moment to better care for patients around the world.
SUMMARY OF RECOMMENDATIONS:

■ Prioritize the development of point-of-care tests when the following conditions apply:
  ■ The cost of an incorrect or late diagnosis is high.
  ■ The wrong treatment could harm the patient.
  ■ The current sample collection technique is risky.
  ■ No test currently exists.
  ■ The current test is requires expensive equipment or highly trained personnel to administer.
  ■ The current test has poor sensitivity or specificity, or returns results too slowly.
  ■ There is a high likelihood of overtreatment.
  ■ Failure to detect has a high public health cost.

■ Invest in the following science and technology areas to support POCT development:
  ■ Biomarkers for:
    ■ Antibiotic resistance
    ■ Immune status
    ■ Inflammation
    ■ Virulence factors
    ■ Disease stage
    ■ Disease progression
    ■ Drug sensitivity
    ■ Response to treatment
  ■ Connectivity — making it possible to capture all POCT results permanently and in real-time
  ■ Batteries and sustainable power
  ■ Refrigeration and heat tolerance
  ■ Micro-fabrication
  ■ Microfluidics
  ■ Machine-learning/artifical intelligence
  ■ Non-invasive sampling technologies, nanotechnologies that require minimal sample volume, sample concentration technologies

■ Incorporate the following characteristics into initial design of all POCTs
  ■ Results and decision support
  ■ Quality control
  ■ Training
  ■ Medical records interface

■ Address systems-level challenges
  ■ Develop new communications channels among stakeholders
  ■ Integrate point-of-care tests into overall health care systems
  ■ Address the inefficiencies of the test approval process
  ■ Develop more efficient means of test quality oversight