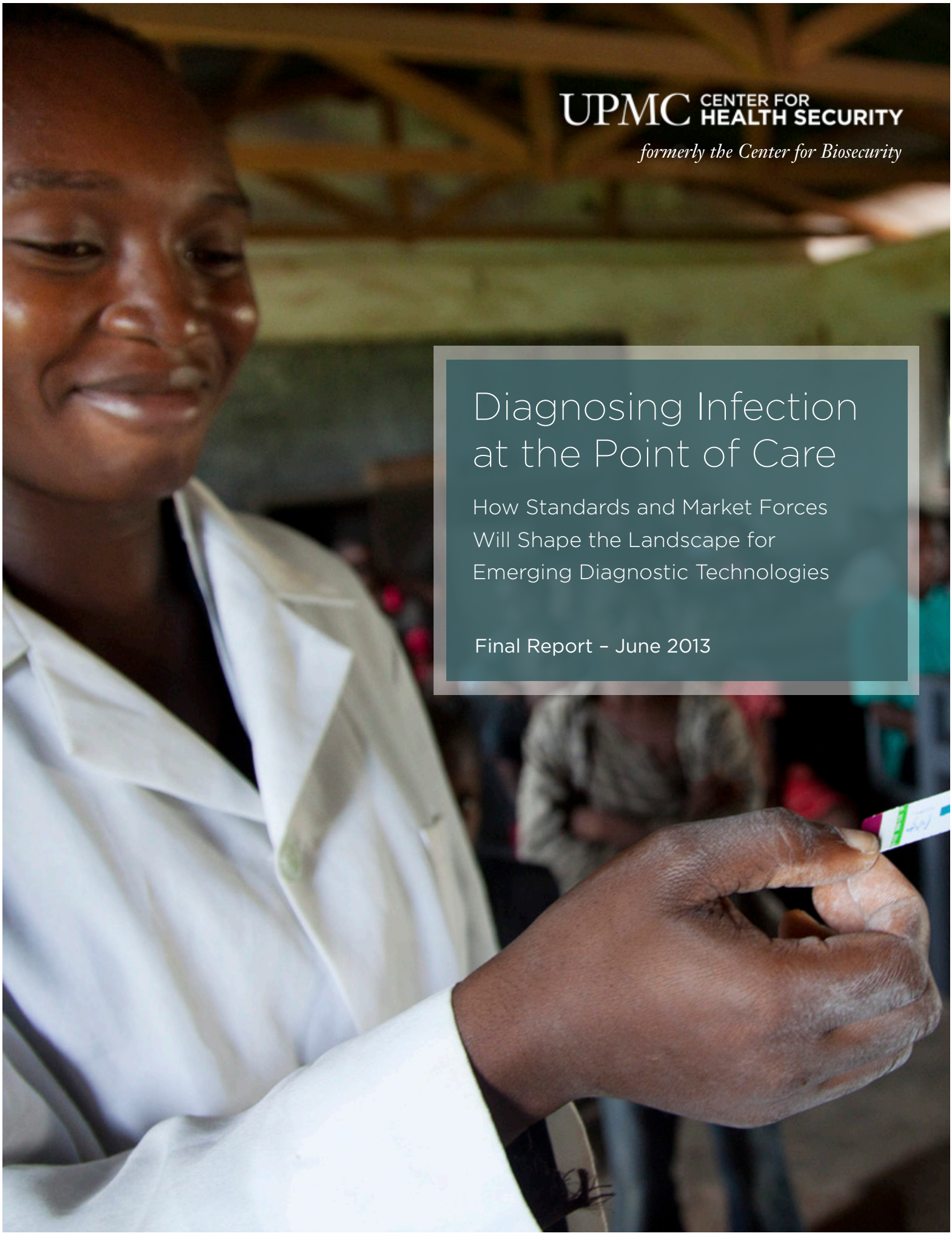


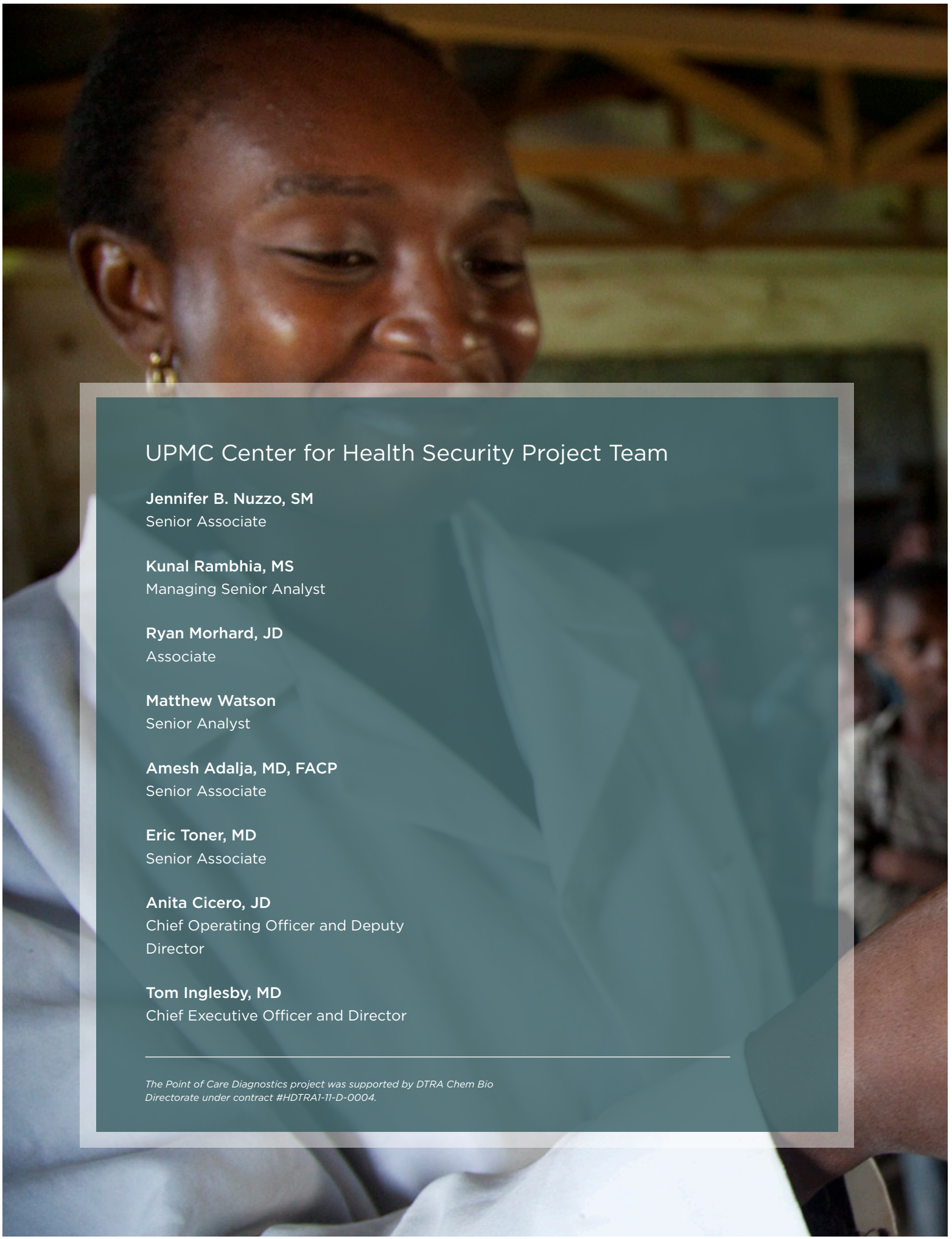
UPMC CENTER FOR HEALTH SECURITY

formerly the Center for Biosecurity

Diagnosing Infection at the Point of Care

How Standards and Market Forces Will Shape the Landscape for Emerging Diagnostic Technologies

Final Report – June 2013



UPMC Center for Health Security Project Team

Jennifer B. Nuzzo, SM
Senior Associate

Kunal Rambhia, MS
Managing Senior Analyst

Ryan Morhard, JD
Associate

Matthew Watson
Senior Analyst

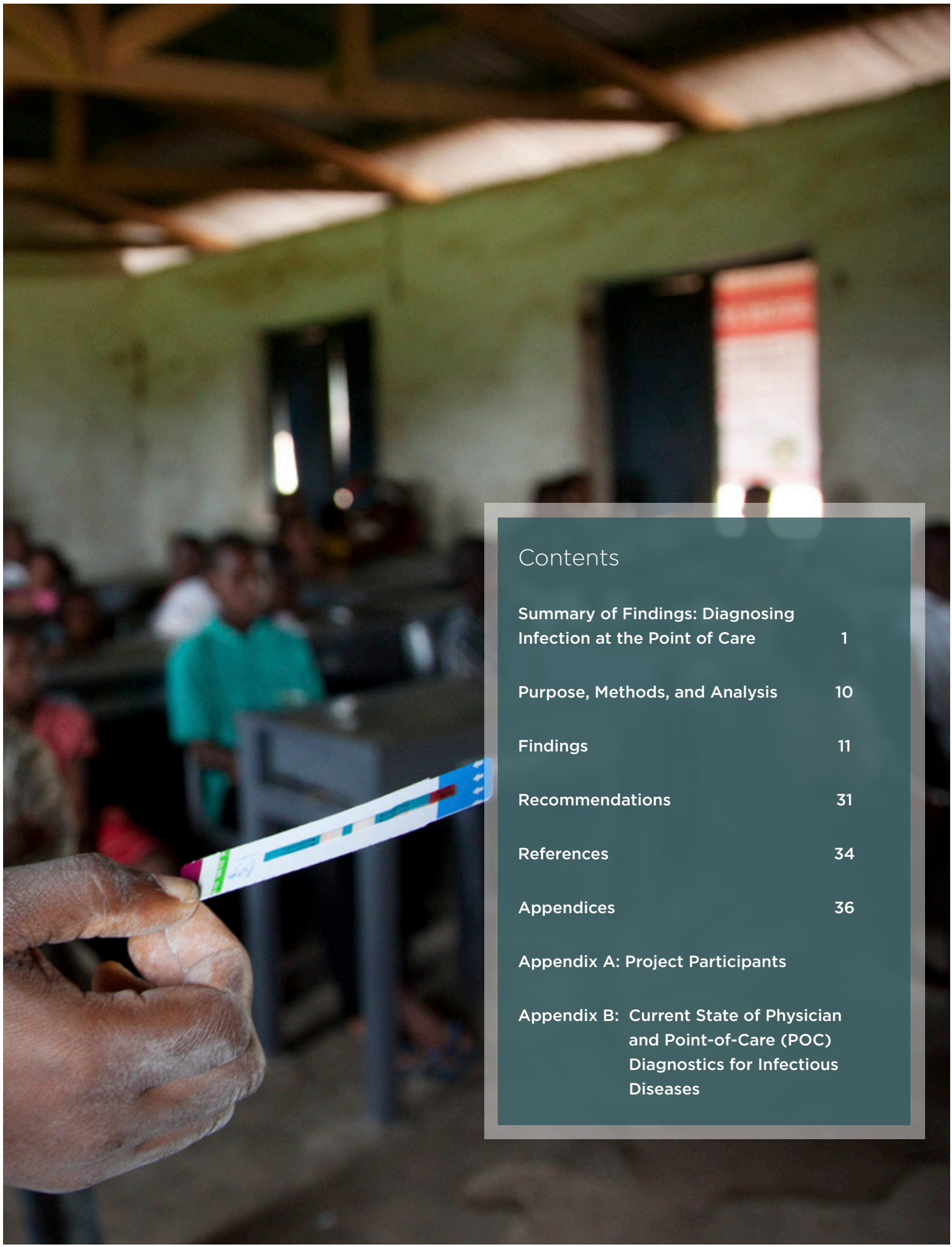
Amesh Adalja, MD, FACP
Senior Associate

Eric Toner, MD
Senior Associate

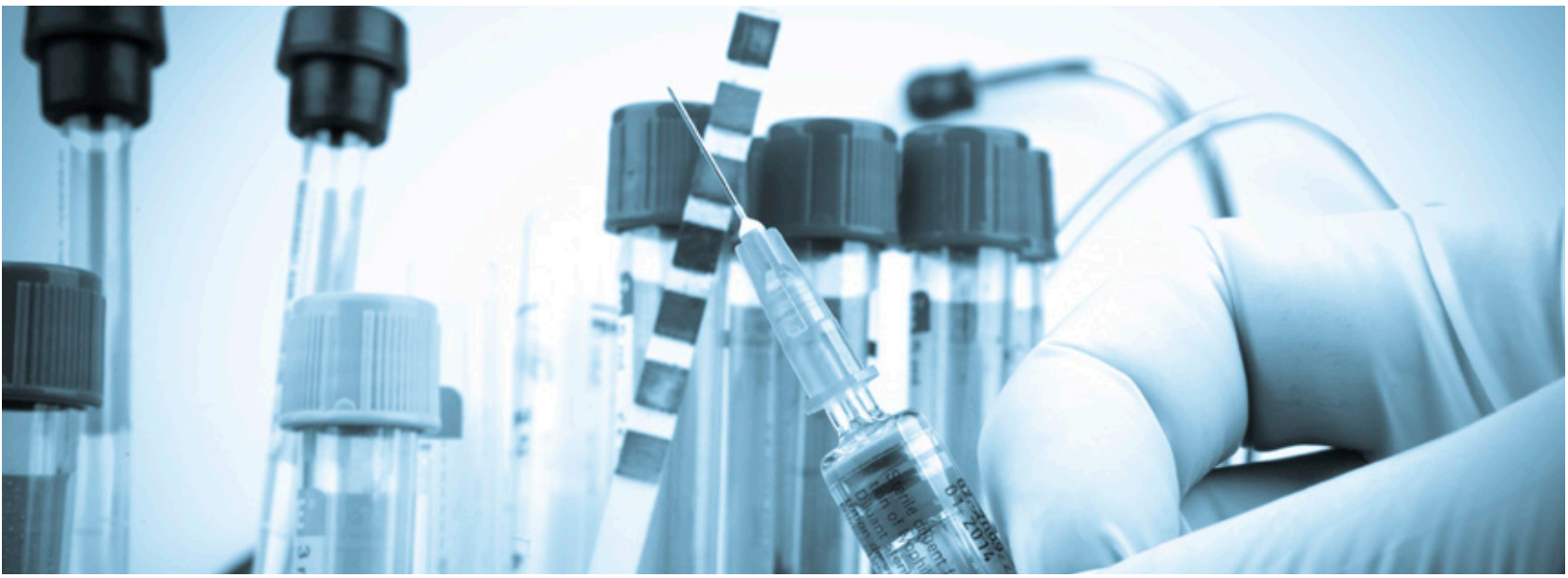
Anita Cicero, JD
Chief Operating Officer and Deputy Director

Tom Inglesby, MD
Chief Executive Officer and Director

The Point of Care Diagnostics project was supported by DTRA Chem Bio Directorate under contract #HDTRA1-11-D-0004.



Contents



Executive Summary

Diagnostic tests are critical for diagnosing diseases in US troops, for domestic and international early disease detection and biosurveillance, and for improving global health.[1] Advances in diagnostics could improve clinical management of a range of diseases in the US healthcare system. The ability to rapidly diagnose infectious disease has been identified as a strategic priority by the White House,[2,3] the US Department of Health and Human Services (HHS),[4] the National Institutes of Health (NIH),[5] the US Centers for Disease Control and Prevention (CDC),[6] and the US Department of Defense (DoD).[7]

One category of diagnostic technologies—rapid point-of-care (POC) tests—offers a number of possible advantages over other diagnostic approaches. POC diagnostics have the potential to expedite clinical decision making, to reduce patient loss to follow up while waiting for test results, and to facilitate the delivery of care outside traditional healthcare settings. POC diagnostics also are appealing for use in lower cost environments because they require less complex infrastructure and training.

While the overall global diagnostics market is projected to surpass $50 billion in 2014, POC tests represent only a small portion of that market: 12% of the total ($5.5 billion). In addition, infectious disease diagnostics represent a small slice of the overall global diagnostic market and the POC market.[8] Currently, the number of infectious disease POC tests that are approved for use in the United States is limited and focuses on a small set of common clinical conditions. Tests cleared by the Food and Drug Administration (FDA) exist only for HIV, HCV, influenza, RSV, EBV, Group A Streptococcus, adenovirus, *Helicobacter pylori*, trichomoniasis, bacterial vaginosis, and *Borrelia burgdorferi* (although cleared by the FDA, the POC test for Lyme disease does not currently appear to be commercially available).[9] There are no POC

tests available for less common but high consequence diseases of concern, including biothreat agents.

There is increasing interest in exploring ways to accelerate the development of new rapid POC diagnostics. The Grand Challenge in Global Health Diagnostics[10] was launched in 2011 by the Bill and Melinda Gates Foundation and Grand Challenges Canada to catalyze the development of a common, open-source platform that could be used to diagnose multiple pathogens at the point of care.[11] Developing and using standards to facilitate diagnostic development has been proposed as part of this effort.[12] In addition, the Defense Threat Reduction Agency (DTRA) is sponsoring the 24-Month Challenge to develop POC diagnostics suitable for both mobile and clinic-based applications.[13]

This report examines the clinical needs, business case, and challenges facing today's POC infectious disease diagnostics market, and it considers what role standards and other approaches may play in catalyzing the development of new POC diagnostic tests.

Purpose of Project: The UPMC Center for Health Security (formerly the Center for Biosecurity of UPMC) conducted this project to provide leaders in DoD, other agencies of the US government, and nongovernmental organizations (NGOs) engaged in global health programs with an assessment of possible strategies and initiatives that could be employed to speed the development of rapid diagnostic tests that would detect, identify, and help inform the treatment of infectious diseases. This project included a focus on the potential development and use of standards for infectious disease diagnostics, as well as on barriers, challenges, and opportunities related to the development and uptake of new diagnostic tests, particularly those at the point of care.

Methodology: To inform this analysis, Center staff conducted a review of the published literature relating to point-of-care infectious disease diagnostics, key policy analyses, and government and nongovernment reports on current technological approaches. The Center held more than 40 conversations with leaders and subject matter experts responsible for infectious disease diagnostic research, development, policy, or practice. Based on those conversations, the Center prepared a preliminary analysis of our findings. Finally, the Center convened a 1-day meeting on January 29, 2013, that was attended by members of industry, academia, nongovernmental organizations, and the government, in which the preliminary analysis was presented and discussed by participants. This report identifies major findings and recommendations emerging from the Center's analysis, the interviews, and workshop discussions. The conversations before the workshop and discussions on January 29 were conducted on a not-for-attribution basis. The recommendations represent the views of the Center and may or may not represent the views of any of the project participants.

Findings

ONE: In the right settings, standards can be used to accelerate emerging technology development.

When applied with the proper scope and at the proper time, standards can help realize desired technical, economic, and/or policy objectives, including technology development and diffusion. Standards can contribute positively to innovation by facilitating cooperation between organizations; increasing product performance, homogeneity, and interoperability; accelerating the diffusion of technical solutions; and improving regulation by enabling comparability, conformity, and predictability.

TWO: When applied too early in the technology development process, standards may contribute to institutionalizing inefficient practices and stifling innovation.

Standards have the potential to limit innovation by promoting the adoption of inferior products, even in the presence of more technologically advanced or more desirable alternatives. The timing of the development and application of standards is highly consequential. One serious concern is that standards can create "lock-in" effects and make the diffusion of more efficient innovations more difficult due to high switching costs.

Some notions of future diagnostic technologies are that platforms will (or should) require compatible, and perhaps proprietary, components, such as cartridges. If such platforms were to gain influence in the market, new technologies may be required to be interoperable within these new technology ecosystems in order to be successful. This kind of networking effect in diagnostic technology development would cut both ways. Network effects enabled by standards might lead to increased technological development, but may also limit commercially viable, but diverse, avenues of innovation.

THREE: Advances in diagnostic technology seem more likely to result from the collective application of standards by private companies with common proprietary goals than from the use of standards to create open platforms.

As standards are considered for diagnostic technology, lessons from the computer revolution suggest that, rather than applying standards early in technology development to create open platforms, standards are most effective when adopted voluntarily by the private sector when it sees clear benefit and at a time of appropriate technology maturity.

Although it might seem logical that "open" platforms would lead to increased access and development of new technologies, as compared to closed platform technologies that are sold for profit, there is not a lot of evidence from the computer industry to support that notion. Ultimately, development and maintenance of advanced technologies are best performed in the private sector, driven by competition for commercial success between proprietary technologies and supplemented by the strategic application of standards to solve common problems.

Findings

FOUR: There are a number of distinct categories of standards that could be adopted for diagnostic technologies, each category with different purposes and limitations.

In order to understand the value and potential drawbacks to standards, it is important to be specific about which types of standards are under consideration. There are at least 5 major categories of standards that are worth distinguishing and examining:

- **Performance standards** define the desired results that a test should be able to provide, such as the test's sensitivity, specificity, limits of detection, cost, and time to result.
- **User interface standards** define product designs to control how the end-user interacts with the instrument to limit potential for user error and/or reduce device complexity.
- **Interoperability standards** define the design of testing platforms and/or consumables to facilitate development of "plug-and-play" devices. There are 2 possible approaches to developing interoperability standards:
    - Interoperability standards can define a specific testing platform in a way that allows manufacturers to develop a variety of testing consumables for the device; or
    - Interoperability standards can define the testing consumables in a way that allows manufacturers to design platforms that are built to enable use of standard consumables.
- **Regulatory standards** would increase the supply of quality-assured diagnostic products by developing standards that could improve the global regulatory environment.
- **Analytic standards** define standardized materials, protocols, or methodologies for the development or evaluation of a new diagnostic technology.

FIVE: The potential for standards to encourage the development of new diagnostic technologies will depend on companies' willingness to embrace them.

The effect that a particular standard will have on the innovation and adoption of POC diagnostics will depend on how the standard is developed and whether it is embraced by developers. A company's willingness to embrace a new diagnostic standard will depend on whether it supports that company's business strategy.

Findings

SIX: There would be high value in creating standard specimen banks to facilitate diagnostics development.

Despite the existence of several culture or sample collections, the lack of availability of clinical or microbiological samples necessary for diagnostic research and testing is a significant barrier to innovation and development. There is a need to develop standard samples and reagents to aid in the early development of new diagnostic technologies. Sample banks would be useful in the performance of validation testing of diagnostics for regulatory clearance evaluations. Emphasis would be placed on ensuring that, for a bank to be of high value, it would need to contain a sufficient variety of strains and would need to have samples that are highly pedigreed.

SEVEN: New diagnostics need to improve clinical decision making in order to be broadly adopted.

The clinical community is the primary end-user of infectious disease diagnostics in the developed and developing worlds. The needs of clinicians and the decisions they make drive the use of diagnostics tests. Clinicians are not likely to use a diagnostic test if the results will not change the treatment or if there is no important clinical decision that depends on the result of that test. Adoption of new tests by the clinical community takes time, because clinical practice patterns are difficult to change. Many diagnoses are made on clinical grounds based on a clinical history and a physical examination. Clinicians are taught that diagnostic tests should be used to rule in or rule out a clinical diagnosis if using such a test would make a difference that is “clinically relevant.”

EIGHT: Diagnostic standards should be flexible enough to accommodate changing user needs, such as the potential increased demand for in-home POC testing.

As POC diagnostic technologies mature and become more widely used, the potential exists for use strategies or trends to differ from the status quo, including the possibility of increased use of diagnostics in the home. Existing or new diagnostic standards may need to be reevaluated depending on how these use trends evolve.

NINE: Commercial market challenges will continue to hinder the development of in vitro diagnostics.

Currently, market forces create disincentives for the development of new POC infectious disease diagnostic tests. Many technical and regulatory challenges exist that will have to be overcome before firms will commit resources to the research and development of diagnostic tests for use at the point of care. Tests must be CLIA (Clinical Laboratory Improvement Amendments) waived to be used at the point of care, and CLIA waiver is perceived by developers to be a significant hurdle. Non-POC tests may offer a more profitable approach to diagnostics development. All of these factors are relevant in considering whether a sustainable business model can be implemented for infectious disease POC diagnostics.

Recommendations

ONE: Define which POC diagnostic tests are most important for US government and NGO needs.

It would be valuable if DoD, other US government agencies, and nongovernmental organizations that are focused on diagnostics development for infectious diseases established a list of top diagnostic development priorities or requirements. The US government might consider sponsoring an ongoing process that includes DoD, the Biomedical Advanced Research and Development Authority (BARDA), CDC, FDA, the Gates Foundation and other entities, including clinicians, with an interest in developing POC and laboratory-based diagnostic tests for infectious diseases. This process should identify specific disease diagnostic priorities, desired characteristics of each diagnostic test on the requirement list, and a concept of use for each diagnostic test requirement.

TWO: Distinguish the settings and infections for which POC diagnostic tests should be the priority versus those for which in-laboratory tests would be of greater value.

Although POC diagnostics can offer a number of advantages over in-lab testing, they should not be the only approach that the US government supports. Only a limited suite of technologies have achieved CLIA waiver or are likely to do so. Therefore, the US government should consider whether testing diseases in a CLIA-approved laboratory will be sufficient or even advantageous. As the US government considers which diagnostic testing priorities it will support, it should also indicate which of those priorities are better pursued with POC strategies versus those that are better pursued by moderately complex or highly complex in-lab tests.

THREE: Consult with industry and NGOs to develop analytic standards, such as clinical sample banks.

The US government should identify those clinical specimens and reagents that are most needed for research, development, and evaluation of priority diagnostic technologies and establish a process for storing, managing, and financing a bank of those analytic standards. This work should build on existing efforts at CDC, the National Institute of Standards and Technology (NIST), and elsewhere.

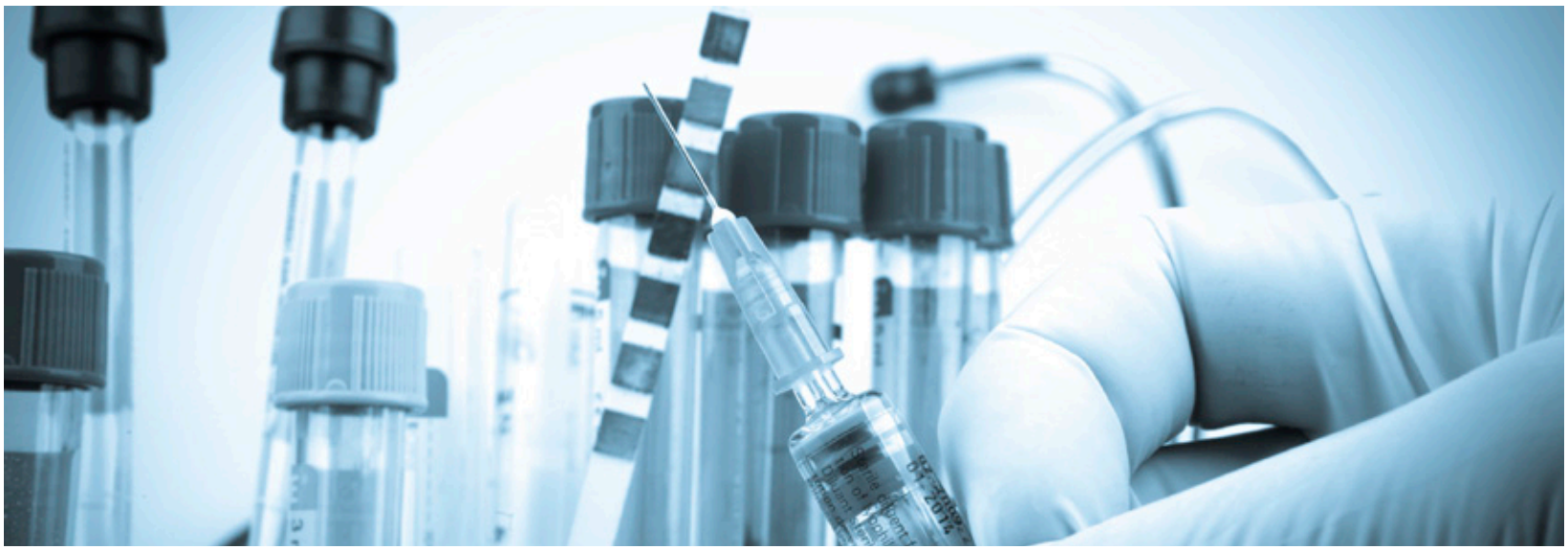
FOUR: Bring together industry and a standards-setting organization to explore specific applications of standards to diagnostics.

The US government should convene key industry stakeholders, along with a standards-setting organization, to collectively identify technical obstacles that are commonly being encountered that might best be solved by standards. A standards-setting organization (eg, the Clinical and Laboratory Standards Institute, or CLSI dedicated to facilitating dialogue across industry could help articulate specific industry needs that might be best addressed by the focused application of standards. In addition to helping to identify opportunities for standardization, a standardsetting organization like CLSI could engage with a new or existing industry consortium to assist in the implementation of the agreed-upon standards.

Recommendations

FIVE: The US government and other organizations wishing to encourage the development of POC infectious disease diagnostics will have to directly assist in the creation of a market for the desired products.

To ensure the availability of needed POC tests, the US government should coordinate with relevant stakeholders to ensure the existence of a viable market. While it remains unclear which procurement model will predominate for POC diagnostic tests, issues regarding reimbursement and cost will continue to be decisive factors in the development and diffusion of these technologies. Selecting the most appropriate purchasing mechanism will require an analysis of local market dynamics, whether in the developed or developing world. Regardless of use setting, however, diagnostic test manufacturers will have to be convinced of the viability of the market demand for their product in order for them to invest in research, development, and manufacturing capacity. As the US government and other organizations consider whether and how to facilitate the development of diagnostic standards and new diagnostics tests, they will also need to consider how to create and sustain a market for these vitally important products.



Diagnosing Infection at the Point of Care

Introduction

Diagnostic tests are critical for diagnosing diseases in US troops, for domestic and international early disease detection and biosurveillance, and for improving global health.[1] Advances in diagnostics could improve clinical management of a range of diseases in the US healthcare system. The ability to rapidly diagnose infectious disease has been identified as a strategic priority by the White House,[2,3] the US Department of Health and Human Services (HHS),[4] the National Institutes of Health,[5] the US Centers for Disease Control and Prevention (CDC),[6] and the US Department of Defense (DoD).[7]

One category of diagnostic technologies—rapid point-of-care (POC) diagnostics—offers a number of possible advantages over other diagnostic approaches. They have the potential to expedite clinical decision making, to reduce patient loss to follow up while waiting for test results, and to facilitate the delivery of care outside traditional healthcare settings. POC diagnostics also are appealing for use in lower cost environments because they require less complex infrastructure and training.

Biopharma companies and academic researchers engaged in the development of POC infectious disease diagnostics face a number of challenges as they try to increase the availability and use of these technologies: The needs of different diagnostic test users vary widely; the environmental conditions may pose problems for testing; the diagnostic requirements of different pathogens or syndromes may differ; and different diagnostic approaches may have different technological strengths and weaknesses. Collectively, these challenges have limited the development and adoption of rapid POC diagnostic tests in both the developed and developing world.

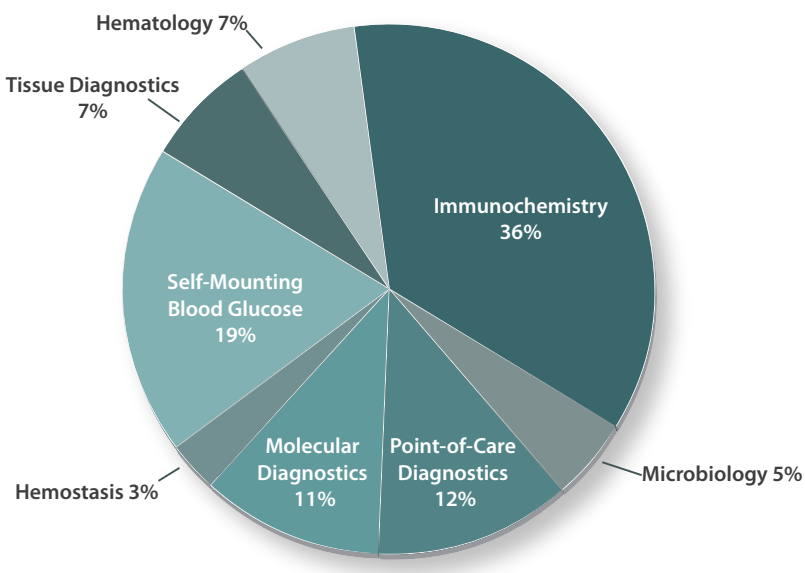
While the overall global diagnostics market is projected to surpass $50 billion in 2014, POC tests represent only a small portion of that market: 12% of the total ($5.5 billion) (Figure 1). In addition, infectious disease diagnostics represent a small slice of the overall global diagnostic market and the POC market.[8] Currently, the number of infectious disease POC tests that are approved for use in the United States is limited and focuses on a small set of common clinical conditions. Tests

cleared by the Food and Drug Administration (FDA) exist only for HIV, HCV, influenza, RSV, EBV, Group A Streptococcus, adenovirus, *Helicobacter pylori*, trichomoniasis, bacterial vaginosis, and *Borrelia burgdorferi* (although cleared by the FDA, the POC test for Lyme disease does not currently appear to be commercially available).[9] There are no POC tests available for less common but high consequence diseases of concern, including biothreat agents. It is likely that market forces alone will not be sufficient to prompt the development of the tests needed to protect troops, improve biosurveillance, and strengthen global health programs.

There is increasing interest in exploring ways to accelerate the development of new rapid POC diagnostics. The Grand Challenge in Global Health Diagnostics[10] was launched in 2011 by the Bill and Melinda Gates Foundation and Grand Challenges Canada to catalyze the development of a common, open-source platform that could be used to diagnose multiple pathogens (HIV, malaria, tuberculosis) at the point of care where traditional laboratory testing is unavailable.[11] Developing and using standards to facilitate diagnostic development has been proposed as part of this effort.[12] In addition, DTRA is sponsoring the 24-Month Challenge.[13] DTRA grantees are charged with developing POC diagnostics suitable for both mobile and clinic-based applications. DTRA also envisions the incorporation of a wireless digital connection to enable rapid reporting and analysis of test results.[13]

This report examines the clinical needs, business case, and challenges facing today's POC infectious disease diagnostics market, and it considers what role standards and other approaches may play in catalyzing the development of new POC diagnostic tests.

Figure 1. Global In Vitro Diagnostics Market 2012



This graphic was originally published in *Genetic Engineering & Biotechnology News* and is sourced to Frost & Sullivan. It is adapted and printed with permission.

Purpose, Methods, and Analysis

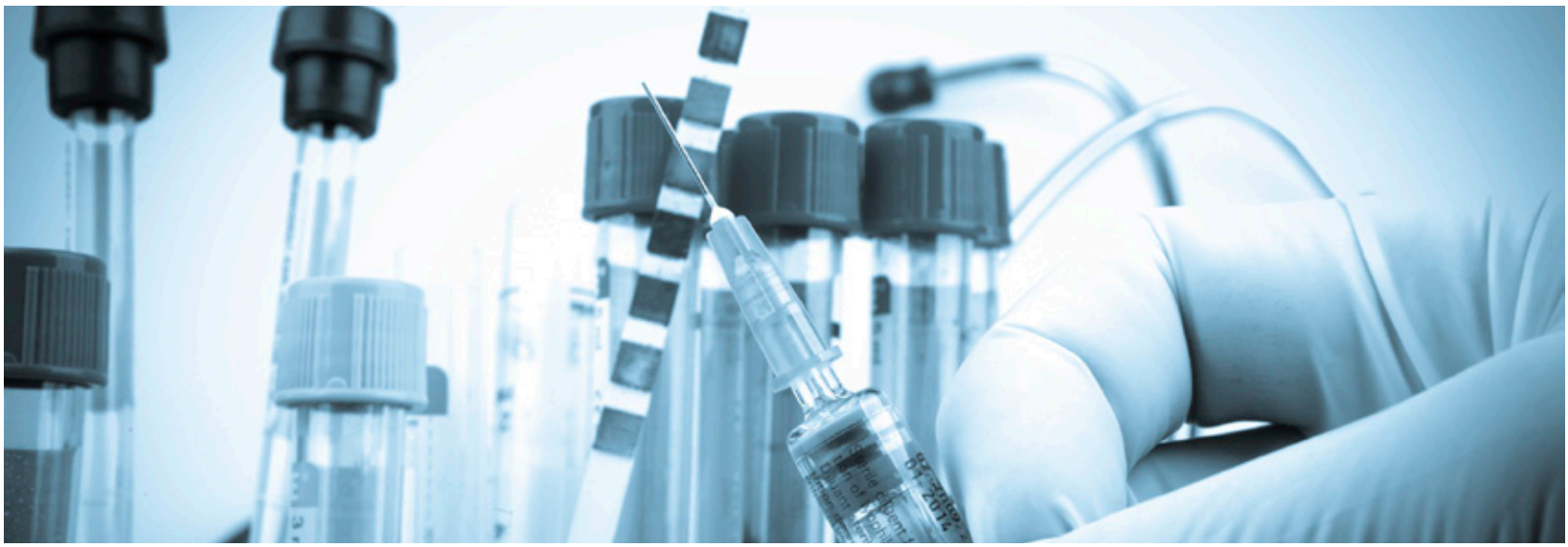
Purpose: The UPMC Center for Health Security conducted this project to provide leaders in DoD, other agencies of the US government, and NGOs engaged in global health programs with an assessment of possible strategies and initiatives that could be employed to speed the development of rapid diagnostic tests that would detect, identify, and help inform the treatment of infectious diseases. This project included a focus on the potential development and use of standards for infectious disease diagnostics, as well as on barriers, challenges, and opportunities related to the development and uptake of new diagnostic tests, particularly those at the point of care.

Methods and Analysis: We reviewed the published literature, key policy analyses, and government and nongovernment reports on current technological approaches used in POC diagnostic development. Additionally, we conducted a literature review to examine the impact of the application of standards on technology development more broadly. We applied those findings to the POC infectious disease diagnostic field, with a focus on how standards and market forces can advance or delay technological development and uptake by the market.

Center staff conducted more than 40 interviews with leaders and technical experts (listed in Appendix A) who have responsibilities related to infectious disease diagnostics research, development, or policy. We spoke with experts from nongovernmental organizations, academia, and the government to receive their opinions regarding opportunities and challenges in this area.

The Center completed a preliminary analysis report, which was informed by our review of the literature and interviews with project participants. Those findings provided the basis for a 1-day meeting on Improving the Development of Point of Care Diagnostics for Infectious Diseases, held on January 29, 2013, at the offices of the UPMC Center for Health Security (formerly the Center for Biosecurity) offices in Baltimore, MD. Meeting participants included members of industry, academia, nongovernmental organizations, and the government. Senior staff from DTRA and TASC attended as well. This report presents the Center's technical assessment of the potential value of standards to facilitate the development of POC infectious disease diagnostic devices. It synthesizes our findings from expert interviews, the literature review, and the proceedings from the January 29 meeting. Both the workshop discussion and our premeeting phone conversations with experts were held on a not-for-attribution basis. Quotes from project participants appear in italics throughout this report but are not attributed to specific individuals. The recommendations represent the views of the Center and may or may not represent the views of any of the project participants.

Funding: This project was funded by the DTRA Chemical and Biological Technologies Directorate (DTRA/RD-CB).



Findings

ONE: In the right settings, standards can be used to accelerate emerging technology development.

Standards provide requirements, specifications, guidelines, or characteristics that are used consistently to ensure that materials, products, processes, and services are fit for their purpose.[14] When applied with the proper scope at the proper time, standards can help realize desired technical, economic, and/or policy objectives, including technology development and diffusion (see Figure 2).

Figure 2: How Standards Can Affect Technology Development

Generally speaking, when applied appropriately, standards have been used effectively to do the following:

- **Exploit economies of scale** (ie, by reducing variety, standards reduce production costs)
- **Divide labor costs** (ie, standards help distribute the burden of innovation and development among firms with shared interests)
- **Increase specialization** (ie, standardization of baseline technical solutions facilitates concentration on advanced questions)
- **Build competencies** (ie, standards can act to ensure that a product achieves a predetermined level of performance)
- **Reduce barriers to entry** (ie, standards can reduce costs associated with research and development, lower intellectual property obstacles, and increase technical know-how), and create network effects (ie, as more people adopt a standard, it becomes more valuable and it is more likely that it will continue to be adopted)
- **Increase trust** between trading partners (ie, standards help create common expectations for product performance).

Standards are typically developed according to a recognized consensus process, which may be a formal de jure process supported by standards organizations (eg, International Organization for Standardization [ISO], American National Standards Institute [ANSI]), an industry or trade organization

with broad interests, or a consortia with a more limited focus (eg, Medical Device Innovation Consortium). In addition to being developed formally, standard practice may also develop de facto as a result of market forces, in which case a standard is followed because of informal convention or dominant use. For example, the VHS video standard was widely adopted in the 1980s, and the Betamax standard was virtually eliminated, due to marketing and distribution forces rather than technical differences between the 2 competing formats or a formal agreement to support the VHS standard.[15] Standards can contribute positively to innovation by facilitating cooperation between organizations; increasing product performance, homogeneity, and interoperability; accelerating the diffusion of technical solutions; and improving regulation by enabling comparability, conformity, and predictability.

TWO: When applied too early in the technology development process, standards may contribute to institutionalizing inefficient practices and stifling innovation.

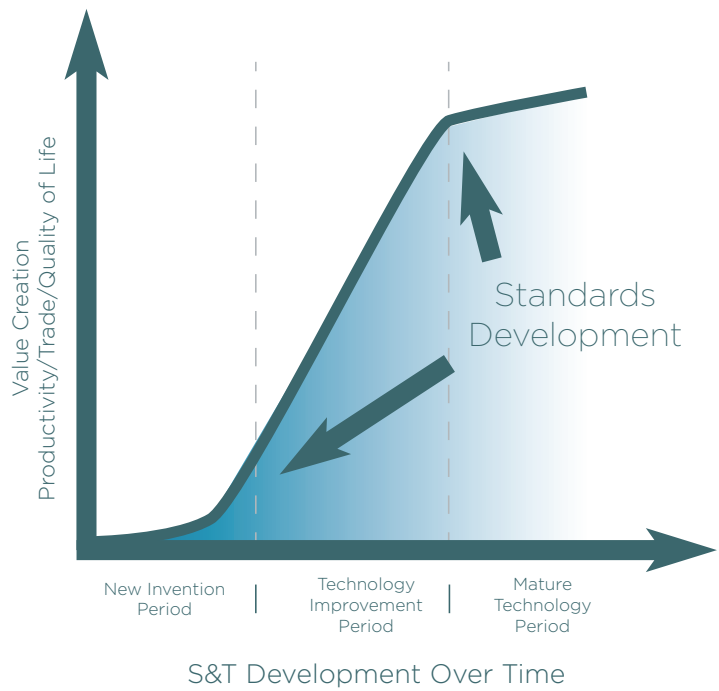
The effectiveness of standardization is influenced by the timing of its implementation relative to the advancement of the technology being standardized (see Figure 3). While standards can help spur technology development, they also have the potential to delay it. One serious concern is that standards can create "lock-in" effects and make the diffusion of more efficient innovations more difficult due to high switching costs. One notable example of this is the QWERTY keyboard. The QWERTY keyboard layout, now over 100 years old, remains the standard keyboard despite efforts to introduce more convenient and technically advanced layouts.[16]

The risk of lock-in, and resulting high switching costs, is particularly high when the diffusion of the technology being standardized has significant network effects. "Network effects" are the effects that users have on the value of a product to other users. For example, the value of a telephone increases as more people purchase compatible telephones, or the value of a social media profile increases as others create profiles on the same social network. Network effects are particularly prevalent for technologies that rely on interoperability or are network-based, such as those that entail the provision of a durable good and a complimentary good or service.[17] Because of interoperability requirements, these technologies also lend themselves to standardization.[18] For example, in the computer industry, software and hardware must be used together, and the dominant proliferation of a given hardware platform (eg, a Windows PC or Apple iPhone) further incentivizes development of software compatible with that platform, perhaps at the expense of other potentially more advanced platforms. A particular platform may become sufficiently dominant to create a de facto standard in a given industry. As network effects become more prevalent, it becomes increasingly beneficial—perhaps even necessary—for new innovations to be compatible with existing systems in order to penetrate the market. In this respect, innovation can be limited by requirements that new developments be compatible with existing systems. Thus, to the extent that early standards lock-in a given technology or platform because of network effects, the diffusion of future innovations may be restricted, making it imperative to carefully consider scope, timing, and technical implications of standardization so as not to unintentionally impede technology development or the commercial viability of new technologies.

Some notions of future diagnostic technologies are that platforms will (or should) require compatible, and perhaps proprietary, components, such as cartridges. If such platforms were to gain influence in the

market, new technologies may be required to be interoperable within these new technology ecosystems in order to be successful. This kind of networking effect in diagnostic technology development would cut both ways. Network effects enabled by standards might lead to increased technological development, but may also limit commercially viable, but diverse, avenues of innovation.

Fig. 3: Science and Technology Development and Value of Standards



Adapted from The NIST 2010 Strategic Plan

THREE: Advances in diagnostic technology seem more likely to result from the collective application of standards by private companies with common proprietary goals than from the use of standards to create open platforms.

As standards are considered for diagnostic technology, lessons from the computer revolution suggest that, rather than applying standards early in technology development to create open platforms, standards are most effective when adopted voluntarily by the private sector when it sees clear benefit and at a time of appropriate technology maturity. The computer revolution offers a recent example of the role of standards in advancing technology. A key factor shaping the personal computer industry's structure was the design of the PC, particularly the IBM, as a modular, open system with standard interfaces, which lowered barriers to the market, allowing newcomers to specialize in one industry segment and develop innovations that could be integrated into any compatible IBM system.[19] Likewise, this practice occurred across the PC industry as companies strategically standardized elements of their products. Over decades, despite being primarily motivated by their own commercial goals and

advancing their own technologies, companies acted collectively to develop more than 100 major hardware standards (eg, Bluetooth and USB) and software standards (eg, HTML and PDF) meant to facilitate greater compatibility and interoperability between mostly proprietary software, systems, platforms, and devices.[7] Meanwhile, fully open-source platforms (ie, technology platforms made available to be adapted and modified from their original design), such as Linux, did not benefit from private sponsorship and were not adopted by the market at the same level as sponsored platforms, such as Microsoft Windows and Apple's Macintosh operating system.[20]

Although it might seem logical that "open" platforms will lead to increased access and development of related, compatible innovations, compared to closed platform technologies sold for profit, there is not a lot of evidence from the computer industry to support that notion. In fact, it is common for sponsored technologies (a sponsor of a technology is an entity that has property rights to the technology and is therefore willing to invest in promoting the growth of the technology) to dominate a given market even in instances where all consumers agree that a rival, nonsponsored technology is superior.[17] Ultimately, development and maintenance of advanced technologies is best performed in the private sector, driven by competition for commercial success between proprietary technologies and supplemented by the strategic application of standards to solve common problems.

FOUR: There are a number of distinct categories of standards that could be adopted for diagnostic technologies, each category with different purposes and limitations.

In order to understand the value and potential drawbacks of standards, it is important to be specific about which type of standards are under consideration. Even within the diagnostic technology community, experts mean different things when they use the generic term "standards." There are at least 5 major categories of standards that are worth distinguishing and examining:

- **Performance standards** define the desired results that a test should be able to provide.
- **User interface standards** define product designs to control how the end-user interacts with the instrument.
- **Interoperability standards** define the design of testing platforms and/or consumables to facilitate development of "plug-and-play" devices.
- **Regulatory standards** normalize the global regulatory environment.
- **Analytic standards** define the reagents, specimens, testing protocols, and sampling methodologies that are used in instrument development and testing.

Performance Standards

Performance standards define the desired results that a given diagnostic test should be able to provide, such as the test's sensitivity, specificity, limits of detection, cost, and time to result. In order for such standards to be meaningful, they would have to be fairly specific—that is, a useful performance standard would need to be applied in relationship to a particular pathogen, stage of disease, clinical specimen, and particular population.

One broadly endorsed approach to the development of performance standards is to develop them by consensus of an expert group. For the development of new diagnostics, such a group should include the likely users of the diagnostic tools (eg, clinicians, researchers, and laboratorians), developers, and regulators. A consensus-based approach has been used successfully in the past to develop performance standards. For example, a WHO-led working group helped to develop clinically meaningful quantitative performance standards for diagnosing cytomegalovirus infection. These standards became a benchmark for the development of new commercial diagnostic tests.[21]

Establishing an expert-endorsed consensus vision of the kinds of diagnostics that are most needed and how they should perform may help to improve the quality and utility of diagnostics that are developed.

> *I can't tell you how many proposals [from industry] I've seen for diagnostic tests that are sensitive and have good limits of detection that are able to identify anthrax bacteremia on 10 microliters of blood. But the problem is, even with a good limit of detection, by the time someone's that bacteremic, they're dead.*

Performance standards developed via a consensus process would spare individual companies from having to identify on their own the type of performance that the users will require. In order to be of greatest value, performance standards should not specify a testing methodology (eg, PCR versus serology) but instead should identify how a test should perform and allow manufacturers to determine the best technical approach for meeting those goals.

Some industry experts are not persuaded that a consensus-based group is needed to develop performance standards. They say that companies create performance standards for their own products all the time.

> *This is what developers do all the time.*

Others questioned whether performance standards would actually lead to the development of higher quality diagnostic tools.

> *The absence of sensitivity and specificity standards is not inhibiting innovation.*

Others noted that performance standards would be useful to industry only if they created an easier path to regulatory approval; however, it does not seem feasible to develop performance standards in advance that, if met, would influence the likelihood that a device would be approved.

> *FDA cannot judge a test based on its clinical utility.*

User Interface Standards

User interface standards define how a product should be designed in order to control how the end-user interacts with the instrument to limit the potential for user error and/or reduce device complexity.

Developing a common, vetted design for diagnostics may make it easier for companies to create products that can be used reliably, which, in turn, could help reduce regulators' concerns about using the device at the point of care (ie, outside of a CLIA-certified laboratory).

> *If you can create a user-friendly design, you may have an easier path to CLIA waiver.*

There are examples in other fields of how the development of a common user interface has led to greater adoption of a technology by making it easier for consumers to figure out how to use a new technology.

> *If you look at cell phones, despite differences in their underlying technologies, there are some common user interface standards that have emerged.*

However, there also would be technical and commercial drawbacks to pursuing user interface standards for POC diagnostics. First, it may be technically difficult to develop or engineer a very simple user interface that would be universal and relevant across technologies and countries. Another potential problem raised by some developers is that user interface standards for diagnostics could potentially undermine a company's competitive advantage:

> *Commercially speaking, the user interface is the primary interaction with the customer. It's how companies differentiate themselves from their competitors. Why would they want to make this standardized?*

> *I don't think that you'll get all the companies to work around the same user interface standard.*

Interoperability standards for diagnostic technologies would standardize the testing platforms and/or consumables in such a way as to facilitate development of "plug-and-play" devices. There are 2 possible approaches to developing interoperability standards:

- Interoperability standards can define a specific testing platform in a way that allows manufacturers to develop a variety of testing consumables for the device; or
- Interoperability standards can define the testing consumables in a way that allows manufacturers to design platforms that are built to enable use of standard consumables.

Interoperability standards would probably work best if they were developed to be open-source so that multiple companies have an opportunity to compete to develop component products for the standardized devices. For example, the development of open-source platform standards could allow manufacturers to develop their own consumables to be used on the platform and would allow users to swap in and out consumables (like cartridges) from multiple companies.

From the point of view of industry, interoperability standards would be beneficial if they expanded market uptake of devices and drove down costs. A commonly cited example of how an interoperability standard could work is WHO's selection of Cepheid's GeneXpert as the standard for rapid tuberculosis testing.[22] Though not an open source technology, GeneExpert benefited from being singled out as the testing platform of reference. As the new global standard, Cepheid saw greater adoption of their technology in laboratories around the world and, thus, expanded the market for consumables made to be used with this platform technology. Some experts felt that these and other benefits could be achieved if an open-source technology was selected as a single, standardized platform of reference.

> *When WHO selected Cepheid, it led to greater adoption of these tests and consumables and reduced costs.*

Interoperability standards also could be used to improve quality control of devices being used in parts of the world without well-developed regulatory structures. These experts argued that if an international organization (such as WHO) is able to select a single platform as the global standard, it may be able to

Figure 4. An Innovative Approach to Developing Standards for Genomic Sequencing: The Archon Genomics X PRIZE

The X PRIZE Foundation is a nonprofit organization that seeks to stimulate innovation and competition in order to "bring about radical breakthroughs for the benefit of humanity." The Foundation creates high-profile competitions in a number of research areas, including energy and environment, exploration, education and global development, and life sciences. The X PRIZE Foundation has initiated several well-known competitions, including the Archon Genomics X PRIZE, the Google Lunar X PRIZE, and the Qualcomm Tricorder X PRIZE (http://www.xprize.org/about/who-we-are). The results of the Qualcomm Tricorder X PRIZE are significant to the advancement of point-of-care diagnostics, as competitors are charged with bringing sophisticated diagnostic capability to the hands of ordinary people.

Separately, the Archon Genomics X PRIZE provides a relevant example of how the X PRIZE Foundation approach was able to stimulate innovation in genomic sequencing and analysis, and how standard setting was needed in this field. The Archon Genomics X PRIZE sought to sequence the genomes of 100 centenarians. The purpose of the competition was to catalyze the transition of genome sequencing from being used primarily to conduct research to a tool that can be commonly used for clinical medicine.

Teams were challenged to achieve both speed and accuracy and to maintain low cost. Each team was required to sequence 100 genomes in 30 days at a maximum cost of $1,000 per genome. The sequences had to be at least 98% complete and contain no more than 1 error per million base pairs. As a function of the competition, metrics for comparing sequencing technologies were needed. Thus, the Archon Genomics X PRIZE created a validation protocol that would allow them to evaluate one team's performance compared to another's.

The establishment of the validation protocol was essentially an exercise in setting a standard. No method previously existed for determining accuracy, completeness, and haplotype phasing quality of sequenced genomes. Standards for these characteristics were established in the prize's validation protocol (http://genomics.xprize.org/sites/genomics.xprize.org/files/docs/Competition_Fact_Sheet.pdf). The protocol included 2 phases: comparison of sequencing results of publicly available genomes in the first phase, and sequencing of competition genomes in the second phase. The protocol emphasizes the challenges of validation when no definitive reference genome exists and as technology and methods evolve rapidly (http://genomics.xprize.org/sites/genomics.xprize.org/files/docs/AGXP_Validation _Protocol.pdf).

The X PRIZE approach may offer lessons in standard setting and in incentivizing innovative research and development on a particular set of problems. This model or some version of it may be considered in determining how to accelerate development of diagnostics for infectious diseases.

exert some control over which consumables or other devices are certified to work on that platform. This may, in turn, reduce the number of non–quality assured products on the market by steering users toward only those consumables or devices that are certified for use with the platform.

Another potential benefit of interoperability standards is that they may be used to streamline the maintenance of devices being used in the field. Adoption of a single plug-and-play system that has multiple potential uses may reduce the number of contracts to maintain the system, as well as reducing the necessary testing materials for the diagnostic system that are required at a given testing facility.

Still, despite the potential benefits of interoperability standards, a number of industry experts interviewed in this project saw clear disadvantages to this approach for POC diagnostics. In particular,

a number of participants were concerned that the development of interoperability standards would require the selection of a specific methodology (eg, PCR, serology, mass spectroscopy) in order to create a standard platform, resulting in the exclusion of companies and developers working on diagnostic devices that do not fit the chosen methodology. One industry expert explained:

> *When you create standard platforms, you could tend to favor one company or type of technology over another. It makes it more difficult for innovative or new technologies to break into that.*

Additionally, there was a concern that the adoption of interoperability standards—in particular the selection of a standard platform—could lead to "lock in" of a widely available technology that might ultimately prove not to be the most advanced or best performing, a situation similar to the adoption of the QWERTY keyboard. For example, some experts pointed out that if a PCR-based platform is selected as the standardized platform of reference, it would likely slow the development of next-generation testing technologies. Instead, an expert suggested to government:

> *Don't pick a winning platform. Tell us what you want the test to do, and we'll figure out what is the best technology to achieve those performance goals.*

Regulatory Standards

Many experts interviewed for this report expressed an interest in increasing the supply of quality-assured diagnostic products by developing standards that could improve the global regulatory market. These experts were hopeful that such standards could obviate the need to have devices approved by multiple regulatory authorities across the globe and mitigate the concern that regulatory controls in some areas of the world are too lax.

Some industry representatives would like regulatory authorities from several countries "to create a single streamlined submission process that would be accepted by multiple regulatory authorities." One expert suggested that "the European approach to patent applications may be a good analogy for what's possible" in terms of the feasibility of attaining international consensus on regulatory matters. (The European Patent Convention provides a harmonized application process for applying for essentially independent, nationally enforceable, nationally revocable patents in the European Union.) Global harmonization of regulatory requirements could also help to address challenges associated with countries that lack a regulatory structure.

Although most experts consulted for this project could identify problems with the current regulatory approaches, many also were quick to point out shortcomings in existing proposals for global regulatory reform. Some pointed out that various proposals to develop a global regulatory process (or to develop mutual recognition between countries of regulatory approvals) have been tried by different groups, with little success.

> *I think it's a hopeless cause. People have tried [to advance a global regulatory approval process] over and over.*

Of all the proposed standards discussed, the feasibility of global regulatory harmonization was met with the greatest resistance by most experts interviewed for this report.

Countries will want to retain their sovereignty in decision making.

The whole premise of global harmonization is a joke.

Others did not think regulatory harmonization was even desirable.

The problem is test performance needs will vary depending on the target population.

In addition to the suggestions related to harmonizing global regulatory processes, some experts suggested that diagnostics developers—particularly those that are inexperienced in shepherding a diagnostic technology through the regulatory approval process—may benefit from having their regulatory submission packages vetted by an outside organization prior to submission to a regulatory body. For example, the creation of an impartial third party to pre-review companies' submission packages might help to improve quality of regulatory submissions by validating or identifying potential problems with a company's claims.

We need to create an Underwriters Laboratories for diagnostics that helps to validate companies' testing data prior to submission.

Other experts questioned the value of the use of third parties to pre-review regulatory submissions:

The third-party concept failed terribly with diagnostics. It keeps being tried, but you wind up getting people who have no clue who have to do a diagnostic submission.

Analytic Standards

Analytic standards would create standardized materials, protocols, or methodologies for the development or evaluation of a new diagnostic technology. For example, the development of a bank of standardized testing reagents and biological specimens may make it easier for companies to develop, and for regulators to evaluate, new diagnostic tests. Experts pointed out that difficulty in obtaining well-characterized biological specimens and the absence of standard testing reagents slows companies' abilities to develop new tests.

The biggest roadblock for companies that want to get into this space is getting access to positive and negative controls.

Some experts pointed out that different types of standardized testing reagents and biological specimens may be needed, depending on whether the standard material being used is for test development or for conducting validation testing for regulatory clearance. For early research and development efforts, developers may need access to a wide variety of specimens so as to determine the limits of their technology to account for the natural variability of pathogens that exist in populations.

The first experiments we did with hepatitis B, we went to Japan and tested their materials. And we missed every single sample, because we had not taken into consideration the variation in the Japanese population. It was so embarrassing. But we didn't have access to those samples, and no one else did either, so we couldn't even have done the [right] experiment. Being able to have access to the right materials . . . will make a very big difference.

Experts interviewed for this report largely agreed that, for validation testing, the availability of gold-standard or pedigreed testing materials may be important in encouraging development of POC diagnostics.

> *I've developed assays that . . . didn't work at all, because I used uncurated, low-quality samples. . . . I think if you want to allow people to enter the market, and you want to foster innovation, then it is beneficial for high-quality, pedigree panels to be available. . . . I think that's something that merits investigation and pursuit.*

Experts also called for standardization of protocols and methodologies for collecting specimens in order to improve ability to compare performance and results obtained from different technologies and laboratories.

> *Sample collection is where most variability is introduced. Before you determine the test or technology, determining how best to collect samples for testing is critical to success.*

Standard testing methodologies have been developed successfully in the past. For example, the M100 standards developed by the Clinical and Laboratory Standards Institute (CLSI) for antibiotic susceptibility testing were widely cited as having helped to improve both the quality of testing conducted by individual laboratories and the ability to compare test results obtained by different laboratories.

> *CLSI developed M100 antimicrobial susceptibility testing standards. This document standardized what were previously variable homebrew testing methods and improved lab testing accuracy.*

Standardization of specimen collection tools and protocols could ensure easier comparison of the results from preclinical and clinical studies through the use of common volumes and facilitate better interpretation of test results. For example, one expert identified the need for blood collection standards, noting that:

> *There's no protocol of what to do before you take blood or what lancet to use. There are lots of brands of lancets that are different.*

Although there was widespread support for the creation of analytic standards, experts had concerns over which parties were best suited to develop them. For example, although a number of standards setting organizations exist, experts questioned whether these parties are sufficient to lead efforts to create and maintain these standards. Some organizations will not invest in a standards development effort unless there is a significant market for the devices.

> *The College of American Pathologists is a great organization, but when we asked them to develop a standard [testing] matrix, the first thing they ask is, "How big is your [current] market?" This was a problem because we were the first to enter this market.*

> *Over time, ISO standards can work well, but there's a need for a more rapid process. . . . Later on in the pipeline for diagnostics, ISO can kick in.*

During the working group meeting, a number of project participants agreed that a new consortium may be necessary to create the analytic standards that could accelerate the development of POC infectious disease diagnostics.

FIVE: The potential for standards to encourage the development of new diagnostic technologies will depend on companies' willingness to embrace them.

In general, there are 2 main goals in creating standards for POC diagnostics. One goal seeks to facilitate the development of new technologies, while the other strives to improve the adoption or adaptation of existing technologies. We did not find compelling evidence that any single standard will help to meet both of these goals simultaneously. Rather, it is possible that, without careful planning, the development of standards to facilitate one of these goals may undermine the other. Interoperability standards provide an example of this tension between technology innovation and product adoption. While the development of interoperability standards may facilitate the adoption of existing diagnostic technologies, it is not clear whether they will encourage innovation toward the development of new diagnostic technologies. Some experts hope that companies would be more willing to develop products for an existing platform that has been installed in clinics or labs throughout the world because developers can count on those places as potential customers for their platform-compatible products. However, we did not find this view to be broadly shared across the industry representatives with whom we spoke.

The effect that a particular standard will have on the innovation and adoption of POC diagnostics will depend on how the standard is developed and whether it is embraced by developers. A company's willingness to embrace a new diagnostic standard will depend on whether it supports that company's business strategy. As one participant described, diagnostic companies function by competing in 3 ways:

- Product leadership—companies make a product that no one else has;
- Production efficiency—companies make products cheaper and/or faster than other companies;
- Customer intimacy—companies have built such strong relationships with their customers such that customers prefer to buy from that company over others that also sell similar products.

As one expert pointed out, companies in each of these 3 categories may be likely to embrace standards differently.

> *A lot of companies that are on the product leadership side are going to have trouble with some of these standardizations, because they're going to see it as taking away from them their ability to compete . . . and they see that as a threat.*

Some experts pointed out that new standards can benefit an industry if they help "knock out" market leaders who are resistant to change and give new companies an opportunity to compete and create novel technologies.

> *The big "players" in the market will want to hinder innovation, to ensure the continuation of their technology's market dominance. Smaller firms will aim to be more disruptive and degrade the incumbent's advantage. For larger firms, there will be no incentive to make huge technological leaps. Unless competition is increased, the progress of innovation will be incremental.*

Allowing additional companies to compete to develop diagnostics may help to drive down costs. However, others cautioned that while knocking out market leaders in favor of companies that are willing to accept smaller profit margins may improve adoption of existing technologies, it may ultimately hinder the development of novel diagnostic technologies in favor of cheaper versions of existing technologies. Those with these concerns argue that companies who are actively engaged in product innovation will have to charge more for products than those who produce copies of existing technologies at reduced costs.

> *Standards may help to stimulate the "generic," or low cost, market for consumables.*

> *The problem with a platform that is "too open" is that other market participants will inevitably start to produce what amounts to generic consumables. This takes away from margin that your company could be realizing. Why would you want to invest in research and development knowing that?*

SIX: There would be high value in creating standard specimen banks to facilitate diagnostics development.

Of all the kinds of standards analyzed in this project, there was greatest support for the development of analytic standards—specifically, the creation of standard specimens and reagents. There was a widely perceived need for developing standard samples and reagents to aid in the early development of new diagnostic technologies. Sample banks would be useful in the performance of validation testing of diagnostics for regulatory clearance evaluations. Emphasis would be placed on ensuring that a variety of strains are included in a sample bank and that standard samples are highly pedigreed. Both of these characteristics would be valuable to facilitating early and advanced development of diagnostics for the diseases of interest to the US government.

Some sample banks already exist (see Figure 5). These serve a valuable function, but they do not represent the full range of pathogens for which POC tests would be an important contribution. Established large developers of diagnostic tests often maintain proprietary sample banks, which are sometimes viewed as a competitive advantage and that are not now accessible to nascent developers. Limited access to sample banks, as well as insufficient resources to develop an in-house version, can pose a high barrier to entry into the market and may also become an obstacle to successful regulatory licensing for smaller developers. The character of specimens needed for evaluating a test changes as a diagnostic test moves from earlier stages to regulatory approval (the latter requiring a known pedigree and standard formulation), so access to specimen banks with varied samples is crucial.

Developers of diagnostics can be hampered by a lack of access to varied samples to perform these tasks. The President's Council of Advisors on Science and Technology (PCAST), in a 2012 report focused on drug discovery, highlighted the difficulties in maintaining sample banks.[23] In 2008, PCAST recommended, in the realm of personalized medicine, the creation of "an integrated, national network of standardized biospecimen repositories,"[24(p34)] highlighting the NIH National Heart Lung and Blood Institute's (NHLBI) Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC).[25]

During the January 29 meeting, one project participant stated:

> *If we walk out of this meeting with nothing but an agreement on what we're going to do with sample banks, . . . I think that would move this entire industry forward and do so with a level playing field for all players, be they well established or newcomers to the industry.*

Reliable sample banks could provide a source from which developers can test the robustness of their diagnostic devices. Such samples would need to be drawn from various geographic sources, stages of disease, and time periods.

Many of the existing sample banks have been established fairly recently, within the past 5 to 7 years. It takes time for experts to decide which samples of a pathogen or group of pathogens to collect and include in the bank. And despite their value, maintaining these sample banks is costly. Samples are generally maintained at multiple institutions, and those in need of samples can request them and pay for shipping of samples through the lead organization. Requests for samples often must be approved in advance of shipping, and some have restricted access. Expanding existing sample banks and creating new banks that include pathogens for which availability and access to samples is considered to be an obstacle among researchers and diagnostic developers should be considered.

SEVEN: New diagnostics need to improve clinical decision making in order to be broadly adopted.

The key consideration in the development of new POC diagnostics is the extent to which they will help to meet the needs of the intended users. Users' needs will likely be the ultimate critical determinant of whether POC tests for infectious disease are adopted. Therefore, any effort to create standards must take into account current and future users' needs.

> *You need to identify the customer and their needs, and the standards derive from that, not the other way around.*

The clinical community, including hospitals, physicians' practices, urgent care facilities, health clinics, and other healthcare providers, as well as clinical laboratories of all levels, are the primary consumers of infectious disease diagnostics in the developed and developing worlds. The needs of clinicians and the decisions they make drive the use of diagnostic tests. As new tests are developed, the most successful ones are likely to be those that have direct clinical relevance.[26]

Adoption of new tests by the clinical community takes time, particularly because clinical practice patterns are difficult to change. Many diagnoses are made on clinical grounds based on a clinical history and a physical examination. Clinicians are taught that diagnostic tests should be used to rule in or rule out a clinical diagnosis if using such a test would make a difference that is "clinically relevant." Clinicians are not likely to use a diagnostic test if the results will not change the treatment or if there is no important clinical decision that depends on the result of that test.

> *Uptake of testing depends on the clinical culture of the hospital and/or cost benefit.*

> *A big challenge is how do we utilize diagnostics to support clinical decisions?*

Confirming a clinical diagnosis with a laboratory test is usually warranted if it leads to a specific treatment or if the result has specific prognostic significance. For example, rapid tests for influenza are often considered worthwhile because antivirals can be prescribed and sometimes antibiotics can be avoided. The test is considered more useful early in a flu season, when the incidence of influenza is relatively low. At the peak of an epidemic, many clinicians forego testing when the clinical presentation is typical.

> *Physicians often say, "We're not testing patients who present with ILI, we're just treating for flu." This makes test developers crazy. But the reality is that, unless there's a therapeutic change that results from a diagnostic result, rapid ID testing really doesn't matter.*

Likewise, a POC test for group A streptococcus from a pharyngeal swab (strep throat) is often useful because the result can guide antibiotic therapy. A rapid test for Epstein-Barr virus is useful not only because it can help avoid unnecessary and possibly harmful antibiotic therapy and guide potential corticosteroid therapy, but also because it leads to specific patient instructions about activity and advice about length of illness.

In contrast, tests for other common self-limited respiratory viral infections (eg, rhinovirus, parainfluenza virus, coronavirus) are not likely to change either therapy or prognosis and therefore are not likely to be ordered routinely. The exception is in patients who are unusually sick and require hospitalization. In these patients, diagnostic testing to guide therapy is more important. However, these patients are likely to require referral to a hospital emergency department regardless of the results of the test, and therefore it is less important that the test be POC. In the US, POC tests exist for most of the common outpatient infectious diseases for which there is a clinical decision to be made. (See Appendix B for list of available POC diagnostics.)

Another issue that relates to the clinical adoption of a test is the ease of specimen collection. Clinicians will weigh the difficulty of collecting the specimen against the likely benefit of the information from the test. This is especially true in the outpatient setting, when dealing with children, and when there is only 1 clinician present. While obtaining blood or pharyngeal specimens from an adult is usually fairly easy, it is more difficult for 1 physician to obtain specimens from a reluctant or uncooperative child.

It can be a challenge for diagnostic developers and manufacturers to get accurate perceptions about clinicians' needs and how those needs are likely to vary for different pathogens, syndromes, and testing environments. One participant in this project earlier had conducted a survey of physicians and diagnostic test developers to compare the needs of clinicians with developers' perceptions of clinicians' needs. Clinicians were willing to give up specificity of a diagnostic if it meant the test would be cheaper, while developers thought clinicians wanted highly sensitive and highly specific tests, regardless of cost.

> *There was a considerable disconnect between what they [developers] thought clinicians wanted and what clinicians said they wanted.*

In thinking about how to develop standards for POC diagnostics, it is also important to consider how the needs of users are likely to differ depending on the specific environments in which the tests will be used.

> *You don't need to test for malaria or TB at Wal-Mart. You would test for diabetes and heart disease.*

A different constellation of infectious diseases are common in the outpatient setting in the developing and developed worlds. This includes many diseases no longer frequently seen in the US, such as measles, mumps, and tuberculosis. There is also a difference based on geography: There are many diseases endemic to the tropics, such as dengue and malaria, that are very rarely seen in the US. Therefore, the size of a potential market for a specific test will vary considerably by geographic location. The calculation of whether a specific POC test is clinically relevant will likely vary by location, the endemic diseases in that location, and the availability of specific therapies.

> *Some global health needs are so different from what you need for a successful diagnostic device in the US market, that it still might not make economic sense for our company to develop tools for the global health setting.*

EIGHT: Diagnostic standards should be flexible enough to accommodate changing user needs, such as the potential increased demand for in-home POC testing.

The rise of in-home POC diagnostics, such as in-home HIV testing and glucose monitoring, raises the possibility that the users of POC tests and the environments in which testing occurs may change over time. Some project participants suggested that in the not-too-distant future, the general population may be a market for in-home testing and that the traditional role of physicians will be reduced. In this line of thinking, individuals would test themselves at home and then go a pharmacy-based clinic to get their medicine.

> *I think as we get better at diagnosing, the amount of expertise needed of a clinician will go away. . . . I think it's going to be less and less about the art of medicine and more and more about the quality of the diagnostic.*

> *We go away from a paradigm where physicians actually make the diagnosis based on a combination of what the patient looks like and the laboratory test data that come back. Now we're going to a test that's much more widely distributed . . . because there's a do-it-yourself test. We ought to think very consciously about the implications of that. . . ."*

> *In 2 to 3 years, our delivery of health care, because of economics, is going to be radically shifted away from that traditional bricks-and-mortar physician office and become dominant in the mobile, at-home, DIY medical space.*

In the long term, the rapidly changing healthcare environment in the US—particularly as electronic health records are adopted and reimbursement mechanisms and decisions change—is likely to influence who are the primary users of POC diagnostics and what are their specific needs. If this vision of the future is correct and POC testing does, in fact, shift to nonclinical environments, it would mark a fundamental change in clinical medicine, the use of clinical laboratories, and the diagnostics market. As a result, the way industry develops tests and, by extension, diagnostic standards will have to anticipate and adapt to these changes. Efforts to create standards for POC diagnostics must also account for potential changes in users' needs that may occur over time.

NINE: Commercial market challenges will continue to hinder the development of in vitro diagnostics.

POC diagnostics are affected by multiple market forces that play a primary role in driving innovation. Currently, many of these market forces create disincentives for the development of new POC infectious disease diagnostic tests. Many technical development challenges exist in making tests that can be used at the point of care. Tests must be CLIA waived to be used at the POC, and CLIA waiver is perceived by developers to be a significant hurdle. Non-POC tests may offer a more profitable approach to diagnostics development. All of these factors are relevant in considering whether a sustainable business model can be implemented for infectious disease POC diagnostics.

Technical Challenges to Developing POC Diagnostics

> *It's more difficult to develop POC tests than it is to develop laboratory tests.*

Developing tests for the point of care, or repurposing laboratory tests to be used at the point of care, is a significant technical hurdle, and it is expensive to achieve. The development process includes simplifying the user interface, miniaturizing processes, and reducing sample volume, and it may include making a test more rugged. One developer observed that "there is a significant premium to be paid for developing a POC assay, versus having a desktop unit that is used in a clinic." Overcoming these technical hurdles may be possible, but as one participant noted:

> *If you want a tricorder-like device that is cost effective and regulatory compliant, that device won't be built and supported by a large commercial entity unless there is significant market need or governmental support agreed upon up front.*

Meeting Requirements for CLIA Waiver Is a Significant Hurdle

To be used truly at the point of care, diagnostic tests need to obtain a CLIA waiver. While some CLIA moderately complex tests are used in physicians' offices, a CLIA waiver is the classification that allows for a more distributed use of a diagnostic test outside of a laboratory. This is perceived to be a significant hurdle for developers and a disincentive to developing POC tests versus diagnostics that are used in clinical laboratories.

FDA is responsible for assigning a CLIA complexity category to a diagnostic test on evaluation of the test (See Figure 6). Among a number of criteria, FDA evaluates complexity based on the simplicity and reliability of a device, the training required to conduct the test, and the likelihood that the test result will be interpreted correctly. Developers consider this to be a high bar and may not choose to invest in the technical advances and user interface requirements needed for POC.

Among the categories of diagnostic tests, only rapid-antibody or rapid-antigen detection tests have obtained CLIA waiver, most commonly in the form of dipstick or lateral flow devices. However, there are a number of emerging technologies and advances in classic microbiology, nucleic acid tests, nuclear magnetic resonance (NMR), mass spectroscopy, and whole or partial genome sequencing.

Figure 5: Existing Infectious Disease and Microbiological Specimen Repositories

- **Malaria Specimen Bank:** Established in 2007, this repository is the result of collaboration between the Foundation for Innovative New Diagnostics (FIND), US CDC, WHO, and other research institutions. The bank consists of standardized dilutions of blood resulting in varied parasite densities. http://www.finddiagnostics.org/programs/malaria-afs/malaria/product_development/specimen_bank.html
- **Human African Trypanosomiasis (HAT) Specimen Bank:** This specimen bank, the result of a collaboration between FIND and WHO, consists of varied specimens from those at risk for HAT, those with confirmed HAT, and those with rapid-test confirmed disease but parasite-negative HAT. http://www.finddiagnostics.org/programs/hat-ond/hat/specimen_bank.html
- **TB Specimen Bank:** Established in 2000, this WHO repository contains specimens from respiratory patients with and without tuberculosis worldwide. Specimens are indexed by specific microbiologic and clinical features. http://www.who.int/tdr/diseases-topics/tuberculosis/specimen-bank/en/index.html. Vincent V, Rigouts L, Nduwamahoro E, et al. The TDR tuberculosis strain bank: a resource for basic science, tool development, and basic science. *Int J Tuberc Lung Dis.* 2012;16:24-31.
- **CDC Lyme Disease Specimen Bank:** Work on this bank, funded by NIH and CDC, began in 2009; it consists of samples from individuals with all stages of Lyme disease as well as those with similar diseases and controls from endemic and nonendemic regions. HHS federal research update on Lyme disease diagnostics activities, September 24, 2012. http://www.cdc.gov/lyme/resources/webinar/09242012_DiagnosticsWebinarTranscript.pdf
- **Columbia University Lyme Disease Specimen Bank:** This university-based bank contains serum and cerebrospinal fluid from patients afflicted with Lyme disease. http://www.columbia-lyme.org/research/columbia_specimen_bank.html
- ***Clostridium difficile* Infection Surveillance Isolate Bank:** This bank, developed by CDC, collects samples from the Emerging Infections Program *Clostridium difficile* infection surveillance activities, which span 10 states. Both community- and hospital-acquired strains are available. http://www.cdc.gov/hai/eip/cdi_iso-bank.html
- **CDC Unexplained Death (UNEX) Specimen Bank:** This broader effort, launched in 1995, to characterize unexplained deaths thought to be secondary to infection included the development of a specimen repository bank for testing future diagnostic tests that might be developed. Hajjeh RA, Relman D, Cieslak PR, et al. Surveillance for unexplained deaths and critical illness. *Emerg Infect Dis.* 2002;8:145-153.
- **WHO Measles Strain Bank:** This bank serves to acquire, store, analyze, and dispense measles strains (wild type and vaccine strains). http://www.hpa.org.uk/ProductsServices/MicrobiologyPathology/LaboratoriesAndReferenceFacilities/VirusReferenceDepartment/ResearchDevelopment/cfi_vrd_rd_RdMeasles/
- **US DHS NBACC National Bioforensics Analysis Center (NBFAC) Bioforensic Reference Repository:** This bank, established via HSPD10 in 2004, contains varied geographic and temporally obtained biological samples that may be required in the course of a forensic investigation. http://www.dhs.gov/news/2011/10/18/testimony-honorable-tara-otoole-md-mph-us-senate-committee-homeland-security-and
- **Smithsonian National Museum of Natural History (NMNH) Biorepository:** Begun in 2011, this collection is believed to be the largest museum-based biorepository, with a capacity of 5 million 2mL cryovials. The biorepository holds animal, plant, and bacterial specimens. Additionally, the NMNH is involved in initiatives to develop authentication criteria for sample banks. http://www.mnh.si.edu/rc/biorepository/
- **Critical Reagents Program (CRP):** Supported by the Joint Program Executive Office for Chemical Biological Defense (JPEO-CBD), CRP provides high-quality, validated, standardized detection assays, including antibodies, inactivated antigens, genomic materials, sampling kits, and multiple assays to facilitate advanced development of diagnostics and medical countermeasures. The collections are managed by BEI Resources, an organization established by the National Institute of Allergy and Infectious Diseases (NIAID) and supported by the American Type Culture Collection (ATCC), which provides reagents, tools, and information for studying a variety of high-threat, emerging, and common infectious disease pathogens. http://www.jpeocbd.osd.mil/packs/Default.aspx?pg=1205 http://www.beiresources.org/About/BEIResources.asp

Innovation in these categories that have not obtained CLIA waiver may be as important to the diagnostic and healthcare delivery systems as POC tests. Some of these technologies are already used in clinical laboratories for confirmatory testing, antimicrobial susceptibility testing, and pathogen characterization. Nucleic acid tests have become increasingly used in clinical laboratories and are relied on for both initial pathogen identification and confirmatory diagnosis.

There remains a doubt as to whether these technologies could be brought to the point of care, because current levels of complexity (ease of use and interpretation of results) that are associated with them stand in the way of a CLIA waiver.

> *I don't see a POC nucleic acid test being CLIA-waived unless massive innovation occurs.*

NMR, mass spectroscopy, and genome sequencing can provide distinct advantages in disease diagnosis, but these technologies are not likely to reach POC in the near term and are dependent on the infrastructure and personnel of a laboratory. Because of the difficulty of obtaining CLIA waiver for some of the more complex technologies, developers are moving toward service-based business models, in which samples are sent to developers to test on a fee-per-test basis. These models, in addition to the growth of laboratory-derived tests, which are the fastest growing segment of the in vitro diagnostics industry, reflect some of the challenges and limitations of the POC diagnostics market. CLIA moderately complex devices placed in physicians' offices might be a suitable alternative to CLIA-waived devices, which "are very likely to run into all kinds of misuse utilization issues."

Creating a Sustainable Business Model is Dependent on a Perceived Profitable Market

In order to develop diagnostics, companies must see a profitable market. Although there are only a handful of CLIA-waived POC diagnostics available in the US market, they address common infections for which there is a clear clinical decision to be made. Development of new POC tests in the infectious disease space will depend on identification of new markets. One developer noted:

> *There are limited commercial needs for POC products, and we are only profitable because we are careful about what markets we choose to participate in.*

Companies are wary about entering new markets, particularly specialized infectious disease markets. Industry participants say they would be more willing to develop POC diagnostics if they had clear product targets and support from funding agencies and/or nonprofit foundations. Low-cost POC diagnostics have small profit margins, and they are typically developed by small companies that face high regulatory hurdles and expensive advanced development costs.

> *Companies are limited in their available resources and have had to carefully prioritize what areas they move into.*

> *Either there needs to be a guaranteed funding source so that businesses know what they're getting into, or there needs to be a confirmed market demand.*

Additionally, there are delays in creation of reimbursement mechanisms for new POC diagnostics. One industry expert made it clear that

. . . Once you get CLIA waiver and 510k approval, you still need the insurance companies to pay for the procedure [CPT code]. These 3 things are absolutely necessary to market a device and these take time.

Companies that develop POC tests must sell directly to clinicians, which presents additional challenges in marketing these devices. First, clinicians represent a relatively new, unfamiliar customer group for most diagnostic companies, which typically sell their products to CLIA-certified laboratories. Second, physicians may be largely unfamiliar with which POC tests are available or the CLIA regulations that apply to their use in clinical offices and, therefore, will need to be educated before they can adopt POC testing in their offices. Third, some states charge physicians who provide CLIA-waived POC tests a yearly fee, which may act as a disincentive to adoption of POC tests. Fourth, if POC tests are not used routinely, physicians may have to run positive and negative controls to ensure that their tests are being used correctly, which can be a costly and nonreimbursable step.

Diagnostic companies also face challenges associated with the global health market, which can increase costs of development (eg, for miniaturization, ruggedization) and decrease profit margins. Thus, diagnostics for global health applications face even higher development barriers.

The cost of developing an assay with such a radically different cost structure from those in a US hospital would be challenging for our company.

Developers' ability to profit from new diagnostic tests is often limited because clinical adoption of new medical products is normally slow. Even if a new test is clinically relevant, inexpensive, and easy to use, adoption may take considerable time. Clinical practice patterns are hard to break. The pharmaceutical industry addresses this challenge by employing a large sales force to provide information to educate clinicians when there are clinically useful products available, but the diagnostics industry does not have comparable sales departments. As a result, most diagnostic companies typically prefer to market their Thus, products to larger purchasers (ie, large clinical laboratories). Developing a product that would be used outside of a laboratory would require that diagnostic companies change their marketing and sales operations to market directly to clinicians.

Even when we have data that the test works and would improve health care and reduce costs, it still takes 10 years to develop a market and get adoption by the clinical community.

Most of the diagnostic manufacturers today sell to laboratories, not doctors. And most of the ones that used to sell to the doctors don't anymore.

All the sales reps that sit over on the pharma side who tell doctors about their drugs and tell them where to use them and tell them how to—they just don't exist in the diagnostics business.

Figure 6: The Complexity of Diagnostic Tests: CLIA

While the Centers for Medicare and Medicaid Services (CMS) regulates laboratory-based tests through the Clinical Laboratory Improvement Amendments Act (CLIA),* FDA administers the CLIA Complexity Program by categorizing commercially marketed diagnostics by level of complexity:

1. Waived Test (Low Complexity)
2. Tests of Moderate Complexity
3. Tests of High Complexity

Complexity refers to how easy the test procedure is to perform. A higher complexity device will be subject to more stringent CMS regulations and inspections. The complexity category determines how the laboratory performing the diagnostic test is regulated by CMS through CLIA.

CLIA status is determined through a point scoring system (1-3, low to high complexity) for each area related to the device: (1) knowledge; (2) training and experience; (3) reagents and materials preparation; (4) characteristics of operational steps; (5) calibration, quality control, and proficiency testing materials; (6) test system troubleshooting and equipment maintenance; and (7) interpretation and judgment.†

Devices with a cumulative score that is greater than 12 are categorized as high complexity. Devices with a cumulative score less than 12 are categorized as moderate complexity. High and moderate complexity tests must be performed in CLIA-certified labs by qualified personnel. CLIA defines labs as any facility used to examine materials derived from the human body.§ CLIA laws apply whenever patient-specific results from the laboratory are used to guide the health care of individual patients.

In some cases, a test is deemed simple and accurate enough to be "CLIA waived." CLIA-waived tests are performed in certified facilities that are subject to the lowest level of oversight. CLIA waivers‖ are granted to the following:

- Any test listed in the 1988 CLIA amendments (dipstick urinalysis for ketones, fecal occult blood tests, ovulation tests, urine pregnancy tests, spun hematocrit).
- Any test system for which the manufacturer applies for a waiver if that test meets the statutory criteria and the manufacturer provides scientifically valid data verifying that the waiver criteria have been met.
- A device must have a CLIA waiver to be used in physicians' office laboratories.
- In order to be used at the point of care, infectious disease diagnostics will have to be granted a CLIA waiver by the FDA.

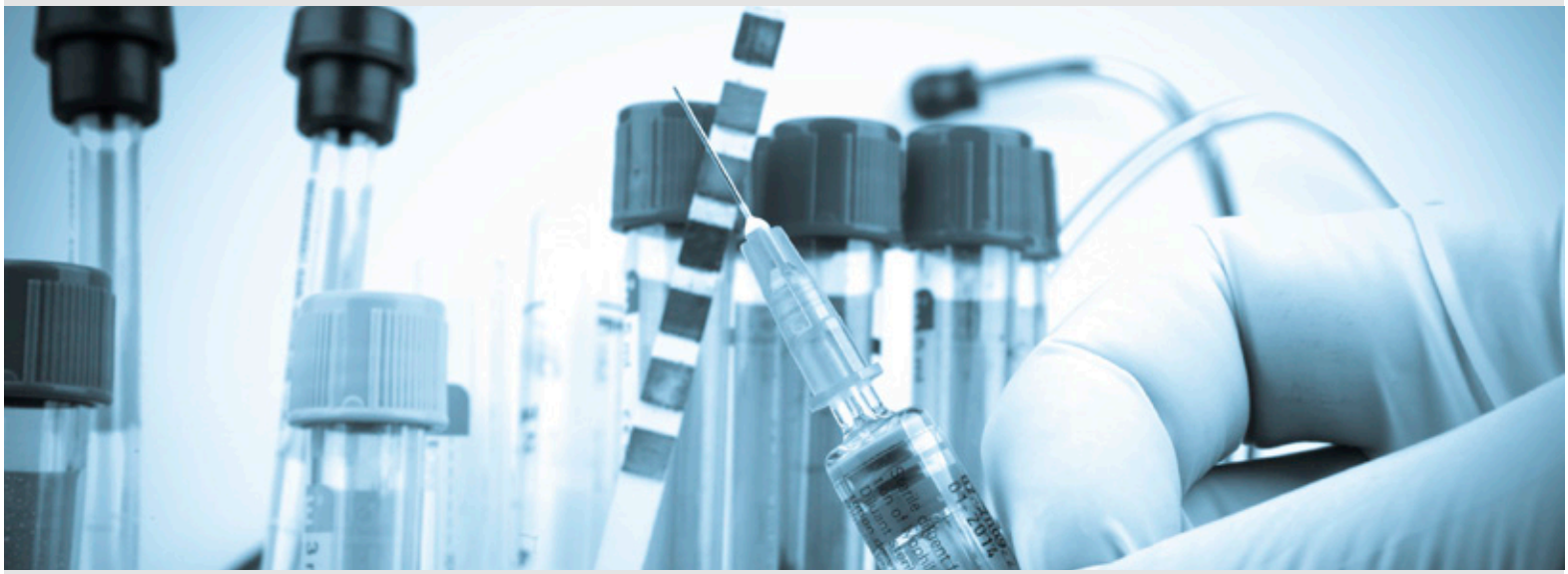
---

* US Centers for Medicare & Medicaid Services. Clinical Laboratory Improvement Amendments (CLIA) overview. June 20, 2011. https://www.cms.gov/clia/. Accessed March 15, 2013.

† US Food and Drug Administration. CLIA categorization criteria. March 20, 2009. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124208.htm. Accessed March 15, 2013.

§ US Centers for Medicare & Medicaid Services. CLIA update: laboratories by type of facility. June 2011. http://www.cms.gov/CLIA/downloads/factype.pdf. Accessed March 15, 2013.

‖ US Food and Drug Administration. CLIA waivers. June 19, 2009. http://www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm124202.htm. Accessed March 15, 2013.



Recommendations

ONE: Define which POC diagnostic tests are most important for US government and NGO needs.

It would be valuable if DoD, other US government agencies, and NGOs focused on diagnostics development for infectious diseases were to establish a list of top diagnostic development priorities or requirements. Normally this kind of market research is conducted by each company individually, but because the market for these tests is uncertain and because the federal government has an interest in promoting their development, it would be valuable to pursue a collaborative approach to this process convened under the auspices of the federal government. The US government might consider sponsoring an ongoing process that would include DoD, BARDA, CDC, FDA, the Gates Foundation, and other entities with an interest in developing POC and laboratory-based diagnostic tests for infectious diseases. This process should engage clinicians from settings where these diagnostic tests would be used (eg, hospitals, urgent care clinics, developing world primary care settings). The result of the process would ideally include specific disease diagnostic priorities, desired characteristics of each diagnostic test on the requirement list, and a concept of use for each diagnostic test requirement.

TWO: Distinguish the settings and infections for which POC diagnostic tests should be the priority versus those for which in-laboratory tests would be of greater value.

Though POC diagnostics can offer a number of advantages over in-lab testing, they should not be the only approach that the US government supports. POC diagnostics will not dominate the market in the near term, nor will they offer all of the diagnostic capacity needed by the test users. Only a limited suite of technologies have achieved CLIA waiver or are likely to do so. Therefore the US government should consider whether testing diseases in a CLIA-approved laboratory will be sufficient or even advantageous. Many technologies are available in clinical laboratories that may offer benefits over POC approaches in sensitivity and specificity, antimicrobial susceptibility, quantitative analysis, or clinical relevance based

on disease progression. In addition, in-lab tests may be sufficient or suitable for infectious disease diagnoses made in hospitalized patients or in clinical settings in which loss to follow up is not a large concern. Given all of these factors, it would be useful if, as the government considers which diagnostic testing priorities it will support, it also indicates which of those priorities are better pursued with POC strategies versus which are better pursued by moderately complex or highly complex in-lab tests.

THREE: Consult with industry and NGOs to develop analytic standards, such as clinical sample banks.

One area where there appears to be both the greatest need and support for the development of standards is the creation of analytic standards, such as sample banks. In our analysis, there was widespread interest among industry representatives in having better access to both a diversity of clinical specimens and other reagents needed for developing new diagnostic technologies, as well as highly pedigreed samples that could be used for validation testing for regulatory compliance.

Although a variety of sample banks currently exist, the purpose and function of these banks vary widely. The types of available samples and access to them differs by disease, and these existing banks are insufficient to support the development of POC diagnostics that are needed by the US government and for global health needs. It would be useful if the DoD were to work with other partners in the government (eg, OSTP, FDA, CDC, NIST, and NIH) to identify those clinical specimens and reagents that are most needed for research, development, and evaluation of priority diagnostic technologies and establish a process for storing, managing, and financing a bank of those analytic standards. This work should build on existing efforts at CDC, NIST, and elsewhere.

FOUR: Bring together industry and a standards-setting organization to explore specific applications of standards to diagnostics.

Future development of POC diagnostics is likely to consist of multiple, potentially disparate emerging technologies and platforms. Efforts to develop beneficial standards for this field will need to be founded on an inclusive dialogue across industry. Developers of diagnostic tests will be the ones most familiar with the kinds of challenges that could be resolved by standards. They are aware of both the negative implications of applying standards too early in the process and of the potential benefits of well-timed standards. In the end, a new standard will be effective in guiding development only to the extent it is actually put into practice, so developers themselves need to be engaged in and supportive of the process.

DTRA and the US government could usefully convene key industry stakeholders, along with a standards-setting organization, to collectively identify technical obstacles that are commonly being encountered that might best be solved by standards. A standards-setting organization (eg, CLSI) dedicated to facilitating dialogue across industry could help articulate specific industry needs that might be best addressed by the focused application of standards. In addition to helping to identify opportunities for standardization, such a standard-setting organization could engage with a new or existing industry consortium to assist in the implementation of the agreed on standards. For example, a similar process has been used by NIST (Genome in a Bottle Consortium) and CLSI (M100 antibiotic susceptibility testing standards).

FIVE: The US government and other organizations wishing to encourage the development of POC infectious disease diagnostics will have to directly assist in the creation of a market for the desired products.

Although standards may play a role in the development and adoption of POC diagnostics, for the foreseeable future, meaningful progress on these fronts will not occur in the absence of a viable market. Demand for novel POC diagnostic tests is primarily driven by clinicians, NGOs engaged in global health efforts, and national governments. Once tests are developed, there are several options for financing the purchase of diagnostics for use by clinicians. Selecting the most appropriate purchasing mechanism will require an analysis of local market dynamics, whether in the developed or developing world. Regardless of use setting, however, diagnostic test manufacturers will have to be convinced of the viability of the market demand for their product in order for them to invest in research, development, and manufacturing capacity.

The most straightforward procurement process is the direct purchase of diagnostic tests by the end-user. However, given the need for manufacturers to recoup research and development costs, newly developed diagnostic tests could be priced above what many countries in the developing world can afford to pay. Higher costs could limit the diffusion of new technologies into the developing world.

Traditionally, procurement for products intended for use in global health settings, including medicines and vaccines, has involved the participation of one or more donors to overcome the issue of product affordability.[27] Applied to the diagnostics field, such an arrangement would entail a donor's either directly purchasing diagnostic tests that meet preestablished criteria and distributing them for use or subsidizing the cost of the tests. In order to make progress in making novel technologies available at the point of care in global health settings, it is likely that some form of donor involvement will be necessary.

While it remains unclear which procurement model will predominate for POC diagnostic tests, issues regarding reimbursement and cost will continue to be decisive factors in the development and diffusion of these technologies. As the US government and other organizations consider whether and how to facilitate the development of diagnostic standards and new diagnostics tests, they will also need to consider how to create and sustain a market for these vitally important products.

References

1. Nuzzo JB, Rambhia KJ, Wollner SB, et al. Diagnostics for Global Biosurveillance: Turning Promising Science into the Tools Needed in the Field. July 2011; http://www.upmc-biosecurity.org/website/resources/publications/2011/pdf/2011-09-13-global-biosurveillance-DTRA.pdf.
2. The White House. National Strategy for Biosurveillance. 2012; http://www.whitehouse.gov/sites/default/files/National_Strategy_for_Biosurveillance_July_2012.pdf. Accessed February 11, 2013.
3. National Security Council. National Strategy for Countering Biological Threats. 2009; December 9, 2009 Available at: http://www.whitehouse.gov/sites/default/files/National_Strategy_for_Countering_BioThreats.pdf. Accessed February 11, 2013.
4. Department of Health and Human Services. National Health Security Strategy of the United States of America. 2009; December 7, 2011 Available at: http://www.phe.gov/Preparedness/planning/authority/nhss/strategy/Documents/nhss-final.pdf. Accessed February 11, 2013.
5. Korte B. Point-of-Care Diagnostic Testing. 2010; http://report.nih.gov/nihfactsheets/Pdfs/PointofCareDiagnosticTesting(NIBIB).pdf.
6. Centers for Disease Control and Prevention. Report to Congress on Internal Laboratory Activites of CDC and Associated Funding Levels May 2012; http://www.cdc.gov/osels/lspppo/pdf/LSPPPO_Report_Signed_V2%20(clear%20version).pdf. Accessed February 11, 2013.
7. Defense Threat Reduction Agency. Chemical and Biological Defense. http://www.dtra.mil/Missions/ChemicalBiologicalDefense/ChemicalBiologicalDefenseHome.aspx. Accessed February 11, 2013
8. Witonsky J. IVD Market Moving Rapidly on an Upward Trajectory. 2012; http://www.genengnews.com/gen-articles/ivd-market-moving-rapidly-on-an-upward-trajectory/4620/. Accessed February 13, 2013.
9. Dekker JP. Infectious Disease Testing at the Point-of-Care. *Point of Care*. 2012;11(2):85-89.
10. Bill and Melinda Gates Foundaiton. Gates Foundation and Grand Challenges Canada Announce over $31 Million for Point-of-Care Diagnostics in the Developing World. December 2011; http://www.grandchallenges.org/about/Newsroom/Pages/POC_DxGrants.aspx. Accessed February 11, 2013.
11. Bill and Melinda Gates Foundation. Grand Challenges in Global Health Diagnostics. 2011; http://www.grandchallenges.org/GCGHDocs/GCGH_Dx_Public_RFP.pdf. Accessed February 11, 2013.
12. Walther G. Enabling POC Diagnostics through Standard Setting. Paper presented at: World Health Summit; 21 October, 2012; Berlin, Germany.
13. Defense Threat Reduction Agency. DTRA Point of Care Diagnostics for Multiplexed Targets. 2012; https://www.fbo.gov/index?s=opportunity&mode=form&id=eb0d8db0d46f190ee282a8e70b7ef768&tab=core&_cview=1.
14. Standards: What is a standard? 2013; http://www.iso.org/iso/home/standards.htm. Accessed February 10, 2013, 2013.
15. Ohashi H. The Role of Network Effects in the US VCR Market, 1978–1986. *Journal of Economics and Management Strategy.* 2004;12(4):447-494.

16. Acquier A. Standards and Innovation in Emerging Fields: Pushing Breakthrough Innovation or Enrolling Actors? An Analysis of Eco-District Standards in France and Denmark. 2011; http://halshs.archives-ouvertes.fr/halshs-00743376. Accessed February 10, 2013, 2013.

17. Katz ML, Shapiro C. Technology Adoption in the Presence of Network Externalities. *Journal of Political Economy.* 1986;94(4):822-841.

18. Cabral LMB, Salant D. Evolving Technologies and Standardization. 2007; http://iber.berkeley.edu/cpc/Conference/conference_papers/Cabral-Salant_paper.pdf. Accessed February 10, 2013, 2013.

19. *Innovation in Global Industries: U.S. Firms Competing in a New World.* National Research Council of the National Academies;2008.

20. Desktop Operating System Market Share. 2013; http://www.netmarketshare.com/#. Accessed February 22, 2013, 2013.

21. Fryer JF, Heath AB, Anderson R, Minor PD. Collaborative Study to Evaluate the Proposed 1st WHO International Standard for Human Cytomegalovirus (HCMV) for Nucleic Acid Amplification (NAT)-Based Assays. 2010. http://apps.who.int/iris/bitstream/10665/70521/1/WHO_BS_10.2138_eng.pdf. Accessed April 10, 2013.

22. World Health Organization. WHO Endorses New Rapid Tuberculosis Test 2010; http://www.who.int/mediacentre/news/releases/2010/tb_test_20101208/en/index.html. Accessed February 18, 2013.

23. President's Council of Advisors on Science and Technology. Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation. September 2012 Available at: http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-fda-final.pdf. Accessed April 8, 2013.

24. President's Council of Advisors on Science and Technology. Priorities for Personalized Medicine. September 2008; http://www.whitehouse.gov/files/documents/ostp/PCAST/pcast_report_v2.pdf. Accessed April 21, 2013.

25. National Hearth Lung and Blood Institute. Biologic Specimen and Data Repository Information Coordinating Center web site. https://biolincc.nhlbi.nih.gov/home/. Accessed April 8, 2013.

26. Weigl BH, Gaydos CA, Kost G, et al. The Value of Clinical Needs Assessments for Point-of-Care Diagnostics. *Point of Care.* 2012;11(2):108-113 110.1097/POC.1090b1013e31825a31241e.

27. Witty A. New strategies for innovation in global health: a pharmaceutical industry perspective. *Health Aff* (Millwood). Jan 2011;30(1):118-126.

Appendix A. Project Participants

Amesh Adalja, UPMC Center for Health Security

Uma Mahesh Babu, Rapid Pathogen Screening, Inc.

Paul Benda, DHS

Roger Breeze, DTRA RD-CB

Grant Campany, X PRIZE Foundation

Rashid Chotani, TASC

May Chu, CDC

Anita Cicero, UPMC Center for Health Security

David Crean,* Mars Corporation

John Dekker,* Massachusetts General Hospital

Karen Dyer, CMS

Michael Eck,* Domus Institute

David Ecker,* Ibis Biosciences, Inc.

Slava Elagin, Meridian Bioscience, Inc.

Glen Fine,* CLSI

Charlotte Gaydos,* Johns Hopkins University

Gigi Gronvall, UPMC Center for Health Security

Jeffrey Guterman, InstantLabs

Syed Hashsham,* AquaBioChip, LLC

Daralyn Hassan, CMS

D. A. Henderson, UPMC Center for Health Security

J. Peyton Hobson, FDA

David Hodge, DHS

Steven Hofstadler, Ibis Biosciences, Inc.

Sally Hojvat, FDA

Rosemary Humes, BARDA

Tom Inglesby, UPMC Center for Health Security

Deval Lashkari, Telegraph Hill Partners

Matthew Lorence, TessArea, LLC

Marcus Lovell Smith, Diagnostics for All, Inc.

Tom Lowery,* T2 Biosystems

Mike Milburn,* Metabolon, Inc.

Ryan Morhard, UPMC Center for Health Security

Jayne Morrow, NIST

Sarah Munro,* NIST

Paul Neuwald, Halteres Associates, LLC

Jennifer Nuzzo, UPMC Center for Health Security

Luann Ochs, CLSI

Jason Paragas, Lawrence Livermore National Laboratory

William (Bill) Pasculle, UPMC Presbyterian

Segaren Pillai, DHS

Kunal Rambhia, UPMC Center for Health Security

Bradley Ringeisen,* DTRA RD-CB

Jason Rolland, Diagnostics for All, Inc.

Seth Rudnick, Canaan Partners

Alan Rudolph, DTRA RD-CB

John Ryals,* Metabolon, Inc.

Harold Schmitz,* Mars Corporation

David Sterry, CLSI

Eric Toner, UPMC Center for Health Security

Mickey Urdea, Halteres Associates, LLC

Eric Van Gieson, DTRA RD-CB

Gene Walther, Gates Foundation

Matthew Watson, UPMC Center for Health Security

Bernhard Weigl,* PATH

Parris Wellman, T2 Biosystems

Carl Wittwer,* University of Utah Medical School/ BioFire Diagnostics, Inc.

**Participated in phone discussions but did not attend January 29 meeting.*

Appendix B. The Current State of Physician and Point-of-Care (POC) Diagnostics for Infectious Diseases

In the daily practice of medicine, there is a pressing need for rapid diagnostic tests to delineate whether a particular disease or disease-state is present. Delays in diagnosis, with the subsequent delays in treatment that may ensue, have been shown to produce deleterious effects with myriad noncommunicable conditions, including myocardial infarction, hypoglycemia, and ectopic pregnancy. Consequently, many healthcare facilities use POC diagnostics to aid in the recognition of these conditions and to expedite treatment. The same need for diagnostic speed exists with certain infectious diseases, for which rapid diagnosis can be coupled with a clinical decision that will have beneficent effects on patient care. However, not all infectious diseases require a POC diagnostic test because the knowledge of a specific diagnosis does not always change clinical care and such tests may delay throughput in a healthcare facility while adding cost to the patient, third-party payers, and the healthcare facility. Additionally, the methods for detecting the presence of certain pathogens are not particularly amenable to CLIA-waivable technology. The several FDA-approved CLIA-waived POC tests for infectious disease are reflective of these facts and rely largely on antigen detection or serology (ie, antibody detection).

CLIA-Waived FDA-Approved POC Tests for Infectious Diseases

Group A Streptococcus: This test, used to detect the presence of Group A Streptococcus in cases of pharyngitis, relies on detection of the bacterium's antigen on a throat swab. It is manufactured by several companies. A positive result on this test would prompt antibacterial therapy for treatment of an acute episode and prevention of rheumatic fever, a serious sequel of untreated infection. Because of its suboptimal sensitivity, culture confirmation is recommended for negative tests in children and adolescents who are at higher risk for both Group A Streptococcus pharyngeal infection and rheumatic fever.

Influenza (A and B subtypes): Rapid influenza antigen detection tests are available from several manufacturers and are performed on nasal or nasopharyngeal swabs. A positive result on this test would prompt initiation of antiviral treatment to ameliorate the symptoms of influenza, possibly prevent serious complications, and potentially reduce contagiousness. Additionally, a positive result for a hospitalized patient will trigger infection control procedures to prevent nosocomial spread of the virus. A secondary benefit of this test is that a positive result, in the setting of an upper respiratory tract infection, can obviate the desire to dispense an antibacterial for a viral illness. Because of the poor sensitivity of these tests, a negative result cannot be relied on.

HIV: HIV POC testing relies on the detection of antibodies against HIV in either saliva or blood. A positive result on this test, while still requiring confirmation with a second type of test, will result in several actions that include: changes in treatment algorithms, changes in risk-taking behavior, initiation of antiviral therapy, and reporting to government health authorities. A limitation of this test is that a short window exists during which anti-HIV antibodies are not detectable with current CLIA-waved POC technology, and other non-POC (PCR or antigen detection) tests would be necessary. A home saliva HIV testing kit also is available.

Hepatitis C virus: POC testing for hepatitis C relies on the detection of antibodies against the virus in blood samples. A positive result on this test would result in linkage to care, counseling on risk-reduction activities, and reporting to government health authorities.

Bacterial Vaginosis: There are 2 types of CLIA-waived tests that are used to diagnose this condition. One test relies on the detection of alterations in the vaginal chemical milieu (pH and amines) induced by the culprit pathogens. Another relies on the detection of enzymatic activity by the culprit pathogens. Both tests are performed on vaginal secretions. A positive result prompts antibacterial therapy.

Respiratory Syncytial Virus (RSV): RSV testing relies on the detection of RSV antigens in nasopharyngeal samples. A positive result on this test does not usually result in the administration of antiviral therapy but does prompt infection control measures in hospitalized patients and diminishes the tendency to prescribe antibacterial therapy for a viral upper respiratory infection. A negative result on the test, because of suboptimal sensitivity, cannot be relied on.

Epstein Barr Virus (EBV): The use of EBV testing is primarily conducted to identify EBV-caused infectious mononucleosis. This test relies on the detection of antibodies induced by the virus in blood. A positive result on this test would prompt counseling regarding risk-reduction activities and prevent prescription of antimicrobial therapy for the viral condition. However, the sensitivity of the test allows for false negative results to occur.

Trichomoniasis: Testing for trichomoniasis relies on an antigen detection test employed on vaginal secretions. A positive result on the test would prompt antimicrobial therapy coupled with risk-reduction counseling activities.

Adenovirus: An antigen detection method to detect the presence of viral antigen in tears is used in this test. A positive result would diminish the likelihood that antibacterial therapy would be employed in this viral illness.

Sources:

Dekker JP. Infectious disease testing at the point-of-care. *Point Care.* 2012;11:85-89.

Rapid Pathogen Screening. http://www.rpsdetectors.com/en/products/adenoplus/. Accessed February 4, 2013.

Oraquick. http://www.oraquick.com/?gclid=CKrE1N6BnbUCFcKaPAodYiUAag. Accessed February 4, 2013.

Editorial and Creative Team

Mary Beth Hansen, MA
Senior IT, Communications, and Editorial Director

Davia Lilly
Director of Design and Production

Jackie Fox
Senior Science Writer

UPMC Center for Health Security

621 E. Pratt Street
Suite 210
Baltimore, MD 21202
Tel: 443.573.3304
Fax: 443.573.3305

UPMCHealthSecurity.org