Center for Biosecurity of UPMC

Diagnostics for Global Biosurveillance:

Turning Promising Science into the Tools Needed in the Field

July 2011

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Executive Summary

The Need to Improve Our Global Diagnostics Tools

The discovery of the 2009 H1N1 influenza pandemic and the emergence of other diseases such as SARS have highlighted the important role that diagnostic tools can play in improving the surveillance of infectious disease threats at the population level. Experiences with these events have shown that recognition of outbreaks, management of epidemics, and development of countermeasures can depend heavily on having access to highly specific surveillance information that is typically obtained from testing clinical specimens. Consequently, the rising threat of emerging diseases and concern about biological weapons has led to an emphasis in governments on improving laboratory and diagnostic capacity in order to improve global biosurveillance for infectious diseases.[1]

The lack of accurate, durable, and reliable diagnostics is a fundamental challenge in global biosurveillance. Insufficient diagnostic capacity in much of the world leads to no or faulty diagnoses, inappropriate treatments, and misreporting of disease prevalence. In many countries, public health laboratories lack the necessary funding, personnel, and tools to conduct disease surveillance. In light of these challenges, the World Health Organization (WHO), the Institute of Medicine, and other organizations have independently concluded there is an urgent need to develop tools to improve diagnostic capacity both in and outside of laboratory settings.[2-6]

There is increasing interest among U.S. government agencies in accelerating the development of infectious disease diagnostic technologies to enhance biosurveillance. In 2009, the U.S. National Security Council (NSC) identified enhanced disease surveillance, detection, and diagnosis as priority goals that the United States government (USG) should work toward for the purposes of improving national security and improving the ability to report any public health emergency of international concern.[1] This NSC strategy calls on international partners to build surveillance, diagnostic, and detection capacity to help countries fulfill their requirements under the International Health Regulations (IHRs).

In addition to being important for global biosurveillance, improved diagnosis of infectious diseases is also a key goal of a number of global health programs. The Obama Administration's Global Health Initiative includes efforts to promote the development and acquisition of infectious disease diagnostic tools.[7,8] Intergovernmental organizations (IGOs) and nongovernmental organizations (NGOs), such as the World Health Organization (WHO), the Foundation for Innovative New Diagnostics (FIND), and PATH, have prioritized clinical diagnostic technology procurement, regulation, and training for high-burden but underdiagnosed diseases, such as tuberculosis.[9]

Purpose

Given this increasingly recognized need to improve global diagnostics, the Center for Biosecurity of UPMC (the Center) conducted an analysis of high-level policy issues that affect diagnostics development and a broad spectrum of diagnostic technologies that are needed for global biosurveillance. The project's aims were to identify:

1. specific ways in which the USG can address global biosurveillance goals through the strategic application of diagnostic technologies;
2. resources necessary to support the deployment of diagnostic technologies in the field;
3. barriers that may limit the development and procurement of infectious disease diagnostics for global biosurveillance; and
4. recommended USG actions that can improve development and deployment of diagnostic tools for biosurveillance.

Analysis and Workshop

To inform this analysis, the Center held a series of discussions with leaders in the field of disease surveillance from academia, industry, IGOs, NGOs, and the USG. Discussion topics were derived from several sources: extensive review of USG global biosurveillance programs; discussions with thought leaders in this field; and review of the published literature, key policy analyses, and reports from IGOs and NGOs, such as WHO, the Gates Foundation, and the National Academy of Sciences. These discussions focused on high-level goals of USG involvement in global biosurveillance, specific in-country needs, market and regulatory factors in the development of diagnostic tests, and opportunities to enhance USG engagement in biosurveillance through diagnostic development and deployment.

The Center completed a Preliminary Analysis Report to provide a synthesis of the literature and information obtained during our conversations with experts. Those findings were used to facilitate the discussion for a workshop on February 17, 2011, with more than 65 participants from academia, industry, IGOs, NGOs, and the USG (see Appendix A, page 34). Senior staff and leadership from Defense Threat Reduction Agency, the Center, and The Tauri Group participated. Consensus was not sought among workshop participants, but the workshop served as a forum for in-depth discussion of goals, needs, challenges, and priorities for USG support of diagnostics for global biosurveillance. This report presents a synthesis of the Center's scientific and policy review, a synopsis of the workshop discussions, and brief summary conclusions from the Center. The project was funded by DTRA Chemical & Biological Technologies Directorate (DTRA/RD-CB) through The Tauri Group.

Findings

Finding 1: There are multiple diagnostic tools that could improve biosurveillance; choosing the right one will depend on what we are trying to achieve.

There are a number of major goals of global biosurveillance, including:

1. Informing and improving clinical diagnosis and treatment of disease in patients and among U.S. civilians or military personnel in a given country;
2. Assessing disease trends in other countries;
3. Facilitating the detection of and response to outbreaks of known infectious diseases;
4. Facilitating the detection of and response to outbreaks caused by new and emerging pathogens; and
5. Anticipating or predicting future disease threats.

At a general level, these goals could all be more effectively pursued if there were better infectious disease diagnostic tools. At a specific level, the different goals of global biosurveillance require the collection of distinct types of data and different approaches to information gathering and analysis. The diagnostic tools needed for these biosurveillance goals are likely to possess different operating characteristics and involve separate development and procurement pathways.

Finding 2: There are many promising new diagnostic technologies, but specific user needs should determine which technologies are deployed and where.

The Center found that a strategy for diagnostics development needs to be built on the information needs of the users of these tools. These include:

1. Molecular-based approaches, which have the potential to decrease the cost and live-agent work needed for diagnosis.
2. Multi-analyte tests, which show promise for identifying a causative pathogen when the clinical or epidemiologic context is vague or when multiple pathogens can cause similar symptoms.
3. Host-side diagnostics, a developing field that seeks to interpret unique host-dependent biomarkers for diagnosis. Of particular interest in this field is presymptomatic diagnosis based on unique biomarker signatures.
4. Culture, the classic microbiological diagnostic method and often considered to be the gold standard, must continue to play a role in a comprehensive diagnostics approach. Work with live agents is not replaceable by other techniques, particularly due to their role in antimicrobial susceptibility testing and vaccine development.
5. New platforms, including mass spectrometry, microfluidics, paper-based diagnostics, and others, may facilitate the deployment and use of diagnostic approaches in the field. Low-cost, noninstrumented engineering designs for diagnosis are appealing for the conditions and infrastructure of low-resource settings.

Finding 3. Diagnostic tools need to be designed for the environments in which they will be used.

The practical limitations in low-resource settings in developing countries should be considered in implementation of diagnostic tools for biosurveillance purposes. Some of these limitations and challenges include:

1. Lack of trained staff due to excess of demand, and difficulty in retention of skilled microbiologists due to lack of incentives for work in low-resource settings.
2. High cost of reagents and diagnostics, which in some cases favors empirical diagnosis over laboratory confirmation.
3. Limited infrastructure, including availability of clean water, reliable power supply, and cold storage, which can disrupt testing and cause unreliable results.
4. Lack of technologies for communicating results to a central authority and back to healthcare providers for administering proper treatments, which can impede proper understanding of clinical and epidemiologic characteristics.
5. High cost of collecting and transporting viable samples under appropriate regulations, which can limit the facilities and/or distance from collection where diagnostic tests must be performed.
6. Implementation of biosafety protocols and maintaining security at laboratories, which can add cost that limits the number of facilities available to provide diagnostic services.

Finding 4. Regulatory challenges have slowed the development of diagnostics needed for global biosurveillance.

A robust and strong regulatory process is necessary to ensure that diagnostic tests produce accurate and reliable results. Ineffective, unreliable tests undermine the USG biosurveillance mission. While the U.S. Food and Drug Administration (FDA) represents the global standard for diagnostic test evaluation, improvements in this framework could facilitate the development of products without sacrificing quality and accuracy of tests. There are a number of considerations pertaining to regulatory affairs:

1. Alternative pathways to market exist, including the European Medicines Agency (EMA), WHO Prequalification, or the U.S. President's Emergency Plan for AIDS Relief (PEPFAR). Some of these pathways may be more expeditious than FDA approval but are not as rigorous.
2. Within the U.S. regulatory structure, a fundamental challenge is lengthy review times that increase costs and delay return on investment for diagnostic test developers. However, recent FDA initiatives indicate that improvements that will facilitate regulatory review are forthcoming.
3. Emergency Use Authorizations (EUAs) are a potential mechanism for marketing of a diagnostic test during an emergency, without full FDA review. EUAs are limited by the inability to distribute tests and train staff prior to the declaration of an emergency. However, changes to the EUA process are being developed and are expected to resolve those issues.

4. Evaluation of multi-analyte tests has been difficult, partially due to the unknown clinical applications of these tests and unclear burden of proof needed to validate their efficacy and reliability. However, following recommendations from the Medical Countermeasure Review released in August 2010, the FDA has established an Action Team dedicated to clarifying regulatory requirements for multi-analyte tests.
5. Evaluation and clearance of tests can also be limited in privately maintained gene banks, whose quality and completeness are unknown. For some pathogens, lack of availability of viable samples can impede validation and clearance of tests. Publicly maintained gene banks and sample collections could improve and facilitate diagnostic development.

Finding 5. There are major barriers in the advanced development of global diagnostics.

The global market for in vitro diagnostic tests is substantial, estimated to be $44 billion in 2010.[10] The economic drivers in this market, however, are not favorable to the missions of global biosurveillance, particularly in developing countries. There are a number of market factors that influence how companies invest in diagnostics that should be considered as the USG decides how to advance global biosurveillance.

1. Incentives are few for developing cheap, deployable tests for low-resource settings in the developing world. Markets are defined by demands in developing countries, mostly for laboratory-based diagnosis of chronic disease, sexually transmitted infections, cancer, and diabetes. There are additional costs and technical difficulties associated with ruggedizing diagnostic tests for use in harsh, low-resource settings. Without reliable and predictable markets, private industry will remain reluctant to develop diagnostics needed for global biosurveillance.
2. USG funding of development of diagnostic tests emphasizes early research, but sufficient funding for clinical trials and advanced development is not available. Because of this gap in advanced development funding, there is a ”cliff of death” for prototype diagnostics that never become commercially manufactured.
3. Development of diagnostics could be facilitated by the creation of standards. Experts suggest that performance standards, platform standards, and operational standards could all reduce costs of development and reduce time to market. While efforts to create standards are under way, there are some concerns as to whether standards for diagnostics are attainable or how they might be used.
4. Investments in diagnostics must be supported in the long term to build and maintain successful programs. Due to staff turnover and the need for equipment maintenance, continued funding for training, equipment servicing, and purchase of reagents is crucial to long-term success.

Recommendations

1. **Specific USG global biosurveillance goals should drive USG investments in diagnostics.**

Each of the USG's biosurveillance goals is distinct and may require different technological approaches. In light of these different needs, the USG should begin any effort to develop or procure new diagnostic tools with an assessment of how a new diagnostic tool can meet an explicit goal of USG biosurveillance. This analysis should include an assessment of user needs and the extent to which a proposed technology is likely to improve the user's routine diagnostic work and, therefore, is likely to be adopted by the intended user.

2. **The USG will need to invest in a mix of diagnostic technologies in order to meet all of its global biosurveillance goals.**

Recent advances in molecular-based approaches and the development of new platform technologies offer the promise of expedited testing of clinical specimens, simultaneously testing for multiple pathogens, and testing in environments outside of the laboratory. Such developments are important and necessary for improving the availability of diagnostic information across the globe. Even with these new approaches, classic techniques, such as culture-based methods, will still be needed in many parts of the world. Therefore, the USG should consider investing in a range of diagnostic technologies. A diversified investment strategy will help to ensure the USG obtains the right mix of diagnostic technologies to help meet all of its surveillance goals.

3. **The development of diagnostic tools should be accompanied by a plan for how these devices will be implemented and maintained in the field.**

Prior to deploying any diagnostic device in the field, the USG should ensure that there are: (1) adequately trained staff to operate the device; (2) appropriate infrastructure (e.g., power, water, temperature) to support the operation of the device; (3) adequate availability of ancillary resources to support the use of the device (e.g., testing reagents and other supplies); (4) adequate and feasible biosafety and biosecurity plans; and (5) appropriate patient therapies to respond to diagnostic test results.

4. **Diagnostic devices that are to be used for biosurveillance should come equipped with an ability to relay data from point of testing to a central public health authority.**

In order to best contribute to the biosurveillance mission, diagnostic devices should be accompanied by a plan for how the data from these tools will be collected and relayed to a central health authority. Although it may not be difficult to equip diagnostic devices with technologies that allow for electronic reporting of data to a surveillance system, the inclusion of such data-capture and -reporting capabilities has to date not been a priority in efforts to develop new infectious disease diagnostic tools.

5. **The USG should work to improve the process for approving multi-analyte tests and for granting Emergency Use Authorization for diagnostic tests.**

In recent years, the FDA has embarked on a number of new initiatives to expedite and streamline the process for clearing in vitro diagnostics. The FDA announced the creation of Action Teams to analyze the process for clearing multi-analyte tests. These teams should give strong consideration to how to expedite clearance of multi-analyte tests, as there is need for such devices in much of the world.

The FDA has also developed a program for granting Emergency Use Authorization for devices and medicines that are likely to be needed during public health emergencies. Additional modifications to this program are necessary to ensure that diagnostic tools that receive EUA are able to be integrated into outbreak response plans and surveillance programs. One needed change is to allow for pre-emergency training and proficiency testing of EUA devices.

6. **The USG should help to improve the regulatory approval of diagnostic devices by supporting efforts to strengthen gene banks and to increase the availability of clinical samples.**

In the absence of data quality standards to ensure that information contained in public and private sector gene banks is accurate, it will continue to be difficult to evaluate diagnostic technologies that must use these databases to demonstrate testing performance. To expedite this process, the USG should explore how it may best support efforts to ensure the quality of information contained in gene banks that are used to demonstrate the validity of diagnostic devices.

To improve the availability of clinical samples, particularly for rare diseases, for companies and for researchers who are working to develop new infectious disease diagnostic tools, the USG should explore ways to support the creation of sample repositories. The Centers for Disease Control and Prevention (CDC) may be an appropriate place to locate and maintain such a repository.

7. **The USG should consider ways of bridging the diagnostics development "cliff of death" by increasing support for advanced development and diagnostic procurement.**

The diagnostic tests that are needed for global biosurveillance have a limited or nonexistent market and, therefore, will require incentives to develop. While current USG investments in diagnostic tests emphasize early scientific research, additional funding is needed to help companies and researchers with promising technologies address challenges encountered during advanced development, clinical evaluation, and scale-up manufacturing.

Any effort to develop and procure diagnostic devices to enhance global biosurveillance will require sustained investments. Initial costs for development of a number of products need to be supported by maintenance, purchase of reagents, and training.

Diagnostics for Global Biosurveillance: Turning Promising Science into the Tools Needed in the Field

The Need to Improve Our Global Diagnostic Tools

In April 2009, laboratory staff at the Naval Health Research Center (NHRC) tested specimens from 2 influenza patients using a novel diagnostic device. Though both tested positive for influenza A, neither specimen matched the influenza A subtypes that are known to infect humans. Follow-up testing conducted at the U.S. Centers for Disease Control and Prevention (CDC) and elsewhere confirmed the NHRC's findings: these 2 specimens represented the first known U.S. cases of the 2009 H1N1 influenza pandemic.[11]

Michele Ginsberg, chief of community epidemiology for San Diego, told *Science* magazine that had specimens not been tested at the NHRC as part of an experimental protocol, they could easily have been missed: "In the usual setting, they would have done a rapid test and found that they were both positive for influenza A, and that's as far as it would have gone," said Ginsberg.

The discovery of the 2009 H1N1 influenza pandemic and the emergence of other diseases such as SARS have highlighted the important role that diagnostic tools can play in improving the surveillance of infectious disease threats at the population level. Experiences with these events have shown that recognition of outbreaks, management of epidemics, and development of countermeasures can depend heavily on having access to highly specific surveillance information that is typically obtained from testing clinical specimens. Consequently, the rising threat of emerging diseases and concern about biological weapons has led to an emphasis in governments on improving laboratory and diagnostic capacity in order to improve global biosurveillance for infectious diseases.[1]

A fundamental challenge in global biosurveillance is the lack of accurate, durable, and reliable diagnostics. Insufficient diagnostic capacity in much of the world leads to no or faulty diagnoses, inappropriate treatments, and misreporting of disease prevalence. Although rapid diagnostic tests are becoming increasingly available for some diseases, such as hepatitis B and HIV, in most places, diseases such as cholera and yellow fever can be confirmed only by testing by specialized personnel at a laboratory, which can be resource intensive and can delay the availability of results.[12] In many countries, public health laboratories lack the necessary funding, personnel, and tools to conduct disease surveillance. The World Health Organization (WHO) has reported that more than 60% of laboratory equipment in developing countries was outdated or not functioning.[12] In light of this and other findings, WHO, the Institute of Medicine, and other organizations have independently concluded there is an urgent need to develop tools to improve diagnostic capacity both in and outside of laboratory settings.[2-6]

[i] Though there is no single, universally accepted definition for biosurveillance, it is generally used to describe the process of monitoring health data (human, animal, and environmental) for discovery and management of new outbreaks of infectious diseases. In this paper, we focus on the use of diagnostic tools in the international setting to improve discovery, understanding, and management of infectious diseases that have the potential to affect the U.S. citizens at home and abroad.

There is increasing interest among U.S. government agencies and international organizations in accelerating the development of infectious disease diagnostic technologies in order to improve global biosurveillance. In 2009, the U.S. National Security Council (NSC) identified enhanced disease surveillance, detection, and diagnosis as priority goals that the United States government (USG) should work toward for the purposes of improving national security and improving the ability to report any public health emergency of international concern.[1] This NSC strategy calls on international partners to build surveillance, diagnostic, and detection capacity to help countries fulfill their requirements under the International Health Regulations (IHRs).

> *Ensuring that communities can quickly and effectively respond to large outbreaks of infectious disease in a manner that greatly reduces their impact is among the most effective ways to deter a deliberate attack and to minimize the consequences should an attack occur. In today's interconnected world, an outbreak of highly communicable disease anywhere on the globe increases the risk to everyone, particularly if that outbreak is of deliberate origin.[1]*

In addition to being important for global biosurveillance, improved diagnosis of infectious diseases is also a key goal of a number of global health initiatives. The Obama Administration's Global Health Initiative includes efforts to promote the development and acquisition of infectious disease diagnostic tools.[7,8] Intergovernmental organizations (IGOs) and nongovernmental organizations (NGOs), such as WHO, the Foundation for Innovative New Diagnostics (FIND), and PATH, have prioritized clinical diagnostic technology procurement, regulation, and training for high-burden but underdiagnosed diseases such as tuberculosis.[9] Two of the 14 Grand Challenges in Global Health—an initiative led by the Gates Foundation and other organizations that aims to encourage innovative developments to address high-priority global health challenges—call for the development of new tools for diagnosing infectious diseases and for assessing the health of population health status.[13]

Given this increasingly recognized need to improve global diagnostics, the Center for Biosecurity of UPMC (the Center), conducted an analysis of high-level policy issues that affect diagnostics development and a broad spectrum of diagnostic technologies that are needed for global biosurveillance. The projects aims were to identify:

1. specific ways in which the USG can address global biosurveillance goals through the strategic application of diagnostic technologies;
2. resources necessary to support the deployment of diagnostic technologies in the field;
3. barriers that may limit the development and procurement of infectious disease diagnostics for global biosurveillance; and
4. recommended USG actions that can improve development and deployment of diagnostic tools for biosurveillance.

The project also sought to foster communication and collaboration among the Defense Threat Reduction Agency's Chemical and Biological Technologies Directorate (DTRA/RD-CB), other USG agencies, intergovernmental organizations (IGOs), nongovernmental organizations (NGOs), academia, industry, and other parties engaged in diagnostic development.

This project built on findings from the Center's 2010 analysis of international disease surveillance. In that analysis, the Center made a series of recommendations to improve international disease surveillance initiatives.[14]

Methods

The Center conducted a series of discussions with leaders in the field of disease surveillance from academia, industry, IGOs, NGOs, and the USG. Discussion topics were derived from several sources: extensive review of USG global biosurveillance programs; discussions with thought leaders in this field; and review of the published literature, key policy analyses, and reports from IGOs and NGOs, such as WHO, the Gates Foundation, and the National Academy of Sciences. In each discussion with an expert, we sought their views on high-level goals of USG involvement in global biosurveillance, specific in-country needs, market and regulatory factors in development of diagnostic tests, and opportunities to enhance USG engagement in biosurveillance through diagnostic development and deployment.

Analysis of these conversations provided the structure for a workshop on February 17, 2011, 70 participants from academia, industry, IGOs, NGOs, and the USG (see Appendix A, page 34). Senior staff and leaders from DTRA RD-CB, the Center, and The Tauri Group participated. Prior to the workshop, the Center completed a Preliminary Analysis Report to provide a synthesis of the literature and information obtained during our conversations with experts. Those findings were used to facilitate the workshop discussion.

This final report presents a synthesis of the Center's scientific and policy review, a synopsis of the workshop discussions, and brief summary conclusions from the Center for Biosecurity. 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. Expert input at the workshop and in the preceding interviews was considered advisory to the analysis. The Center did not attempt to achieve consensus in its discussions with experts. Accordingly the findings and recommendations in this report represent the analysis and judgments of the Center for Biosecurity, although it is our view that most of the recommendations would be supported by the majority of the experts who participated in this project. The project was funded by DTRA/RD-CB through The Tauri Group.

Finding 1: There are multiple diagnostic tools that could improve biosurveillance; choosing the right one will depend on what we are trying to achieve.

There are a number of major goals of global biosurveillance, including:

1. Informing and improving clinical diagnosis and treatment of disease in patients and among U.S. civilians or military personnel in a given country;
2. Assessing disease trends in other countries;
3. Facilitating the detection of and response to outbreaks of known infectious diseases;
4. Facilitating the detection of and response to outbreaks caused by new and emerging pathogens; and
5. Anticipating or predicting future disease threats.

At a general level, these goals could all be more effectively pursued if there were better infectious disease diagnostic tools. At a specific level, the different goals of global biosurveillance require the collection of distinct types of data and different approaches to information gathering and analysis. The diagnostic tools needed for these biosurveillance goals are likely to possess different operating characteristics and involve separate development and procurement pathways.

Below is a description of each of the 5 goals, including several distinguishing characteristics that may determine the type of diagnostic approach that is required to meet each goal.

Goal 1: Informing and improving clinical diagnosis and treatment of disease in patients and among U.S. civilians or military personnel in a given country

Improving the ability to capture information from the clinical sector is critical for strengthening biosurveillance, and to do this requires accurate, durable, and reliable diagnostics. In the absence of such tools, clinicians in many parts of the world must rely on patients' symptoms in order to diagnose diseases. Because symptoms for many diseases may be nonspecific, the diagnosis of disease based on clinical symptoms can be inaccurate and may lead to incorrect treatment of patients and misreporting of cases of disease to public health authorities.

"Lack of access to good-quality diagnostic tests for infectious diseases is a major contributor to the enormous burden of infectious diseases in the developing world."

"At health facilities a diagnosis of malaria is based solely on clinical features such as fever. This practice leads to high rates of over-diagnosis and over-treatment of malaria."

Adoption of new diagnostic tools by clinicians will depend on the practical utility of these tools to the practitioner and the patient. Ideally, a clinical diagnostic should: (1) be easy to use by clinical staff; (2) provide results quickly (i.e., before the patient leaves the health clinic); and (3) provide quality

information to improve the ability of a clinician to care for the patient beyond what was possible without a diagnostic test.

Goal 2: Assessing disease trends in other countries

Another fundamental challenge for global biosurveillance is an inadequate understanding of the background levels of diseases in countries around the world. It is important for public health agencies to have an accurate understanding of which diseases are occurring, how much of the population is affected, and how frequently cases are occurring in order to determine whether outbreaks are occurring and to make decisions about how best to control disease spread. Ground-level data about disease trends provide important information regarding infectious disease threats to in-country populations (including U.S. personnel deployed oversees) and help to assess the potential of the disease to spread beyond a country's borders.

> *"In order to understand the severity of a disease, you need to know the denominator of people infected."*

The diagnostic approaches required for conducting population-level assessments of disease differ from those used for diagnosing patients in clinical settings. Though diagnostic information from the clinical sector may help improve understanding of existing disease trends, for many diseases it may not be feasible or necessary to get data on individual patients in order to assess disease burden. To get this information, it is currently often necessary to conduct specialized studies by characterizing samples collected from sentinel populations or by conducting representative population-level studies. In such studies, testing may be conducted at public health and research laboratories. In many countries, the ability to conduct such assessment is limited by either a lack of sufficient laboratory capacity or an inability to collect and transport clinical samples to laboratories for characterization, or both. Ideally, diagnostics developed for this purpose would be able to detect not only those pathogens that are expected in a given area (known, high-burden diseases), but also those not normally expected. In addition to being able to identify those pathogens that are circulating in a population, diagnostics are needed to describe the extent to which a pathogen is infecting a community. This may require being able to conduct host-side analyses of immune response (e.g., serologic analyses) in infected individuals.

Goal 3: Facilitating the detection of and response to outbreaks of known infectious diseases

As demonstrated during the 2009 H1N1 influenza pandemic, the detection of outbreaks requires both clinical and laboratory information. Diagnostics are necessary to confirm the clinician's suspicions and help gauge the number of patients affected with the same pathogen. In addition, public health, clinical, and research laboratories can provide important information, such as an understanding of strain type, virulence, transmissibility, antimicrobial susceptibility, and pathogen evolution, to guide medical and public health responses.

> *"Although 2009 H1N1 cases were first seen in hospitals, it was a laboratory test that made us recognize that we were on the cusp of a pandemic."*

Decisions on appropriate clinical treatments, deployment of stockpiled medicines, and community mitigation measures are often based on information provided by diagnostic tests. Information from diagnostic tools will be needed to help guide

response to outbreaks of novel pathogens. In order to perform a thorough investigation, it would helpful to be able to track results back to a specific patient or location to conduct follow-up work. Ideally, diagnostics developed for this purpose would be able to: (1) rapidly determine which pathogen is causing an outbreak: (2) characterize the organism at a level fine enough to be able to understand its major epidemiologic characteristics (e.g., enough genetic information to be able to link cases, identify source of infection, determine whether the organism is susceptible to medical countermeasures, etc.); and (3) provide enough host-side information to describe the degree of spread within a population (e.g., measure immune response). It would also be ideal if the detection of outbreaks could occur as temporally and geographically close to the start of the outbreak as possible, so as to help contain disease spread. New diagnostic technologies may one day make it possible to identify who was exposed, even before onset of symptoms, and which patients are at greatest risk for severe infection, which could also change the way in which outbreaks are detected and managed.

Goal 4: Facilitating the detection of and response to outbreaks caused by new and emerging pathogens

Detection of outbreaks, for both known and emerging diseases, is receiving increased emphasis as countries work to fulfill their obligations under the IHRs to be able to report public health emergencies of international concern. Testing first for known agents helps to rule out the most likely causes and alerts officials to a possible novel outbreak. The detection of novel pathogen outbreaks will, however, require the use or development of different diagnostic tools than those used to detect outbreaks of known diseases. Ideally, diagnostics developed for this purpose should be able to rapidly assess or rule out whether an outbreak is being caused by a known pathogen. If a known pathogen is ruled out, additional characterization will be needed which may require transport of samples to a reference laboratory or research facility.

> *"How do you create diagnostic tools in advance to detect an 'unknown unknown'?"*
>
> *"You do not know what you are going to need tomorrow."*

Goal 5: Anticipating or predicting future disease threats

There is an increasing interest in approaches to predicting new pathogenic threats to humans before these pathogens emerge and cause significant disease in humans. There is a growing consensus that one key approach to predicting human threats involves monitoring disease in animals. This strategy is rooted in the observation that the vast majority of human pandemics have been caused by animal pathogens that developed the ability to infect human hosts (e.g., SARS, H5N1, H1N1, Ebola, Marburg, Nipah, Hendra, and HIV). Among those working to develop methods for predicting new pathogenic threats, different approaches are being taken.

Two of these are:

1. Collecting samples from human and/or animal populations and characterizing the population's baseline microbial ecology to help differentiate pathogenic "signals" from normal microbial "noise." Those involved in these efforts may look for increasing frequency of new pathogens within a population or may study the pathogens themselves in order to identify genes associated with increased virulence of infectivity.
2. Monitoring high-risk human populations (e.g., bush meat hunters) for the emergence of new pathogens. This may involve finding evidence of infection (serologic analysis) or isolation of new pathogens from within these pathogens. In both cases, researchers are looking for evidence that a particular novel pathogen is becoming more likely to infect humans, which may indicate its potential to spread beyond the high-risk population. This approach also requires an understanding of the social and behavioral patterns that make populations uniquely vulnerable to infection.

Ideally, diagnostics developed for this purpose would be able to: (1) identify the new or emerging pathogen, (2) describe the virulence and transmissibility of the pathogen, and (3) determine the likelihood that the pathogen will cause significant human disease or outbreaks.

> *"We anticipated an H5N1 strain from Southeast Asia only to be broadsided by an H1N1 strain out of Mexico. Our pre-pandemic vaccines had no utility."*

> *"If there is strong chatter ongoing among species, you have a pre-epidemic window of opportunity to act."*

Finding 2: There are many promising new diagnostic technologies, but specific user needs should determine which technologies are deployed and where.

A strategy for diagnostics development needs to be built on the information needs of the users of these tools. Different users may require different types of biosurveillance information. While biosurveillance information clearly exists within the clinical sector, clinical communities are unlikely to use diagnostic tools for biosurveillance unless they also provide data that help their patients. From the perspective of a clinician, a useful diagnostic tool may be one that simply distinguishes a viral illness from one caused by a bacterium. However, from the public health perspective, it may not be enough to know whether a person is infected with a particular virus or bacteria when a detailed genetic analysis of an organism is needed to link cases epidemiologically.

Different classes of diagnostic technologies have their own strengths and challenges, which are important to understand as they are being considered for different applications and users in the field.

Molecular-based technologies

Interest both in reducing the cost of building and maintaining biocontainment facilities and in lowering numbers of labs that do live-agent work has contributed to increased interest in molecular diagnostics and other non-culture-based tools. Proponents of this approach have suggested that enhanced diagnostic tools, such as those that rely on molecular-based technologies, may eliminate the need for culturing organisms and, as a result, reduce the need for laboratories that handle live agents. With this approach, any remaining need for work that requires the use of live cultures can be performed by reference laboratories.

On other hand, molecular-based techniques cannot provide some forms of critical information that classical microbiological techniques offer. For example, while molecular diagnostics may be helpful in determining the presence or absence of a specific known pathogen in a clinical or environmental sample, such techniques are largely not sufficient for determining whether that pathogen is viable and capable of causing disease.

> *"We have PCR-based machines, but they don't tell us if the organism is viable, which is important for assessing whether or not a patient will infect others."*

Multi-analyte diagnostic tests

Often a patient will present with symptoms that could be caused by any number of pathogens (e.g., fever). Multi-analyte diagnostic testing offers the promise of facilitating diagnosis because it can analyze patient samples for the specific gene sequences or protein signatures of multiple pathogens simultaneously. In some cases, these tests can now be done within

hours at the point of need with a device the size of a toaster oven.

The ability to test for multiple pathogens at once, using a single patient sample, could provide useful clinical and public health information on what is causing disease. For example, a fall 2010 yellow fever outbreak in Uganda underscores how determining the cause of an outbreak may require simultaneous testing for multiple pathogens. Having not seen a case of yellow fever in Uganda for decades, health officials had a low level of clinical suspicion for yellow fever and initially suspected plague as the cause of the outbreak.[15] Some have argued that had a multi-analyte test that included yellow fever been available, it may have allowed the cause of the outbreak to be identified more quickly.

Another example of a useful application of multi-analyte tests is their use during influenza season, when multiple pathogens may cause influenzalike illness. In most places, rather than testing patients to determine the causative agent of an influenzalike illness, clinicians may diagnose patients with influenza based on patients' symptoms. For those illnesses caused by something other than influenza viruses, opportunities to provide appropriate treatment are lost. Some argue that expanded use of multi-analyte diagnostic tests may change this scenario by distinguishing illnesses caused by influenza viruses from other viral or bacterial infections.

> *"I have my own personal experience with* Mycoplasma pneumoniae *being the causative agent instead of flu during flu season, and that actually does involve a change in treatment decision for the patient. But if the testing isn't done, there is no opportunity to provide the right treatment. And that's what multi-analyte diagnostics brings to the table."*

Although multi-analyte approaches have been shown to be informative and accurate, there are some limitations and drawbacks to multi-analyte testing methods. To date, the equipment needed to support multi-analyte testing has been large and expensive, and the process has involved expensive reagents. Such requirements limit the practical application of these approaches in the field. Additionally, multi-analyte diagnostics may not be as adaptable as they need to be. Pathogen mutations can cause problems, because a test is designed to search for known nucleic acid or protein patterns. It can be difficult to change these tests "on the fly" or to add a new target. Some experts also are concerned that low clinician interest in using these devices could hinder their applicability for biosurveillance purposes. Clinicians may have little interest in testing for a range of pathogens when they have low suspicion for many pathogens on the multi-anaylte panel or when no treatment is available for many of the pathogens being tested for.

Key to assessing how multi-analyte tests should contribute to biosurveillance will be to establish the clinical significance of results they generate. A key question is: does finding evidence that there is genetic material of a pathogen in a patient indicate that that pathogen is causing disease in that patient? The discovery of co-infections or carriage of multiple organisms may raise additional questions about the clinical relevance of test results.

> *"We don't know what we are going to find when we apply multi-analyte tests to a population."*

Host-side diagnostics

Host-side diagnostics are a potentially promising technology for improving global biosurveillance. Host-side diagnostics refers to the ability to measure biochemical or immunologic changes in an individual infected with a pathogen, rather than cultivating or identifying the presence of the genetic material of a pathogen. For various reasons, diagnostic tools that rely on pathogen growth or pathogen nucleic acid or antigen detection can be ineffective. The window of opportunity to isolate a pathogen from an infected person may be short, depending on the clinical progression of the disease. Additionally, nucleic acid sequences of the pathogen may not be abundant enough for detection. Host-side diagnostics offers a potential solution. Using different human biological markers, including protein expression, DNA methylation, miRNA excitement, and chemokine/cytokine levels, developers of this technology can create a unique profile for cellular and molecular response to infections caused by different agents.

These profiles or signatures can be used to determine the cause of an infection, without having to obtain the pathogen or its genetic material. Traditionally, host-side diagnostic approaches have focused on antibody response and nonspecific markers such as the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, and pro-calcitonin levels. However, advances in understanding of innate and adaptive immune response offer new potential for more specific diagnoses based on other host-side markers.

Much of the emphasis in host-side diagnostics has focused on presymptomatic and preclinical phases of an infection, a strategy that searches for early evidence of infection that occurs before onset of clinical symptoms. Unique profiles of biological markers can be observed and used for diagnosis days before currently available tests. Research in this field is rapidly improving the understanding of pathogenesis and the early human immune responses. In the future, scientists hope to develop a test that can determine not only exposure to a pathogen, but also whether an individual will have a self-limiting, serious, or fatal infection. Research on malaria and anthrax shows some evidence of the proposed utility of presymptomatic diagnosis.[16,17] This diagnostic approach would be particularly useful for making clinical decisions about exposure to a pathogen and need for treatment, either routinely or during an epidemic. However, validation, regulatory approval, and implementation of these approaches are remaining challenges, and it is unlikely that they will become available for routine use for some time.

Culture-based and other traditional microbiological approaches

Although researchers have been looking to identify cellular markers of infectivity and viability, the growth of a pathogen remains the gold standard of assessing viability. Similarly, culture-based approaches are needed to understand treatment protocols and develop vaccines. For example, culture is still required to assess whether a patient's tuberculosis can be treated using the WHO-recommended 4-antibiotic combination therapy.[18]

A number of experts consulted for this project expressed concern that an increased emphasis on molecular diagnostics may reduce the number of clinical samples available for pathogen characterization and vaccine development. As the USG pursues policies that aim to consolidate live agent work by developing diagnostic approaches that do not require live agents, it should do so by considering how to preserve the availability of clinical specimens for further characterization.

There is a strong need for tests that are easy to use, easy to interpret, and inexpensive. Even the simplest diagnostic tool could make a big difference in detecting and managing outbreaks in resource-limited settings. For example, a recent report showed that most infections in post-earthquake Haiti were caused by gram-negative bacteria and not the gram-positive bacteria for which many doctors had been treating.[19] A simple gram stain test, which has been in existence since the late 19th century, could have better helped to determine appropriate therapy among patients in Haiti.

Platform technologies

In addition to new biochemical approaches for detecting pathogens (i.e., detecting a microbe's DNA or RNA versus detecting human antibodies to provide evidence of infection), advanced diagnostic technologies may also employ new platforms or engineering designs that facilitate the biochemical reactions of diagnostic testing. Most platforms, such as PCR or mass spectrometry, require instruments, infrastructure, electricity, and trained personnel usually found in clinical laboratories. Microfluidics-based diagnostic devices offer the promise of noninstrumented, disposable diagnostics that can be cheaply manufactured using off-the-shelf components, like paper, and small of amounts of pathogen-specific reagents.[20] Paper strip tests would be stable in warm temperatures and durable for low-resource setting field deployment. Similar to a home pregnancy test in size and operability, these devices use immunoassay technology that would display colors indicating either a positive or negative test when the reagent binds to disease-specific antigen. Although in its early stages, microfluidics can also be harnessed to perform molecular-based diagnostic tests using isothermal nucleic acid amplification technology. These tests would operate with the advantageous sensitivity and specificity of PCR, but they would not require electricity to perform the heating and cooling cycles of normal PCR. Early pilot testing for the detection of human African trypanosomiasis has demonstrated the feasibility of using these isothermal molecular-based tests in low-resource regions like West Africa, where the endemic disease burden is high.[21] The low cost, simplicity, and flexibility of microfluidics-based tests are promising for addressing the health needs and infrastructure and logistical limitations of developing countries.[22]

Finding 3. Diagnostic tools need to be designed for the environments in which they will be used.

In much of the world, the diagnosis of disease takes place in low-resource environments like rudimentary health clinics that are staffed by community health workers with limited training.[23] In these environments, there are a number of challenges to the use of diagnostic tests.

Lack of availability of trained staff

In many places in the world, there is a shortage of trained laboratorians and healthcare workers. The workload at laboratories often exceeds capacity.[24] One reason cited for this is the lack of incentives for highly trained laboratorians to work in rural settings. Experienced, qualified laboratorians are needed to operate sophisticated devices as well as to build quality assurance systems.[25,26] Rapid personnel turnover requires frequent training for technical skills that can take time to obtain and master.[27]

Cost of diagnostic tools, reagents, and treatment

Diagnostic tools need to be affordable in the areas in which they are used. Key determinants of affordability include not only the cost of diagnostic technology itself, but the cost of reagents and consumables, overhead, and laboratory staff. When all of these costs are factored in, they can quickly place many diagnostic tools out of reach for many. For example, in many places the high cost of malaria diagnostics makes it cheaper to treat patients based on clinical symptoms instead of obtaining diagnostic confirmation.[28] However, a recent investigation found that clinical symptoms alone can be a poor predictor of whether or not someone has malaria; on average, 60% of patients who are diagnosed this way likely do not have the disease.[29] Even when diagnostic tools and supplies are offered at a reduced cost to countries, the cost and availability of providing treatment to the additional infectious cases that will be detected can make these tools impractical.

> *"We were given a [rapid diagnostic machine] to use and some funding to buy supplies. The machine works well, but we don't know how long the funding will last. Also, though this device enables us to find more cases, we only have enough funding to treat an additional 40 patients. This makes it difficult to integrate this technology into our surveillance program."*

Infrastructure challenges

Many diagnostic tests require specific infrastructure to maintain the accuracy and reliability of tests. Lack of clean water, a reliable power supply, and temperature control can create major obstacles for deploying diagnostic tools in the developing world. Cold storage is often necessary for maintaining viable specimens as well as preserving reagents. Without it, patient specimens would require immediate analysis, and reagents would need to be replenished more frequently.[6] Excess heat and dust can disrupt testing and cause unreliable results.

Capturing and communicating test results

The utility of diagnostic tools would be greatly enhanced if communication technology were integrated with tools to enable them to rapidly communicate test results to a central health authority. As results are obtained at a laboratory, communicating these results to healthcare providers is important for ensuring that appropriate treatment is initiated and information is included in patient records.[27] Though no project participant knew of any diagnostic tools that were already equipped with the capability to relay testing results to a surveillance database, most felt that doing so would not require much of a technological leap. In recent years, there have been a number of successful efforts to develop cell phone–based handheld devices to help staff in rural clinics report patient data to health agencies. Participants thought that diagnostic tools could be outfitted with similar capabilities to automate or at least facilitate the reporting of test results.

Collecting, preserving, and transporting specimens

Collecting, maintaining, and transporting viable patient specimens to appropriate laboratories is critical for obtaining accurate and reliable results with many diagnostic tests. There are a number of challenges to doing this. Many biological samples are easily degraded during sample collection and transport, making them useless for subsequent laboratory analysis. To maintain these samples during transport to a laboratory is expensive. Legal restrictions (or, in some cases, the perception of legal restrictions) can make it difficult to ship samples from a clinic or outbreak site to a laboratory where an analysis will be performed. For U.S. entities, select agent regulations make it difficult to collect and ship samples that potentially contain select agent pathogens. Many commercial carriers will refuse to move diagnostic specimens due to concerns about complying with select agent and other rules.

Ensuring biosafety and security

Protecting laboratory workers, properly disposing of laboratory waste, and preventing the theft of biological agents are requirements for diagnostic facilities, though it is difficult to apply U.S. security standards in many settings. It is not easy to comply with U.S. select agent restrictions in areas where a number of such pathogens are highly endemic. Improving biosafety of facilities that do diagnostic work is also important; however, the costs associated with common biosecurity practices (e.g., personal protective equipment, maintaining laboratory biosafety equipment) are out of reach for many laboratories.

Finding 4. Regulatory challenges have slowed the development of diagnostics needed for global biosurveillance.

Ineffective and unreliable diagnostic tests undermine the USG biosurveillance mission. In developed countries, regulatory agencies ensure that diagnostic products are both safe and efficacious before they can be sold. In developing countries, however, a lack of regulatory processes has resulted in some cases of substandard or fake diagnostics that do not serve their intended purpose.

> *"A diagnostic test is never going to be solely for surveillance—some results will be reported back to physicians; so false positives may present risks to patients. Therefore, there is a need to regulate these devices."*

In the U.S., all diagnostic tests must receive clearance or approval from the FDA. Following FDA clearance or approval, the device is subject to the quality assurance standards of the Clinical Laboratory Improvement Amendments (CLIA), which are administered through the Centers for Medicare and Medicaid Services (CMS). The FDA assigns a CLIA complexity score to every device it clears or approves. This score determines where the lab test can be performed (e.g., hospital laboratory, doctor's office, or home). To be administered outside a CLIA-approved laboratory, a diagnostic test must receive a CLIA waiver. For a more in-depth description of the U.S. regulatory system for infectious diagnostics, refer to Appendix B, Page 24.

> *"If the world weren't resource constrained, most everybody would want to have a system kind of like the FDA—at least like the new FDA."*

Diagnostic tests that are destined for foreign markets may go through alternative pre-market regulatory pathways. Some diagnostic developers seek approval by foreign agencies, such as the European Medicines Agency (EMA), the European Union's regulatory agency. The EMA's regulatory pathway is viewed by many as a less burdensome and faster route to markets outside the U.S. Following the passage of the FDA Export Reform and Enhancement Act of 1996, U.S. companies were allowed to export diagnostic devices to foreign markets without obtaining FDA clearance or approval. Many U.S. companies now sell diagnostic tests abroad that cannot be purchased in the U.S.

> *"We usually go for European approval first so we can earn revenue—EMA has different standards than FDA."*

In response to concerns about widespread use of faulty diagnostic tests and in an effort to increase access to quality-controlled products, WHO established a prequalification program for diagnostics that has a set of criteria for development of tests as well as a mechanism for evaluating those tests. While the pipeline for products pursuing WHO prequalification is robust, as of July 2011, only 1 product has been prequalified since this program's inception.[30,31] In the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), diagnostics must be FDA approved or CDC evaluated.

> *"Uncleared devices are being distributed through WHO Collaborating Centers."*

Time to clearance

Many experts who participated in this project noted that the time required for evaluation and clearance of diagnostic tests is a fundamental challenge to development of diagnostics for infectious diseases. A commonly cited challenge is the validation of the performance. A number of technical and practical problems can arise when diagnostic developers try to demonstrate that their test can perform accurately and reliably for its intended use. As one example of such challenges, manufacturers noted that, for rare diseases (which may pose low clinical burdens but may be of great public health consequence should they occur and therefore are of great importance for biosurveillance), it is often hard to get enough clinical samples to use for validation of a test. Developers also noted the absence of a guidance document from FDA that discusses how to prepare assays/samples.

> *"There are no clear standards to be met for clearance. A 'we'll know it when we see it' stance is frustrating."*

The FDA has acknowledged concerns regarding time to clearance and recently unveiled a plan containing 25 actions it intends to implement during 2011 to improve the regulatory path for medical devices.[32]

> *"There is a correlation between engaging the FDA early and the quality of the submission that is sent to the FDA."*

Emergency Use Authorizations (EUA)

A number of project participants cited the FDA's Emergency Use Authorization Program as a positive step toward greater regulatory flexibility on diagnostic tools. Under the Project BioShield Act of 2004[33], the FDA Commissioner may authorize the use of an uncleared diagnostic device during a declared emergency. Uncleared diagnostic devices and medical countermeasures that receive an EUA can be used only during a declared public health emergency. Although EUA approval would not be available to devices used for routine clinical surveillance, it may have important applications to global biosurveillance during public health emergencies, such as a pandemic or bioterrorist attack.[34] In addition to allowing the emergency use of an uncleared diagnostic device, EUAs also would permit the use of devices without the normal procedural requirements for experimental devices (e.g., informed consent), which would make it easier to conduct surveillance during public health emergencies. The FDA has encouraged companies to initiate a "pre-EUA" process, which would give the FDA the necessary information about a test and its intended use and could accelerate the EUA process in the event of an emergency.

> *"The FDA's pre-EUA process is a positive development and could expedite use of diagnostics in an emergency."*

Although the FDA's EUA program is generally viewed as a positive development, some experts expressed concerns about the operational restrictions associated with EUA devices that slow the use of such devices during emergencies. For example, the program does not allow for an EUA device to be predeployed in advance of a declared emergency. This stipulation prevents laboratories from training staff in how to use these new devices and from performing validation tests to ensure accuracy of diagnostics in advance of a declared emergency. Instead, validation and training must be coordinated in the midst of increased demand on laboratory services during an infectious disease emergency. In March 2011, the FDA acknowledged these limitations and noted that it is currently working to improve the EUA process to allow products to be authorized prior to an emergency so that they can be stockpiled and used more quickly.[35]

Challenges of evaluating multi-analyte tests

Multi-analyte tests may be important for biosurveillance in that they can simultaneously test for multiple pathogens. However, only a few multi-analyte tests are commercially available, in part because of the challenges they pose for regulatory approval. The FDA's primary concern with multi-analyte tests is whether clinical utility can be demonstrated and whether there will be repercussions for patient care. If a multi-analyte test shows several positive results for one sample, it is unclear how that would or should inform patient treatment.

> *"Determining the clinical relevance of a multiplex test is a major challenge. Just because you've detected genetic material of an organism, what does it mean for the patient?"*

> *"Every time you add an analyte, you exponentially magnify the level of criteria that must be met to demonstrate that the test works, because you have to test all combinations."*

> *"Adding new analytes to a multiplex diagnostic test is not a technical challenge. It is a regulatory and market challenge. Often decisions are made within industry that are business-based [and] that aren't necessarily the best thing for the community, but make the most sense from a bottom-line perspective considering the cost of clinical trials."*

> *"Part of the complexity with a multiplex tool is that you may find something unexpected. But just finding it does not mean you can report it back. We have examples where we have found agents that were present that should have been reported back to the patient because it would be beneficial for the patient to know, but we are not allowed to report that back because the physician did not ask for it."*

Some project participants reported that uncertain regulatory requirements have prevented companies from investing in the advanced development and clinical trials needed to clear multi-analyte tests. Because of the uncertainty and large costs, these products, with few exceptions, have not been developed, approved, and implemented despite their potential for improving surveillance and diagnosis of disease. In August 2010, the Department of Health and Human Services (HHS) published the Medical Countermeasures Review, which outlined plans for the development of countermeasures against 21st century biological threats. One of the goals of this review is to advance regulatory science.[36] As part of the improvements to the regulatory environment, the FDA outlined the creation of Action Teams to address difficult regulatory issues in medical countermeasure development. The first of these Action Teams has been convened to alleviate the current regulatory concerns regarding multiplex diagnostic tests.[35]

> *"I think a lot of manufacturers, in many respects, are having to sit on the sidelines, almost, and our 510(k) pre-IDE is essentially on hold because we can't afford to move ahead under the current guidelines."*

Gene banks and availability of clinical samples

Delays in clearance of a diagnostic device have also been associated with regulatory agencies' concerns about companies' use of gene banks to demonstrate the performance of diagnostic tests. Gene banks are electronic libraries that contain the known genetic sequences of specific pathogens; they are often used by companies to establish the validity of test. The extent to which these gene banks can be used to accurately establish the validity of a diagnostic test depends on the accuracy of the gene sequences contained in the databases. The

FDA has expressed concerns about the accuracy of the information contained in both public sector and proprietary, private-sector gene banks. In the absence of standards to ensure the surety and accuracy of information contained in these gene banks, it is difficult for regulatory agencies to be sure of the true accuracy of a test whose performance is demonstrated by comparison to gene bank sequences.

> *"How are they going to qualify these gene databases and how are they going to be readily curated and how are they going to be updated?"*

> *"How do we determine the performance of these devices in the long run given the potential for pathogens to mutate?"*

Similarly, difficulties in obtaining clinical samples to test devices can also delay the development and clearance of new diagnostic tools, particularly for rare diseases. Project participants noted that it is frequently difficult to obtain the number of samples that FDA requires to demonstrate test validity.

> *"There are not enough samples available to validate assays for tularemia and smallpox."*

Finding 5. There are major barriers in the advanced development of diagnostics for global biosurveillance.

Development of diagnostic tests to serve the goals of global biosurveillance face many of the same challenges as development of drugs and vaccines for the developing world. Although the global in vitro diagnostic (IVD) market is considered to be a sizeable one—an estimated $44 billion in 2010[10]—the development of new diagnostics is largely driven by the search for rapid diagnosis of genetic conditions, cardiovascular disease, diabetes, cancers, and other chronic diseases.[37] Of those IVDs that are being developed to diagnose infectious diseases, the majority are for the diagnosis of sexually transmitted infections in developed world settings. Many of the new IVDs that are in use or are in development will have limited applicability to global biosurviellance for infectious diseases, as they are either too costly for use in the developing world and/or they require more infrastructure support than can be sustained in much of the world. Dedicated efforts are needed to encourage the development of diagnostic tools that can be used for global biosurveillance.

Few incentives to develop products for low-resource settings

Without a reliable and predictable market for low-cost infectious disease diagnostic devices, private industry will remain reluctant to invest in developing technologies that are needed for global biosurveillance. Infectious disease diagnostic tests are not as profitable as tests for cancer, diabetes, and other chronic diseases. Most commercially available infectious disease diagnostic devices are too costly for use by the developing world. In addition to the cost of the devices themselves, the costs of reagents and maintaining diagnostic devices post-deployment can put them out of reach for many developing countries.

Developing tests that are suitable for use in low-resource settings or by lay people adds a level of complexity to the development and manufacture of a test. Costs associated with having to harden or simplify diagnostic technologies so that they can be used in low-resource settings are significant and drive many manufacturers away from development of these products. In the developed world, there is little commercial demand for point-of-care, field deployable, or ruggedized diagnostics, as most healthcare providers are connected to clinical or public health laboratories from which they can order testing services as needed.

> *"There is almost no market in the United States for a $1 diagnostic test that can operate on a battery and test for several different pathogens."*

Limited funding for advanced development

Current USG investments in diagnostic tests for surveillance largely fund early stage scientific research. By contrast, there are fewer funding opportunities for advanced development and clinical evaluation. Project participants noted that USG-funded research in diagnostics often results in new approaches or prototypes,

many of which never go on to be evaluated by the FDA or produced on a commercial scale. Costs associated with advancing a technology from a prototype to a commercial product—which include clinical evaluation and full-scale manufacturing of devices such that they meet quality systems regulations—have been significant barriers for the development of tests that have a limited or nonexistent domestic market.

In the development of medical countermeasures, the lack of funding for advanced development has been referred to as a "valley of death"—that is, a gap in government funding exists between early stage development activities and the government procurement contracts for approved products. In the case of infectious disease diagnostics, because there is a limited commercial market and because governments have not typically focused on procuring such devices, the decline in support for advanced development is more appropriately described as a "cliff of death" (see Figure 1). Although some NGOs have identified the need to support advanced development and procurement of diagnostics and have begun to address the issue[38], this remains a significant barrier to the availability of needed infectious disease diagnostics.

> *"USG portfolio has lots of very good basic, early-stage research for diagnostics and detection. However, it is not clear how many of these projects would/could ultimately be operationalized and used in the real world."*

Standards to facilitate the development and use of diagnostic tests

In addition to targeted investments in advanced development and long-term maintenance of diagnostics, some experts suggested that creation of standards could facilitate development of diagnostics. Experts described 3 types of standards that could conceivably reduce the time and burden for regulatory approval:

- Performance standards—standards that clearly define what constitutes a positive or negative test result so that results from a test performed in one location can be compared to results from another location.

- Platform standards—specifications for how diagnostic devices and component parts should be built. Some have suggested that platform standards should be "open source" to enable various manufacturers to develop component parts for diagnostic devices that can be swapped in and out.

- Operational standards—criteria that govern how a test is performed and interpreted by the user. Given a global shortage of highly trained laboratorians[27,39,] there has been increased interest in simplifying and standardizing the user interface for diagnostic devices to enable them to be used by less trained workers and to reduce the amount of user training that is necessary.

Efforts are under way to develop such criteria. Organizations and agencies such as the Gates Foundation and DARPA have suggested that an agreed upon set of standards could "have a transformative impact on the performance, health impact, and costs of Point of Care Diagnostics."[40,41] They are interested in investing in prototype technologies that could represent a standard, as well as documents to outline how the standards could be applied.[40]

In addition to these efforts, the Standards for the Reporting of Diagnostic Accuracy Studies Initiative (STARD Initiative) helped to establish a 25-item checklist and flowchart to improve the reporting

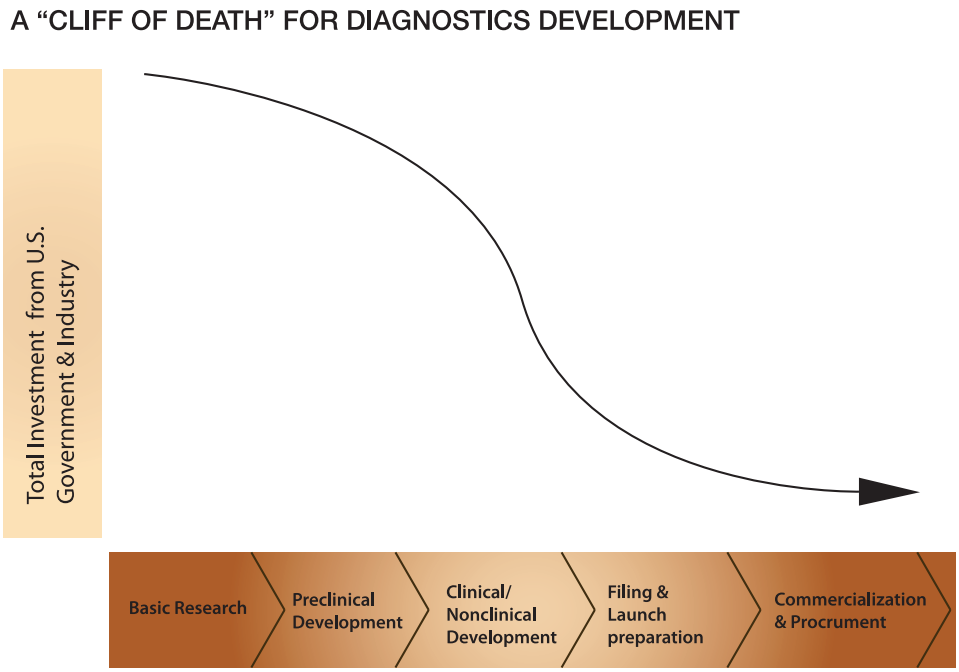

Figure 1: Areas of USG Investments in Diagnostic Development

of diagnostic information for clinical trials in the published literature. This initiative aims to improve the accuracy and completeness of studies that examine diagnostic tests to help improve readers' ability to gauge potential bias and how generalizable the results of a study are. Developed in 2000 and published in 2003, the STARD guidelines are now included in instructions to authors for more than 200 academic journals.[42]

Despite these efforts, some experts are concerned that the development standards may not be an attainable goal for diagnostics development. Several participants expressed skepticism about the feasibility of identifying a common set of performance, platform, and operational requirements toward which all diagnostics developers must strive in order to make devices (or even parts of devices) from multiple manufacturers interoperable.

Long-term investments needed

Project participants stressed that any effort to develop and procure diagnostic devices to enhance global biosurveillance will require sustained investments once they are placed in the field. Initial costs for developing a number of products need to be supported by maintenance, purchase of reagents, and training. Dust, excessive heat, short shelf lives of reagents, and high staff turnover can cause products to break down or lose utility over time. Without continued financial support and training resources to address these issues, it is likely that the ability of local users to detect and report known and emerging diseases will not be sustained. To maintain these local capacities and build a successful diagnostics program, long-term investments are critical.

> *"Success is based on longevity in the field and lasting, relevant support for a country's needs."*

Recommendations

1. Specific USG global biosurveillance goals should drive USG investments in diagnostics.

Each of the USG's biosurveillance goals is distinct and may require different technological approaches. For example, improving the diagnosis and care of patients will likely require different diagnostic tools from those required to better describe the background rates of illness at the population level. In the first case, simple, rapid, point-of-care technologies that test for common, treatable diseases will likely be needed, whereas in the second instance, multi-analyte devices that test for a range of potential pathogens may be important.

In light of these different needs, the USG should begin any effort to develop or procure new diagnostic tools with an assessment of how a new diagnostic tool can meet an explicit goal of USG biosurveillance. This analysis should include an assessment of user needs and the extent to which a proposed technology is likely to improve the user's routine diagnostic work and, therefore, is likely to be adopted by the intended user.

2. The USG will need to invest in a mix of diagnostic technologies in order to meet all of its global biosurveillance goals.

Recent advances in molecular-based approaches and the development of new platform technologies offer the promise of expedited testing of clinical specimens, simultaneously testing for multiple pathogens, and testing in environments outside of the laboratory. Such developments are important and necessary for improving the availability of diagnostic information across the globe. However, even with these new approaches, classic techniques, such as culture-based methods, will still be needed in many parts of the world. Therefore, the USG should consider investing in a range of diagnostic technologies. A diversified investment strategy will help to ensure the USG obtains the right mix of diagnostic technologies to help meet all of its surveillance goals.

3. The development of diagnostic tools should be accompanied by a plan for how these devices will be implemented and maintained in the field.

Employing diagnostic technologies for global biosurveillance will require having more than just a plan for the development and procurement of needed technologies. Successful deployment of diagnostic technologies will also require having a plan for how these tools will be implemented and maintained in the field. Given the number of resource (financial and human) and infrastructure constraints that exist in many of the environments in which diagnostic tools are needed most, the USG should ensure that diagnostic tools developed for the purposes of biosurveillance are appropriate for the environments in which they will be used. Prior to deploying any diagnostic device in the field, the USG should ensure that there are: (1) adequately trained staff to operate the device; (2) appropriate infrastructure (e.g., power, water, temperature) to support the operation of the device; (3) adequate availability of ancillary resources to support the use of the device (e.g., testing reagents and other supplies); (4) adequate and feasible biosafety and biosecurity plans; and (5) appropriate patient therapies to respond to diagnostic test results.

4. Diagnostic devices that are to be used for biosurveillance should come equipped with an ability to relay data from the point of testing to a central public health authority.

In order to best contribute to the biosurveillance mission, diagnostic devices should be accompanied by a plan for how the data from these tools will be collected and relayed to a central health authority. Although it may not be difficult to equip diagnostic devices with technologies that allow for electronic reporting of data to a surveillance system, the inclusion of such data-capture and -reporting capabilities has to date not been a priority in efforts to develop new infectious disease diagnostic tools.

5. The USG should work to improve the process for approving multi-analyte tests and for granting Emergency Use Authorization for diagnostic tests.

In recent years, the FDA has embarked on a number of new initiatives to expedite and streamline the process for clearing in vitro diagnostics. The FDA announced the creation of Action Teams to analyze the process for clearing multi-analyte tests. These teams should give strong consideration to how to expedite clearance of multi-analyte tests, as there is a need for such devices in much of the world, yet few multi-analyte technologies have received FDA approval.

The FDA has also developed a program for granting EUA for devices and medicines that are likely to be needed during public health emergencies. Such efforts are important steps; however, additional modifications to this program (and the legislation that authorizes it) are necessary to ensure that diagnostic tools that receive EUA are able to be integrated into outbreak response plans and surveillance programs. Key to this will be to allow for pre-emergency training of personnel and proficiency testing of EUA devices.

6. The USG should help to improve the regulatory approval of diagnostic devices by supporting efforts to strengthen gene banks and to increase the availability of clinical samples.

Questions regarding the accuracy of information contained in public and private-sector gene banks can cause delays in the evaluation and clearance of new diagnostic devices. In the absence of data quality standards to ensure that information contained in public and private-sector gene banks is accurate, it will continue to be difficult to evaluate diagnostic technologies that must use these databases to demonstrate testing performance. To expedite this process, the USG should explore how it might best support efforts to ensure the quality of information contained in gene banks that are used to demonstrate the validity of diagnostic devices.

Similarly, difficulties in obtaining clinical samples to test devices also delay the development and clearance of new diagnostic tools, particularly for rare diseases. To improve the availability of clinical samples for companies and for researchers who are working to develop new infectious disease diagnostic tools, the USG should explore ways to support the creation of sample repositories. CDC may be an appropriate place to locate and maintain such a repository.

7. The USG should consider ways of bridging the diagnostics development "cliff of death" by increasing support for advanced development and diagnostic procurement.

The kinds of infectious disease tests that are needed for global biosurveillance have a limited or nonexistent market and, therefore, will require incentives to develop. Although there is significant USG-funded research in diagnostics, few technologies ever make it through advanced development to a commercial product. Current USG investment in diagnostic tests, which emphasize early scientific research, is insufficient to help promising technologies address challenges encountered during clinical evaluation and scale-up manufacturing.

Additional funding is needed to ensure the availability of diagnostic tools for global biosurveillance of infectious diseases. The USG should consider ways of bridging the diagnostics development "cliff of death" by finding ways to support advanced development and diagnostic procurement. Any effort to develop and procure diagnostic devices to enhance global biosurveillance will require sustained investment. Initial costs for development of a number of products need to be supported by maintenance, purchase of reagents, and training. Without continued financial support and training resources, it is likely that diagnostic-based surveillance efforts will not be sustained.

Appendix A. Workshop Participants

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Appendix B. Overview of U.S. Regulatory Environment for Diagnostic Tests

What Is the Regulatory Definition of an In Vitro Diagnostic Device?

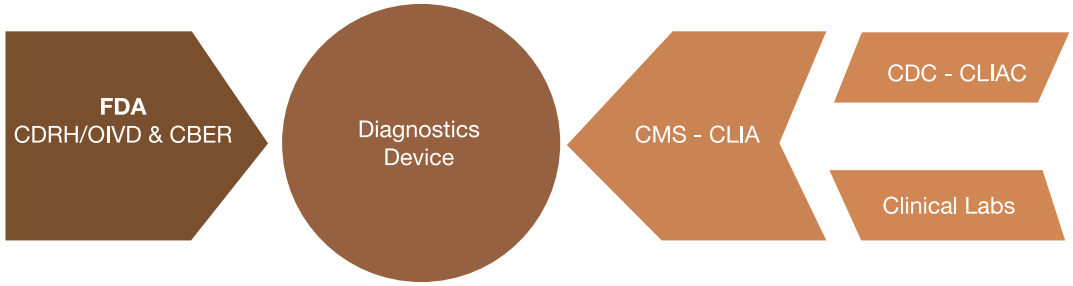
In broad terms, an in vitro diagnostic product (IVD) is any component involved in the process of diagnosing a disease or condition. The Food and Drug Administration (FDA) treats all products intended for use in the collection, preparation, and examination of specimens from the human body as IVD products.[43] For example, both a basic microbiological device, like an incubator, and a more specific diagnostic platform, like the human papillomavirus (HPV) diagnostic test, are identified as IVDs.

From a legislative perspective, IVDs fall under the jurisdiction of 3 federal laws. Under the Federal Food, Drug, and Cosmetic Act (FD&C Act), IVDs are designated as medical devices to be regulated by the FDA. Under the Public Service Act, IVDs that use blood or blood components are regulated as biological products to be regulated by the Center for Biologics Evaluation and Research (CBER). Additionally, IVDs are also subject to lab testing quality assurance regulations that are administered through the Centers for Medicare & Medicaid (CMS) under the Clinical Laboratory Improvement Amendments Act (CLIA).

Which Agencies Regulate Diagnostic Products?

In total, 3 operating divisions of the U.S. Department of Health & Human Services are involved in the regulation of IVDs (Figure 1).

Figure 1. Agencies involved in regulating a clinical diagnostic device used on humans in the U.S.



Federal Drug Administration (FDA)/ Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) & Center for Biologics Evaluation and Research (CBER)

The FDA has primary authority to evaluate all IVDs prior to their sale, distribution, and use in the U.S. Specifically, the Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD), a division of the FDA's Center for Devices and Radiological Health (CDRH), evaluates almost all premarket submissions from IVD manufacturers. The OIVD is divided into postmarket and premarket responsibilities. The premarket responsibilities are further divided among

3 areas: Chemistry & Toxicology, Immunology & Hematology, and Microbiology Devices.[44] Blood screening and HIV diagnostic device premarket submissions are exceptional; they are evaluated by CBER through an intercenter agreement between CBER and CDRH.[45]

Centers for Medicare & Medicaid (CMS)/Clinical Laboratory Improvement Amendments Program

CMS regulates all laboratories performing diagnostic tests on humans in the U.S. through the Clinical Laboratory Improvement Amendments Act (CLIA). The objective of the CLIA program is to ensure quality laboratory testing. The CLIA program regulates diagnostic tests based on the complexity category determined by the OIVD. [46]

Centers for Disease Control (CDC)/ Clinical Laboratory Improvement Amendments Committee (CLIAC)

CDC provides scientific and technical guidance to CMS about laboratory testing and its impact on clinical practice through a 20-member panel of experts in laboratory medicine, pathology, public health, and clinical practice, known as the Clinical Laboratory Improvement Amendments Committee (CLIAC). CLIAC makes recommendations on laboratory testing standards and the impact revisions would have on medical and lab practice. The Committee also advises CMS on modifications to accommodate technological advances and includes consumer and industry representatives in the process.[47]

Routes to the Market for a Diagnostic Test

Diagnostic Device or Diagnostic Service

A company that markets a diagnostic device in the U.S. must pursue FDA clearance or approval. In tandem with its clearance or approval, the FDA also gives the device a CLIA complexity rating, which determines how CMS will regulate the device once it has reached the market. Alternatively, some companies market a diagnostic service for which FDA clearance or approval is not necessary. The "service" product would be marketed as a laboratory developed test (LDT), known also as a "homebrew" test. A company marketing an LDT does, however, need to pursue CLIA accreditation for the lab in which the diagnostic service is performed in order to market the service. A CLIA-accredited lab is subject to routine CMS inspections for quality control and held to certain standards in personnel qualifications and proficiency testing.

The "homebrew" test pathway has come under scrutiny as it has grown in market share. Historically, LDTs were originally intended to address unmet needs for rare diseases and conditions and to be performed on a small scale with well-understood techniques and well-trained laboratory staff.[48] However, in recent years the annual growth rate of the LDT segment of the U.S. IVD market has increased considerably: in 2009 it was almost double (32%) that of the major molecular diagnostics companies (17%) and nearly quadruple the growth rate for the IVD industry as a whole (6%).[49] The FDA has traditionally exercised "enforcement discretion" in exempting these tests from more intensive premarket evaluation; however, the FDA has recently begun to consider taking a greater role in evaluating these tests.[48]

According to the FDA, LDTs were initially simple, well-understood tests used by physicians to diagnose rare conditions. However, in recent years, the reliance on LDTs has grown in scope and now includes more complex technologies. The advent of molecular techniques and genome sequencing has created significant tension between LDT service providers, who see it as an appealing option to rapidly develop and market innovative tests, and the FDA, who views the growing popularity of LDTs among diagnostic companies as an unregulated use

of the leniency originally granted to LDTs in a different context. The FDA initially responded by implementing an analyte-specific reagent (ASR) rule through which it would regulate the reagents, or "ingredients," used in LDTs, while continuing to exercise enforcement discretion over the general practice of LDT. But as LDTs grow in complexity and demand, the FDA has signaled that it is going to take more aggressive actions in regulating LDTs out of concern for their validity and clinical utility.[50]

2. **Class III – High Risk** (e.g., human papillomavirus genotypying test); subject to highest regulatory scrutiny and close postmarket surveillance

The greater the risk level, the higher the regulatory requirements for proving that a diagnostic is safe and effective. For example, a test for human papilloma virus (HPV) is considered more "risky" than a test for influenza, given that HPV is associated with cervical cancer.

Increasing Reliance on Laboratory Developed Tests Could Reduce the Availability of Tests that Are Deployable in the Field

In the context of global biosurveillance, the relative growth of LDTs versus commercially available diagnostic devices raises concern regarding the availability of tests that can be deployed to other countries. Although LDTs are routinely used for surveillance of infectious diseases, some argue that sustainable global biosurveillance efforts cannot rely on transport of samples to commercial laboratories that perform LDTs.

The increasing reliance on LDTs for diagnosis of infectious diseases may have consequences for biosurveillance. Since LDTs cannot be sold outside of the laboratory in which they are developed, it is not likely that such tests will be available for deployment to areas in need of enhanced diagnostic tools. Should the market continue to favor development of these approaches over commercially available diagnostic tests, it could limit the availability of infectious disease diagnostics outside of the service area of the LDTs.

FDA Classifications

Each device reviewed by the FDA is assigned to 1 of 3 regulatory classes based on risk level and the FDA's familiarity with, or "knowledge" about, the test (see Figure 2):

1. **Class I – Low Risk** (e.g., microbiological incubator); subject to minimal regulatory review and postmarket controls
1. **Class II – Moderate Risk** (e.g., albumin immunological test system); subject to moderate regulatory review and postmarket surveillance

Because risk is determined by potential harm to the patient (and the user), the intended use of the device plays a decisive role in determining the classification. For example, a nucleic acid amplification test to determine viral load could be a Class II/Moderate Risk device when intended for monitoring disease progression in a patient with HIV/AIDS. The identical test would become a Class III device, and subject to more intensive review, if it were to be used to diagnose HIV/AIDS.

FDA Clearance or Approval

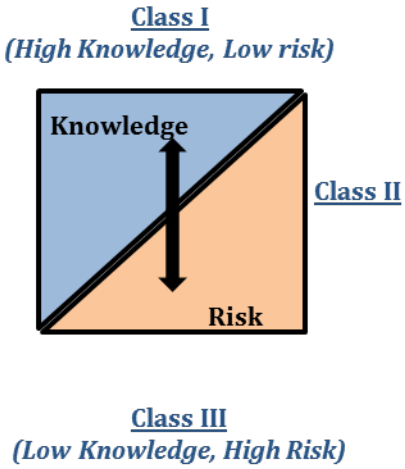
Risk classification will, in general, determine the regulatory pathway through which an IVD will be evaluated prior to market entry. To facilitate the process, the FDA has classified approximately 1,700 "generic" types of devices in 16 general categories (anesthesiology, cardiovascular, dental, orthopedic, immunology and microbiology, etc.). Most medical devices can be classified by finding a matching description of the device in Title 21 of the Code of Federal Regulations.[51] Because of this extensive list of generic devices with their respective risk classification and regulatory review requirements, most premarket clearance routes are fairly straightforward. In other words, a manufacturer will have a good idea which risk category and premarket notification protocol it must follow. In some cases, however, a device may involve some novel components or unprecedented technology. As a general principle, the FDA encourages companies to meet with the OIVD to discuss the planned premarket submission and determine the best way to proceed to minimize turnaround time.

Exempt from Premarket Notification (Class I Devices)

The FDA has exempted almost all Class I devices from the premarket submission requirement. Examples of exempt devices are tongue depressors and thermometers. If a manufacturer's device falls into the exempt category, the manufacturer is not required to submit a premarket notification. Instead, the manufacturer is required to list the generic category or classification name using the FDA's registration and listing system prior to market entry.[52]

Exempt devices are still regulated under quality control and manufacturing standards. An exempt device must be suitable for intended use, be adequately packaged and properly labeled, have establishment registration and device listing forms on file with the FDA, and be manufactured under a quality system.

Figure 2. FDA Risk Classification Strategy[ii]



Premarket Notification (Class II and III Devices)

510(k) Application – Demonstrating Substantial Equivalence to a Predicate Device

A company that is introducing a nonexempt device into commercial distribution is required to submit a 510(k) premarket notification at least 90 days before the device is sold on the market. A 510(k) application must demonstrate that the device to be marketed is at least as safe and effective (i.e., "substantially equivalent") to a device that has already been cleared or approved by the FDA (i.e., "predicate device"). The fee associated with a 510(k) application is approximately $5,000 ($2,500 for a small company). The Department of Defense's Joint Biological Agent Identification and Diagnostic System (JBAIDS) platform, a ruggedized real-time molecular diagnostic device for field deployment, is 510(k) cleared.[iii] A 510(k) application includes device description, intended use, predicate device, and performance summary.

Device manufacturers contend that the 510(k) process has been unpredictable and inconsistent, as the standards and breadth of data used in the performance summary are subject to the FDA's discretion. Conversely, healthcare professional groups and consumers have voiced concerns that the 510(k) represents an attractive "loophole" for companies to evade more intensive premarket evaluation pathways, thereby potentially compromising safety and effectiveness standards.[53] Therefore, the 510(k) process is likely to see significant changes in the short term as the FDA moves to both streamline the process and become more transparent and consistent with their standards for 510(k) evaluation.[54]

Understanding a Predicate Device

The "predicate device" may be either (1) a device that was on the market prior to May 28, 1976, or (2) one that has subsequently been cleared by the FDA. A product can serve as a "predicate device" even if it is no longer on the market (as long as it received 510(k) clearance or approval from the FDA when it was introduced).

The technologies underlying the new IVD and the

iii JBAIDS was developed by Idaho Technology through a Department of Defense contract to ruggedize a portable real-time PCR diagnostic platform for field deployment. The platform has FDA-cleared tests for H5N1, anthrax, plague, and tularemia. Tests are performed in under an hour by military-certified technicians.

ii Figure adapted from "FDA Regulatory Structure and Paradigm" by Sally Hojvat, PhD (presentation).

predicate device do not need to be identical. For example, a monoclonal antibody–based assay can serve as a predicate for a PCR assay. In 1998, Roche successfully contended substantial equivalence between the COBAS AMPLICOR PCR diagnostic, which uses molecular-based technologies, and the existing cell culture diagnostics, which used antibody-based assays, for chlamydia based on the commonality that the "biochemical properties of the target organism are all encoded in the DNA of the organism, essentially reducing each device to a test for genetic characteristics of the organism."[55] Paired with adequate nonclinical and clinical performance data, this was sufficient grounds for the FDA to provide Roche with a 510(k) clearance. Roche subsequently used the COBAS AMPLICOR to claim substantial equivalence with next-generation, automated PCR technology, the COBAS TaqMan in 2002.[56] Roche then claimed substantial equivalence to the COBAS TaqMan in gaining 510(k) clearance for their LightCycler automated PCR technology.[57] In 2005, Idaho Technology received FDA clearance for the JBAIDS Anthrax Detection System by citing the Roche LightCycler as a substantially equivalent predicate device (Figure 3).[58]

Figure 3. Sequence of predicate devices used prior to JBAIDS clearance in 2005.

Premarket Approval (PMA) Application

All nonexempt IVDs first go through a 510(k) application. A premarket application (PMA) would follow a 510(k) application for which the OIVD determines that a device has no standard equivalent (i.e., a de novo device). In this case, following the 510(k) decision, the OIVD sends a manufacturer a "not substantially equivalent" (NSE) letter and invites the manufacturer to submit a PMA application. The fee associated with a PMA application is approximately $230,000 ($59,000 for a small business). If the manufacturer submits a PMA application, the FDA conducts an in-depth internal review and, in some cases, convenes a panel review. A panel review will incur an additional $177,000 fee ($44,000 for a small business). This process is analogous to the review process for a new therapeutic drug and can be expensive and time-consuming. There is a 180-day FDA response timeline (as opposed to a 90-day for the 510(k)). A successful PMA grants the device FDA approval (as opposed to 510(k) clearance) for marketing a device in the U.S. An example of a test requiring a PMA and successfully achieving FDA approval is the genotyping test to diagnose HPV (marketed as Cervista HPV 16/18©).

The FDA evaluates PMA applications according to 4 parameters: (1) analytic validity, (2) clinical validity, (3) clinical utility, and (4) intended setting. In order to start compiling this data, a manufacturer applies for an investigational device exemption (IDE) for the de novo device from the FDA and institutional review board (IRB) approval from the host site (usually a medical center) to begin clinical trials.[59]

For many new multiplex molecular diagnostic tests, the FDA has voiced concerns about the validity of proprietary software algorithms behind automated diagnostic interpretations in multiplex machines, as well as the ambiguous clinical utility of testing for tens of different pathogen strains or gene sequences. For example, should a clinician use a multiplex molecular diagnostic that can detect up to 20 different pathogen strains that are known to

cause fever, and a patient tests positive for 3 different strains, how will this affect the clinician's approach to treatment? Furthermore, assuming an increased potential for cross-reactivity as the number of simultaneous tests increases, can the manufacturer guarantee few or no false results? These are the types of questions, according to the FDA, that are best answered by the more rigorous evaluation and clinical trials involved in the PMA process.

Complexity Category

In conjunction with the IVD clearance and approval process, the FDA administers the CLIA Complexity Program for the CMS by categorizing commercially marketed in vitro diagnostics by level of complexity:

1. Waived Test (Low Complexity)

3. Tests of Moderate Complexity

4. 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 IVD test will be 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.[60]

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-accredited labs by qualified personnel. CLIA defines labs as any facility used to examine materials derived from the human body (e.g., physician's office, community clinic, assisted living facility, hospital, etc.).[61] CLIA laws apply whenever patient-specific results from the laboratory are used for the health care of individual patients.

In some cases, a test is deemed simple and accurate enough to be "CLIA Waived." CLIA-waived tests can be performed outside accredited labs and are not subject to regular CMS inspections or personnel requirements (e.g., a physician's office performing a strep A test).

CLIA waiver is given to:[62]

- Any test listed in the 1988 CLIA amendments (dipstick urinalysis for ketones, fecal occult blood, 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
- Any test systems cleared by the FDA for home use
- A device must have a CLIA waiver to be used in physicians' office laboratories (POL).

A "home use" diagnostic test can be sold directly to an individual consumer (e.g., a pregnancy test) to be used outside a healthcare setting.

Emergency Use Authorization (EUA)

As part of the Project BioShield Act of 2004, the FDA is permitted to grant an emergency use authorization (EUA) to drugs, devices, and medical products that were not previously approved, cleared, or licensed by the FDA.[34] In order for EUAs to be granted,

the Secretary of the U.S. Department of Health and Human Services must issue a Declaration of Emergency. During the H1N1 pandemic of 2009, the FDA authorized Emergency Use of the CDC-developed rRT-PCR Swine Flu Panel diagnostic test.[63] The FDA encourages relevant companies to file pre-emergency applications to facilitate the process should an emergency occur.[64] For some manufacturers that have devices under review by the FDA for an emerging threat (e.g., an H5N1 diagnostic test), a "pre-EUA" submission affords the company rapid access to the market in the event of an emergency and the FDA an opportunity to prepare.

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