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Center for Science, Technology, and Engineering

Health Care

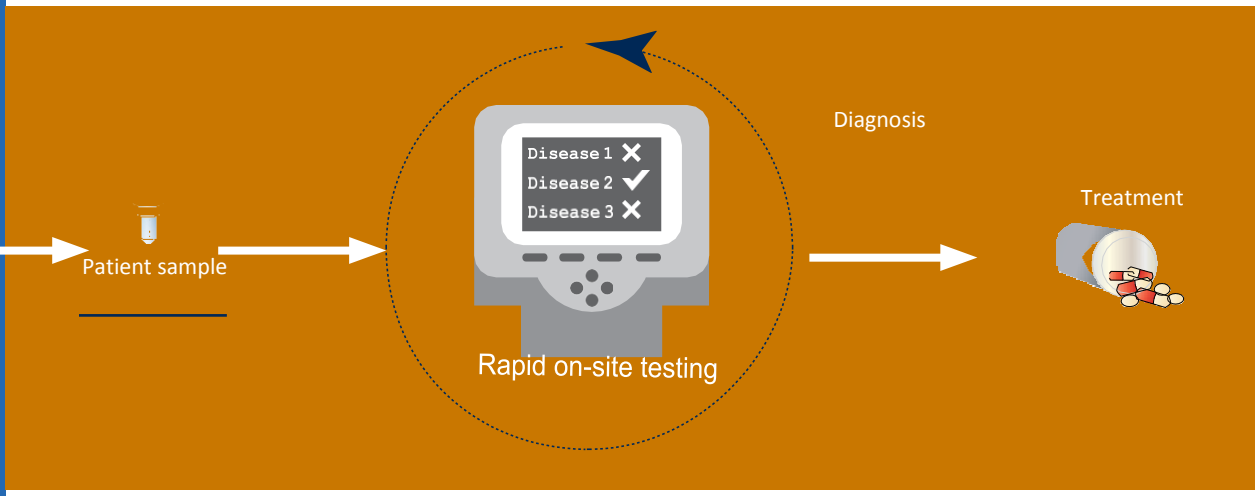
Report to Congressional Requesters

TECHNOLOGY ASSESSMENT

August 2017

Medical devices

Capabilities and challenges of technologies to enable rapid diagnoses of infectious diseases



Accessible Version

The cover image is GAO's rendition of a medical diagnostic process using multiplex point-of-care technologies.A sample is acquired from a patient with one or more symptoms. Multiplex point-of-care diagnostic technologies can test the sample for the presence of multiple disease pathogens near the site of patientcare, such as a doctor's office or clinic, sometimes providing results within 30 minutes. Results from these technologies can help medical professionals arrive at a diagnosis. Subsequently, the medical professional can decide on a treatment plan, potentially during the same patient visit.

Highlights of GAO-17-347, a report to congressional requesters

August 2017

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Why GAO did this study

Infectious diseases continue to represent a threat to the health and livelihoods of people worldwide. Many infectious diseases can initially present with similar symptoms, making diagnosis challenging.

To address this challenge, federal agencies have identified technologies that can help diagnose infectious diseases by using multiplex assays—simultaneously testing for, or measuring, the presence of different pathogens. These technologies can also be deployed at or near the site of patient care. In this report, GAO discusses (1) the reported performance characteristics and costs of these technologies, (2) the technical challenges associated with multiplexing assays, and (3) the potential benefits and reported implementation challenges associated with these technologies.

To conduct this technology assessment, GAO reviewed Department of Defense (DOD), Department of Homeland Security (DHS), and Food and Drug Administration (FDA) documentation and scientific literature, and interviewed agency officials, developers and users of these technologies. GAO conducted site visits to eight developers identified by DOD and DHS market surveys. Experts convened with the assistance of the National Academies provided technical advice to GAO and reviewed a draft of this report. GAO incorporated their comments in the final report as appropriate..

View GAO-17-347. For more information, contact Chief Scientist Timothy M. Persons at (202) 512-6412 or personst@gao.gov.

What GAO found

Commercially available multiplex point-of-care technologies (MPOCTs) have a range of performance characteristics that describe, among other things, the ability of the technology to correctly identify the presence or absence of a pathogen. Some of these characteristics are used by the FDA to evaluate the technologies prior to approval; other attributes are considered by developers in designing and marketing their technologies. Technologies GAO examined have varying features such as physical size, number of diseases being tested for at the same time, and throughput – or the number of patient samples that can be simultaneously run. The amount of time it took for the technologies to return results to users ranged from 20 minutes to 2 hours. Among available technologies offered by the eight developers that GAO visited, procurement costs ranged from $25,000 to $530,000, and per-test operational costs ranged from $20 to $200.

Developers identified several technical challenges to developing multiplex assays that can slow MPOCT development and raise costs. For example, challenges include lack of patient sample access or reliable genetic databases for developing the assays. Modifying multiplex assays poses another challenge, because developers have to consider possible new interactions based on the modification and go through FDA review before the modified test can be marketed. Further, limitations in the number of targets—the part of the pathogen being detected—that can be detected, and identification of genetic targets used for detecting the pathogen, can constrain the performance of these technologies, in part as a result of design limitations.

Potential benefits of MPOCTs include improved patient health care and management, more appropriate use of antibiotics, improved ability to limit the spread of disease, and health care cost savings. However, developers and users disagreed on the strength of evidence showing the extent of MPOCT improvement on patient outcomes. Some stakeholders GAO spoke to identified the need for more clinical studies to establish the benefits of these technologies. Implementation challenges included reluctance by medical users to adopt these technologies, due to factors such as (1) lack of familiarity with such technologies, (2) costs and resources to use them, and (3) reluctance to order, and pay for, all of the tests for a given multiplex assay. Further, in some situations, positive test results for rare diseases are more likely to be false positives; thus systematic testing for such diseases may result in wasted resources to address all patients who test positive. Developers told us additional implementation challenges include the regulatory review process for getting approval or clearance to market their technologies. Another challenging aspect of the regulatory review process developers identified is in applying for waivers to allow untrained users to use their technologies. In some cases, selected developers believed that the performance by an untrained user may need to surpass the performance by trained users for such waivers. FDA officials confirmed that this could occur but nevertheless believed that their review process is necessary to ensure the technologies are safe and effective, while being accurate and simple to use when waived.

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Abbreviations

ASSURED	affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free, and delivered
CAP	community acquired pneumonia
CDC	Centers for Disease Control and Prevention
CLIA	Clinical Laboratory Improvement Amendments
CMS	Centers for Medicare and Medicaid Services
DHS	Department of Homeland Security
DOD	Department of Defense
DOE	Department of Energy
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
LDT	laboratory-developed test
LLNL	Lawrence Livermore National Laboratory
MPOCT	multiplex point-of-care technology
NPA	negative percent agreement
NPV	negative predictive value
PCR	polymerase chain reaction
PMA	premarket approval
POC	point-of-care
PPA	positive percent agreement
PPV	positive predictive value
WHO	World Health Organization

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The Honorable Ron Johnson
Chairman
The Honorable Claire McCaskill
Ranking Member
Committee on Homeland Security and Governmental Affairs
United States Senate

The Honorable Greg Walden
Chairman
Committee on Energy and Commerce
House of Representatives

The Honorable Fred Upton
House of Representatives

Infectious diseases, including emerging infectious diseases, continue to threaten the health and livelihoods of people worldwide despite many advances in medical research and treatments made during the past century.[1] Infectious diseases range from common ailments, such as seasonal colds or influenza, to serious illnesses caused by select agents, such as *Bacillus anthracis,* the bacterium that causes anthrax, and can be caused by pathogens such as bacteria, viruses, parasites, or fungi.[2] In addition to causing nearly one in five human deaths worldwide, infectious diseases impose a heavy societal and economic burden on individuals, families, communities, and countries.[3] For example, the Centers for Disease Control and Prevention (CDC) estimates that 310,000 people in the United States were hospitalized for flu-related illness during the 2015-16 influenza season. Many infectious diseases, including those caused by select agents, initially present with similar symptoms, regardless of the causative infectious agent. Therefore, making a diagnosis solely from clinical presentation can be a challenge. Whether for general medical diagnosis or homeland security, early detection of infection in a patient can help direct treatment and is a key component to assessing the potential spread and effect of the disease in the case of dangerous pathogens.[4]

From a homeland security and public health perspective, threats of bioterrorism, such as anthrax attacks, and high-profile disease outbreaks, such as Ebola and emerging arboviruses like dengue, chikungunya and Zika, highlight the continued need for diagnostic tests that provide early detection and warning about biological threats to humans.[5] As we previously reported,

[1]An emerging infectious disease is an infection whose incidence has increased recently or is threatening to increase in the near future, such as Zika, Ebola, and new variants of influenza, among others.

[2]A select agent is a biological agent that has the potential to pose a severe threat to human and animal health and safety, plant health and safety, or to the safety of animal or plant products.

[3]GAO, *Biodefense: The Nation Faces Multiple Challenges in Building and Maintaining Biodefense and Biosurveillance,* GAO-16-547T (Washington, D.C.: Apr. 14, 2016).

[4]GAO, *Biosurveillance: Nonfederal Capabilities Should Be Considered in Creating a National Biosurveillance Strategy,* GAO-12-55 (Washington, D.C.: Oct. 31, 2011), and *Influenza Pandemic: Efforts Under Way to Address Constraints on Using Antivirals and Vaccines to Forestall a Pandemic,* GAO-08-92 (Washington, D.C.: Dec. 21, 2007).

[5]Arthropod-borne viruses, also known as arboviruses, are any of a group of viruses that are transmitted by mosquitoes, ticks, or other arthropods (an animal such as an insect or spider).

timely detection of signs of unusual and potentially dangerous disease is a first step in an effective response to a natural, accidental, or intentional outbreak of a biological event.[6] We also found that early detection of potentially serious disease indications nearly always occurs first at the local level, making the personnel, training, response systems, and equipment that support detection at the state and local level a cornerstone of our nation's biodefense posture. Early detection may depend on an astute clinician diagnosing the first few cases, or recognizing suspicious clinical signs that require further investigation. Diagnostic test users provide critical expertise to effectively identify and respond to public-health emergencies through testing and monitoring of diseases.

Multiplex point-of-care technologies (MPOCTs) are technologies that can simultaneously test for more than one type of human infectious disease pathogen from a single patient sample (such as blood, urine, or sputum) in one run at or near the site of a patient.[7] MPOCTs can enable rapid testing while the patient is at the doctor's office, clinic, or other testing location, including the home.[8] The part of these tests that measures the amount, activity, or potency of a particular pathogen in a sample is called an assay. MPOCTs can be used for different diseases, including more common diseases such as influenza, emerging infectious diseases, or diseases caused by select agents.

The U.S. Department of Defense (DOD) and U.S. Department of Homeland Security (DHS) have sought technologies beneficial to diagnosing infectious diseases for biodefense and biosurveillance systems.[9] These agencies performed market surveys published in 2012 and 2015, respectively, to evaluate MPOCTs they identified against program requirements. The agencies were particularly interested in identifying MPOCTs that addressed requirements such as detecting multiple targets simultaneously from a single sample, identifying a targeted pathogen rapidly, and being easy to use and accurate.[10] The DOD market survey did not identify which MPOCTs met or approached its requirements. The DHS market survey found that no MPOCTs fulfilled all program requirements; however it identified four MPOCTs as coming very close to doing so.

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[6]GAO-12-55

[7]In terms of MPOCTs, one run means that the user prepares and inserts one sample into the device and later receives an output with results of tests for more than one human infectious disease. Within the device, multiple tests may be run in parallel or sequence.

[8]Christopher P. Price, Andrew St. John, and Larry J. Kricka, "Putting Point-of-Care Testing into Context: Moving Beyond Innovation to Adoption," in Christopher C. Price, Andrew St. John, and Larry J. Kricka (eds.), *Point-of-Care Testing: Needs, Opportunity, and Innovation,* 3rd ed. (Washington, D.C.: AACP Press, 2010): 1-20.; see also A. St John and C. P. Price, "Existing and Emerging Technologies for Point-of-Care Testing," *The Clinical Biochemist Reviews*, Vol. 35, no. 3 (2014): 155-67.

[9]Biodefense includes measures to prevent, detect, respond to, and recover from harm or damage caused by microorganisms or biological toxins to humans, animals, or the food supply. Biosurveillance, is the ongoing process of gathering, integrating, interpreting, and communicating essential information related to all-hazards threats or disease activity affecting human, animal, or plant health, for the purpose of (1) achieving early detection and warning, (2) contributing to overall situational awareness of the health aspects of the incident, and (3) enabling better decision-making at all levels.

[10]For the technologies discussed in this report, targets are genetic material of disease-causing pathogens selected to help uniquely identify the pathogen.

In light of federal government interest in new diagnostic technologies, such as investments in biosurveillance and biodefense technologies, you asked us to conduct a technology assessment on MPOCTs for the detection of human infectious diseases, including those caused by select agents. In this report we discuss:

- the reported performance characteristics and costs of MPOCTs;
- the technical challenges associated with multiplexing assays; and
- the potential benefits and reported implementation challenges associated with MPOCTs.

To address all objectives, we interviewed federal agency officials from DHS, DOD, the U.S. Department of Energy (DOE), including the Pacific Northwest National Laboratory, Sandia National Laboratories, and the Lawrence Livermore National Laboratory, which are involved in developing or evaluating MPOCTs; and the Department of Health and Human Services (HHS), including the CDC, the Food and Drug Administration (FDA), and the Centers for Medicare & Medicaid Services (CMS). In addition to the federal agencies and officials we contacted, we interviewed users knowledgeable about MPOCTs—including laboratory users, who use the technologies to obtain clinical results, and physicians, who use the technologies and the clinical results to inform patient care. These interviewees included academic and laboratory organizations, and scientific and medical professional organizations, such as those involved in laboratory chemistry or microbiology (a full list is in appendix I).

To address the first objective, we analyzed market surveys of MPOCTs from DHS and DOD. These market surveys identified existing MPOCTs and assessed them against each agency's listed program requirements.[11] From the DHS market survey, we selected for further review developers whose MPOCTs were identified as coming very close to meeting program requirements. From the DOD market survey, we selected all developers of MPOCTs listed because the agency did not identify which MPOCTs met or approached its requirements.

To address all objectives, we conducted nine site visits to the selected developers to discuss their experiences developing and deploying MPOCTs. One developer had left the MPOCT development market and was excluded from further analysis. We also visited DOE's Lawrence Livermore National Laboratory in Livermore, California, to discuss its ongoing work in MPOCT development. Finally, we reviewed scientific literature describing current and developing technologies, and we attended two relevant conferences on MPOCTs.

In addition, we convened—with the assistance of the National Academies of Sciences, Engineering, and Medicine —a 2-day meeting of 18 experts on MPOCTs to obtain additional advice and information on significant areas of all objectives in this review. We selected experts

[11]These market surveys list candidate technologies, their developers and features, and discussion of the potential suitability of the technologies for purposes each agency specified. The features described include technical specifications, such as speed and number of targets.

from academia, industry, laboratory, scientific and medical professional organizations, and federal government agencies to represent three categories: (1) developers of the technologies, (2) users, and (3) regulatory experts, who are people knowledgeable in the regulatory process for MPOCTs. We continued to draw on the expertise of these 18 individuals throughout our review. Consistent with our quality assurance framework, we provided the experts with a draft of our report and solicited their feedback, which we incorporated as appropriate.

We limited the scope of our review to MPOCTs identified in market surveys conducted by DHS and DOD as described above, as applied to testing for human infectious diseases.[12] We did not assess all available or developing technologies.[13] For example, all of the MPOCTs identified by the market surveys, and therefore those we selected for further review, were polymerase chain reaction (PCR)-based technologies.[14] Other technologies, such as lateral flow assays, were discussed during the expert meeting as well as at conferences we attended; however, our report focuses primarily on PCR-based technologies.[15] Additional technologies, such as microarray technology and next-generation sequencing, were identified in scientific literature and conferences but were at early stages of development, and we excluded them from our analysis.[16] We also excluded MPOCTs developed outside the United States and those intended primarily for deployment outside the United States (appendix I contains additional information on our scope and methodology).

We conducted our work from September 2015 to August 2017 in accordance with all sections of GAO's Quality Assurance Framework that are relevant to technology assessments. The framework requires that we plan and perform the engagement to obtain sufficient and appropriate evidence to meet our stated objectives and to discuss any limitations to our work. We believe that the information and data obtained, and the analysis conducted, provide a reasonable basis for any findings and conclusions in this product.

[12]For example, we do not examine detection of toxins, such as ricin.

[13]We combine discussion of different contexts for MPOCT use, including routine clinical, emerging infectious disease, and select agent detection excepting situations where the specific context was provided.

[14]Sometimes also called molecular photocopying, PCR is a technique used to detect nucleic acid signatures. It is used to amplify and detect genetic material, or nucleic acids, of organisms. By amplifying (i.e., repeatedly duplicating) sections of genes associated with certain biological agents, PCR can be used as the basis for a test, or assay, for the presence of genetic signatures, or markers, associated with specific biological organisms.

[15]Lateral flow assays are typically based on antibody-based detection of disease-causing organisms. Their configuration is similar to a home pregnancy test "dipstick," whereby a liquid sample is applied to an absorbent material that draws the sample across a detector. Positive detections can be indicated by the appearance of lines in the readout region.

[16]Additional information on microarray technology and next-generation sequencing is in appendix II.

1 Background

1.1 Clinical laboratories are used for diagnostic testing

Clinical laboratories play a pivotal role in the nation's health care system by helping diagnose many diseases, including potentially life-threatening diseases, so that individuals receive appropriate medical care.[17] Such diseases can include infectious diseases caused by pathogens, as well as noninfectious diseases and chronic conditions, such as cancer and diabetes. The results of clinical laboratory tests—what we refer to as diagnostic tests—affect an estimated 70 percent of medical decisions, according to the American Clinical Laboratory Association.[18] Laboratories perform diagnostic tests on a patient sample to see if it contains different substances, such as pathogens, and to measure amounts of such substances. Depending on the test, the presence, absence, or amount of the substance can be used to indicate whether a patient does or does not have a particular condition. In order to make a clinical diagnosis, users must then interpret the results obtained from diagnostic testing in conjunction with other factors, including the patient's overall health and the results of other relevant exams or tests.

Diagnostic testing of human infectious diseases serves a number of functions, including detecting known and new pathogens, assessing a patient's response to treatment and prognosis, as well as informing disease or public-health surveillance.[19] Diseases addressed by such testing include those classified as emerging infectious diseases or caused by select agents. Thus, in addition to potentially improving patient care, advances in diagnostic technologies could affect the detection of, and response to, epidemics or bioterrorism events in the United States.[20]

1.2 How performance characteristics describe diagnostic test accuracy

Performance characteristics of diagnostic tests describe how well such tests can detect the presence of a disease-causing pathogen in a patient sample, among other things. Such characteristics can be taken into consideration by users when deciding whether to adopt such a test. For example, the diagnostic accuracy of a test indicates its ability to determine which patients do or do not have the disease.[21] Multiple performance characteristics describe diagnostic accuracy, including the sensitivity and specificity of the

[17] A clinical laboratory is generally defined as a facility that examines specimens derived from humans for the purpose of disease diagnosis, prevention, and treatment, or health assessment of individuals.

[18] American Clinical Laboratory Association, "Clinical Laboratory Testing: Life Saving Medicine Starts Here," accessed March 15, 2017, https://www.acla.com/wp-content/uploads/2013/12/ACLA_Overview_OneSheet_v07.pdf.

[19] A. M. Caliendo and others, "Better Tests, Better Care: Improved Diagnostics for Infectious Diseases," *Clinical Infectious Diseases,* Vol. 57, no. S3 (2013).

[20] N. A. Doggett and others, "Culture-Independent Diagnostics for Health Security," *Health Security,* Vol. 14, no. 3 (2016). A. Deshpande and others, "Surveillance for Emerging Diseases with Multiplexed Point-of-Care Diagnostics," *Healthy Security,* Vol. 14, no. 3 (2016).

[21] Diagnostic accuracy can also refer to the extent of agreement between the outcome of a new test and the reference standard—the best available method for establishing the presence or absence of the target condition.

test, among others. These characteristics have different meanings when being discussed in the analytical or clinical contexts.

- Analytical sensitivity is the minimum amount of target in a sample that can be accurately measured by a given test. This metric is alternatively referred to as the limit of detection.
- Clinical sensitivity describes a given test's ability to accurately confirm that a sick patient is ill with a particular disease (i.e., the true positive rate). It is the probability that a patient with the disease tests positive for that disease (N_{TP}/N_S, Table 1). High analytical sensitivity does not necessarily indicate high clinical sensitivity. For example, a sample from an infected patient may not contain the target detected by the test once the sample has been processed. In this case, a test with high analytical sensitivity would return a false negative and could result in an incorrect diagnosis.
- Analytical specificity is the ability of a test to detect the particular target for which it was designed and not others in a sample.
- Clinical specificity describes a given test's ability to accurately confirm that a healthy patient does not have a particular disease (i.e., the true negative rate). It is the probability that a patient without the disease tests negative for that disease (N_{TN}/N_H, Table 1).

To illustrate what these terms mean, consider a patient population with both people who are ill with a particular disease and people who are not ill with that disease.[22] Table 1 summarizes the nomenclature for different diagnostic test outcomes for a patient population. These performance characteristics are important for describing screening or diagnostic capabilities because they relate directly to a test's ability to determine whether or not a patient has a particular disease.[23]

Other performance characteristics, such as predictive values, can depend on the prevalence of a disease within a population when the test is not perfect. Positive predictive value (PPV) is the probability that a positive test result means a patient has a disease (N_{TP}/N_P in Table 1), and negative predictive value (NPV) is the probability that a negative result means a patient does not have a disease (N_{TN}/N_N in Table 1).

For diseases that change in prevalence over time, predictive values of diagnostic tests will correspondingly change. For example, during winter, influenza prevalence can be high, and during summer, influenza prevalence can be low. For a given influenza test, the PPV will correspondingly vary, being lower in the summer and higher in the winter. Similarly, NPV will be higher in the summer and lower in the winter. Predictive values thus help test users understand the likelihood that a particular result is true, based on both the clinical characteristics of the patient and other factors including population, setting, and time of year.

[22]The second population could be people who are healthy, or ill with a different disease.

[23]Screening refers to when patients are tested for some disease when the patient has not actively sought medical attention for that disease.

Table 1: Diagnostic test outcomes for a patient population

	Ill with the tested disease (N_S)	**Not ill with the tested disease (N_H)**	**Total patients (N_T)**
Patient tests positive	True positive (N_{TP})	False positive (N_{FP})	Total positive tests (N_P)
Patient tests negative	False negative (N_{FN})	True negative (N_{TN})	Total negative tests (N_N)

Source: GAO analysis of the literature. | GAO-17-347

Note: Columns indicate the actual condition of a patient, ill with the disease being tested for or not ill with the disease being tested for, whereas rows indicate the results of the diagnostic test, positive (target detected) or negative (target not detected).

Disease prevalence and positive predictive values

Physicians told us they can use diagnostic test results to help guide treatment plans. However, factors affecting the likelihood of disease, such as patient risk factors or symptoms, could be used in considering whether a test should even be performed. Additionally, the prevalence of a disease may influence whether it is appropriate to use the test. For example, in the absence of perfect tests, there will be false positive or false negative results that incorrectly indicate the presence of a disease pathogen when it's not there, or the absence of a disease pathogen that's present, respectively. Clinicians may make decisions, in part, based on their assessment regarding whether a particular case is likely to be a false positive. That is, clinicians consider the positive predictive value (PPV) of a test, among other things, when deciding whether to conduct a test. For example, a low PPV means that a positive test is more likely to be a false positive.

For example, consider a test which is 95 percent sensitive for a given disease, meaning it will correctly identify – on average – 95 out of 100 ill people as being ill with the disease being tested. Assume further that this test is 95 percent specific, meaning it will correctly identify – on average – 95 out of 100 healthy people as being healthy ("healthy" in this case may refer to patients who have no symptoms and are being screened, or are ill but do not have the disease being tested for). Next, apply the test to a population of 10,000 people.

Case 1: 20 percent of the population has the given disease

	Ill	Healthy	Total
Tests positive	1,900	400	2,300
Tests negative	100	7,600	7,700

The PPV, or chance that a given person who tested positive is also ill is 1,900/(1,900+400), or about 83 percent, so it may make sense to treat everyone who tests positive.

Case 2: 0.2 percent of the population has the given disease

	Ill	Healthy	Total
Tests positive	19	499	518
Tests negative	1	9,481	9,482

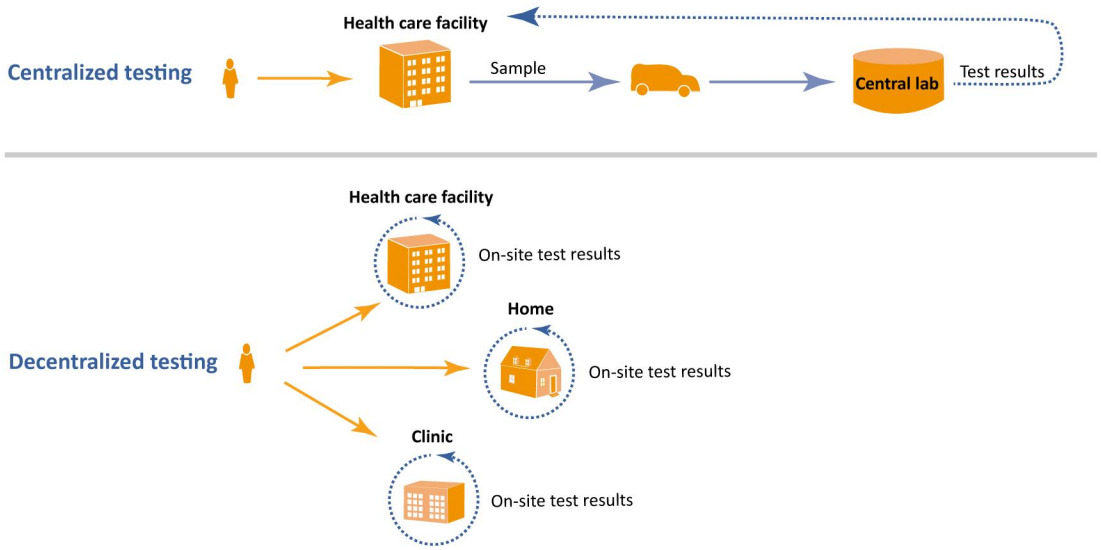
The PPV, or chance that a given person who tested positive is also ill, is now 19/(19+499), or about 4 percent, so it may not make sense to treat anyone who tests positive. Even though the test sensitivity and specificity remains the same in both cases, the PPV changes with disease prevalence. In cases where a disease is expected to be rare, in the absence of additional factors such as patient risk factors, it may not be cost-effective to test for such diseases because the PPV is low. In some cases, follow-up or confirmatory testing may be used to clarify initial test results, but could incur additional time and costs.

Source: GAO analysis of interviews and literature. | GAO-17-347

1.3 Point-of-care technologies bring diagnostic testing closer to patients

Diagnostic testing for diseases can be performed in a number of different settings that can be far from, or close to, patients being tested. In the centralized model shown in the top part of figure 1, patient samples are sent to large clinical laboratories for testing, outside the patient-care setting. Central laboratories can analyze large numbers of samples at relatively low cost through automation of analytical processes and consolidation of services. Large regional hospitals also often have clinical laboratories that perform tests for smaller hospitals. Within clinical laboratories, tests can be commercial tests manufactured by developers and overseen by FDA, or laboratory developed tests (LDT) designed, manufactured and used within a single laboratory and generally not overseen by the

Figure 1: Centralized and decentralized models of testing



Source: GAO analysis of literature. | GAO-17-347

FDA.[24] Certain diagnostic testing technologies can help decentralize medical testing, by bringing testing closer to patients at the point of care, as shown in the bottom part of figure 1.[25]

In a patient-centered model, health care is organized around the patient rather than the provider. One component of this concept is greater availability of patient testing in primary care and community facilities and decreased emphasis on such testing in large, regional hospitals.

Point-of-care (POC) testing can also serve as a tool to improve health care in remote or low-resource settings—such as developing countries or sparsely populated rural areas—where patients may have to travel long distances and health care providers may not have access to clinical laboratories.[26] In such circumstances, the ability to test for disease and prescribe treatment based on test results within a single patient visit can be of increased importance. Generally, there are four steps that occur during POC testing: (1) sample collection – acquiring a sample from a patient, (2) sample preparation – processing of the sample for compatibility with the assay, (3) the assay step, which detects and/or measures the pathogens being tested, and (4) displaying the test results. POC testing thus reduces or eliminates the need to ship patient samples elsewhere and to wait for test results to be returned.

Features of POC testing technologies are influenced by both users' needs and clinical settings. For example, the World Health Organization has developed specific guidelines for POC testing technologies for detecting sexually transmitted infections, primarily in low-resource settings. These guidelines are known as ASSURED—Affordable, Sensitive, Specific, User-friendly, Rapid and Robust, Equipment-free, and Delivered.[27] While the design of a given technology must meet the clinical needs of the specific user and remain cost-effective, some features are common to many POC technologies: (1) the technology is easy to use; (2) necessary chemicals can be stored for long periods of time; (3) the results from the test are consistent with those that would be obtained from standard laboratory methods; and (4) the technology, as well as any necessary chemicals, do not expose the user to hazards.

1.4 Detecting multiple disease pathogens from a single run

Diagnostic testing technologies can be designed to test in a multiplex configuration. According to FDA and CMS officials, "multiplex" does not have a regulatory definition. While federal agency officials and experts we spoke to have varying definitions for multiplex testing, a common theme is that multiplex tests simultaneously test for more

[24]According to FDA officials, LDTs currently fall under a policy of enforcement discretion and are therefore, in general, not overseen by FDA. Further, FDA officials stated that tests can be partially designed or manufactured outside a lab, being neither purely a commercial test nor a pure LDT.

[25]Point-of-care (POC) testing can be defined as "testing that is performed near or at the site of a patient." Interest in this model of testing is associated with a patient-centered approach to health care. An example of a point-of-care test is a home pregnancy test.

[26]R. W. Peeling and D. Mabey, "Point-of-care tests for diagnosing infections in the developing world," *Clinical Microbiology and Infection,* Vol. 16 (2010).

[27]Hannah Kettler, Karen White, and Sarah Hawkes, *Mapping the Landscape of Diagnostics for Sexually Transmitted Infections: Key Findings and Recommendations*, (Geneva: World Health Organization, 2004).

than one human infectious disease pathogen from a single patient sample.[28] The set of tests on a multiplex technology is called a test panel.[29] Syndromic test panels, which test for multiple diseases associated with a similar set of symptoms, or a syndrome, are increasingly available to assist users in determining the cause of disease at the point of care.[30] Respiratory panels and gastrointestinal panels are two examples of syndromic panels.

Although we limited the scope of this study to human infectious disease applications of MPOCTs in the United States, these technologies are also currently being tested and are reported to show promise for diagnosis and management of other diseases or chronic conditions, such as cancer or heart disease. They also are being used internationally. While some features of MPOCTs are specific to multiplex testing and others are specific to POC testing, we considered and present them in the context of the MPOCT discussion in this report. More generally, the potential effect of MPOCTs on public health may extend beyond the roles discussed in this report.

[28]Some MPOCT developers and users we spoke to consider other factors, such as antibiotic resistance or subtype identification, in determining whether a test is multiplex. In such cases, experts prefer to define multiplex as detecting more than one target, rather than disease.

[29]Multiplex test panels can test for as few as two pathogens or can be highly multiplexed, meaning able to detect 20 or more pathogens according to FDA guidance on nucleic-acid based technologies. The number of pathogens can vary with the user or market targeted by the developer.

[30]N. A. Doggett and others, "Culture-Independent Diagnostics for Health Security," *Health Security,* Vol., 14, no. 3 (2016): 135.

1.5 Federal agencies' roles in multiplex point-of-care technologies

Because MPOCTs intended for clinical use are considered medical devices, FDA is responsible for overseeing their safety and effectiveness when marketed in the United States. FDA classifies medical devices based on their associated risks. Class I devices are low risk and subject to general controls, while class II devices are subject to general and special controls. Class III devices are generally the highest-risk devices and subject to general controls and premarket approval (PMA).

In general, FDA classifies MPOCTs as class II or class III. For class III devices, a PMA application is required, and the developer must provide evidence—typically including clinical data—that provides reasonable assurance that the new device is safe and effective before it may be legally marketed in the United States. The PMA process is the most stringent type of premarket review and includes annual reporting of changes to a device. A successful PMA submission results in FDA approval.[31]

For class II devices, unless exempted by regulation, a premarket notification (510(k)) is required before the device may be legally marketed in the United States. In a 510(k) submission, a developer must demonstrate to FDA that its new device is substantially equivalent to a device already legally on the market that is not subject to PMA. A successful submission of a 510(k) application results in FDA clearance.

[31]FDA officials also identified the *de novo* regulatory pathway, which allows devices without predicates to be classified as Class I or II.

Similarly, FDA categorizes MPOCTs and their associated testing based on the complexity of the technology. The Clinical Laboratory Improvement Amendments of 1988 (CLIA) include federal standards applicable to all U.S. facilities or sites that examine materials derived from the human body for a health assessment, or for the purpose of providing information for the diagnosis, prevention, or treatment of disease or impairment.[32] For tests that have been FDA-cleared or -approved, based on the information provided by the developers, FDA assigns the tests to one of three CLIA complexity categories—waived, moderate complexity, or high complexity—that determine which laboratories can use the tests once they are on the market. For example, waived tests can be conducted by laypeople or by laboratories with a certificate of waiver; laboratories with a certificate of waiver are not subject to a routine inspection under the CLIA Program but may be subject to oversight under certain conditions—for example, in response to a complaint. As of January 2017, laboratories with a certificate of waiver represent 72 percent of laboratories registered through CLIA in non-exempt states.[33] Waived tests are tests that FDA has approved for home use or that are simple tests with a low risk for an incorrect result.[34] Laboratories conducting non-waived tests, including moderate and high complexity, are subject to routine oversight and must meet personnel requirements stipulated by CLIA.

CMS also plays a role in the regulation and adoption of diagnostic tests, including tests run by MPOCTs. Specifically, CMS is responsible for overseeing clinical laboratory compliance with CLIA requirements. CLIA requires that all clinical laboratories be certified by their state, as applicable, as well as by CMS before they can accept human samples for diagnostic testing. Laboratories can obtain multiple types of CLIA certificates, based on the kinds of diagnostic tests they conduct.[35] Clinical laboratories that conduct moderate- to high-complexity tests undergo biennial inspections--also referred to as surveys—that assess laboratory compliance with mandated personnel and testing standards.[36] In addition, surveyed laboratories must participate in proficiency testing, a program that requires them to test samples with unknown characteristics that are then graded by an external party. Laboratories with serious deficiencies may be sanctioned, e.g., required to cease testing. Laboratories with a certificate of waiver may conduct only waived tests and must (1) enroll in the CLIA program, (2) pay applicable certificate fees biennially, and (3) follow developers' test instructions. Routine on-site surveys are not required for laboratories with a certificate of waiver unless there is a complaint.

[32]To improve oversight of clinical laboratories, Congress passed the Clinical Laboratories Improvement Act of 1967; renewed concerns about quality, including errors in Pap smear tests used to diagnose cervical cancer, resulted in enactment of the Clinical Laboratory Improvement Amendments of 1988 (Pub. L. No. 100-578, 102 Stat. 2903 (Oct. 31, 1988)).

[33]CLIA-exempt laboratories are those that have been licensed or approved by a state where CMS has determined that the state has enacted laws relating to laboratory requirements that are equal to, or more stringent than, CLIA requirements and the state licensure program has been approved by CMS.

[34]See 42 U.S.C. § 263a(d)(3); 42 C.F.R. § 493.15.

[35]Laboratories obtain a CLIA certificate that corresponds to the complexity of the testing they conduct. Generally, each laboratory has one certificate, but a large hospital with multiple laboratories may have a corresponding number of certificates. By regulation, laboratories that are within a hospital campus and under common direction are allowed to file either a single application for a certificate or multiple applications for multiple certificates.

[36]Those laboratories that must be surveyed routinely; i.e. those performing moderate and/or high complexity testing, can choose whether they wish to be surveyed by CMS or by a private accrediting organization.

2 MPOCT performance characteristics and costs vary

MPOCTs have a range of key performance characteristics that are used by the FDA to evaluate the technologies, and by developers to market their technologies. Two key characteristics considered by FDA in evaluating MPOCTs for clinical use are sensitivity and specificity. Performance characteristics that developers consider in designing and marketing their MPOCTs to users include: (1) panel size, or the number of disease targets that can be tested in one sample run; (2) time to test result; (3) throughput, or the number of patient samples that can be run simultaneously; and (4) usability characteristics.[37] Regarding the costs of MPOCTs, they vary widely and are based on several factors, such as the intended use of the technology, the complexity of the technology, and developer business strategies.

2.1 FDA evaluates certain MPOCT performance characteristics for clinical use

FDA evaluates performance characteristics in order to approve or clear an MPOCT for clinical use. According to FDA guidance for 510(k) applications, the importance of specific performance characteristics depends on the intended use of the MPOCT, among other things. FDA has discretion in the type of information it ultimately deems necessary for approval or clearance of MPOCTs, although FDA applies least burdensome principles when reviewing PMA, 510(k) and *de novo* submissions.

We found that two characteristics are repeatedly presented in scientific literature and product descriptions, and are considered important for FDA's evaluation of MPOCTs:

- Sensitivity, which includes analytical and clinical sensitivity;
- Specificity, which includes analytical and clinical specificity.[38]

As previously noted, analytical sensitivity is the minimum amount of target in a sample that can be accurately measured by a given test – also called the limit of detection, while clinical sensitivity describes a given test's ability to accurately confirm that a sick patient is ill with a particular disease. Regarding specificity, analytical specificity is the ability of a test to detect the particular target for which it was designed, and clinical specificity describes a given test's ability to accurately confirm that a healthy patient does not have a particular disease.

Because it is not always possible to evaluate a given diagnostic technology against a "gold standard" test, sometimes positive percent agreement (PPA) and negative percent agreement (NPA) are reported instead of

[37]Some of these characteristics may be classified as device or operational characteristics, but for simplicity we refer to them as performance characteristics.

[38]Analytical sensitivity and analytical specificity are important. However, clinical measures are more direct measures of an MPOCT's ability to correctly identify positive samples.

sensitivity and specificity in product inserts.[39] These characteristics describe the percentage of time two different diagnostic technologies agree on whether a sample does or does not contain a pathogen.[40] PPA and NPA can be used when a new diagnostic technology is being evaluated against an existing diagnostic technology. If the existing diagnostic technology is not a "gold standard," then there is increased risk that both technologies might agree on a result but that the result is incorrect – for example, both testing positive for a pathogen when the pathogen was absent. Because of this limitation, PPA and NPA are used in lieu of sensitivity and specificity to indicate that what is being reported is agreement between the devices and not necessarily to a clinically-accepted disease status.

In seeking approval from FDA to market an MPOCT, developers provide a document called a product or package insert, which describes performance characteristics of the MPOCT, including results from clinical studies. For example, these inserts must include, as appropriate, information on such characteristics as sensitivity and specificity.[41] Developers use these inserts to show how the technology performed in analytical and clinical studies, as well as how to properly use the technology. The inserts can contain different information based on a specific MPOCT and the test that runs on it.

To illustrate performance characteristics for a common disease, we examined the reported clinical sensitivity and specificity for influenza A from 6 different MPOCTs.[42] Our analysis shows that performance characteristics varied to some degree among MPOCTs.[43] Most of the reported sensitivities and specificities for the tests, or PPAs and NPAs, were greater than 90 percent. For example, one MPOCT that can test for 20 pathogens reported 94.9 percent sensitivity (with a 95 percent confidence interval of 91.5 percent to 97.2 percent) and 98 percent specificity (with a 95 percent confidence interval of 97.3 percent to 98.6 percent) for influenza A. Another MPOCT that can test for two diseases reported 100 percent sensitivity (with a 95 percent confidence interval of 97.4 percent to 100 percent) and a specificity of 98.5 percent (with a confidence interval of 97.0 percent to 99.3 percent) for influenza A.

False positive and false negative rates of MPOCTs are determined by sensitivity and specificity, and have implications for clinical decision-making.[44] For example, if a false positive result is given for a bacterial infection, then antibiotics may be unnecessarily prescribed to treat it. An MPOCT that has high rates of false positives may lead to overuse of antibiotics; alternatively, loss of confidence in an MPOCT may lead to the technology being ignored or not used altogether.

[39]A "gold standard" or reference standard is "considered to be the best available method for establishing the presence or absence of the target condition," according to FDA guidance.

[40]A test could detect a component, or target, of the pathogen, such as the nucleic acid, in the absence of the entire pathogen. However, for the purposes of this report, we assume that the target's presence indicates that the pathogen is present.

[41]21 C.F.R. 809.10(b)(12).

[42]Tests provided information in different ways, thus some of the sensitivities and specificities presented in this report may be PPA and NPA.

[43]FDA officials told us variance in performance characteristics may depend on disease variance and prevalence, among other things.

[44]A false positive is the proportion of patients who tested positive but do not have the tested disease. A false negative is the proportion of patients who tested negative but have the tested disease.

In examining, the performance characteristics of different MPOCTs, we determined that making comparisons is challenging for four reasons:

- Information sources are not always available. We were not always able to obtain product inserts from the developer's website, for example. Additionally, when we requested product inserts directly from the developer, they were not always provided.[45]
- Provided information may not be directly comparable. Developers can report either clinical sensitivities and specificities, or positive and negative percent agreements. The percent agreements are used when "gold standards" are not used for demonstrating the performance characteristics of an MPOCT. Some product inserts specify sensitivities and specificities; others use positive and negative percent agreement; yet another commingles these characteristics based on the particular pathogens being detected.
- Supporting information is limited. Even when information sources are available, limited information may preclude a complete understanding of the methods used to obtain performance characteristics. For example, one product insert we reviewed does not specify a comparator test by name,[46] stating that the MPOCT assay was compared against an "FDA-cleared assay." Further, comparisons against a named comparator test require familiarity with the performance of the comparator test in order to have a basis for judgment.
- Some product inserts report large ranges for the 95 percent confidence intervals. For example, one MPOCT reported sensitivity for influenza A of 90 percent, with a 95 percent confidence interval of 55.5 percent to 99.8 percent. Large confidence interval ranges can increase uncertainty in determining the true performance of a given MPOCT. A large confidence interval can result from calculating measures based on a small number of cases. In this case, while this MPOCT used 853 samples to test for influenza A, only 10 samples could be used to establish sensitivity, and 843 samples to establish specificity. The developer of this MPOCT acknowledged the small number of positive samples and supplemented its prospective samples with retrospective samples to obtain FDA clearance. The number of clinical samples used to determine individual performance characteristics across the different MPOCTS varied from a few hundred to over 1,800.[47]

According to FDA guidance, in addition to sensitivity and specificity, FDA may use other

[45]Some information could be obtained from examining the FDA approval documents, which requires familiarity with the FDA website and document formats.

[46]The performance of a comparator test is used as a standard against which the new test is being compared.

[47]We examined data on prospective samples, which are collected from patients that exhibited symptoms of a pathogen of interest at the clinical testing site during a specified date range that meet inclusion criteria for the clinical study, according to FDA officials. Such samples have an unknown positive or negative status for a pathogen prior to testing, and may be collected fresh or archived, but would be tested separately. Retrospective samples have the same composition as prospective samples, but the positive or negative status for a pathogen has been confirmed by a different type of testing. Retrospective samples are only used when developers were unable to collect a sufficient number of prospective samples.

performance characteristics in its evaluation, including:[48]

- Sample types, such as tissue samples or bodily fluids, which the MPOCT tests for the presence of pathogens. Appropriate sample types depend on a variety of factors, including the site of infection and the pathogen target. For example, a sample should be collected from the appropriate anatomical site or source at the appropriate time in the clinical progression of disease. Handling needs for the samples, such as transport, storage time, and temperature are also important.
- Nucleic acid extraction efficiency, which depends on the method used to extract nucleic acids from the sample and affects the amount of nucleic acid remaining in the sample. The extraction efficiency affects the amount of target available for the test.
- Analytical reactivity, which specifies if the test accounts for potential genetic variation in a target in the test. For example, different strains of influenza A can circulate each year, so demonstrating that a test can (or cannot) detect them may affect the usefulness of the test.
- Cross-reactivity, which specifies if the test has reactivity in the absence of the correct target and is one component of analytical specificity. There is the possibility of cross-reactivity between two targets in the same test, such as inability to differentiate between strains or variants of influenza A, or a false positive test for influenza A when the positive should have been for influenza B.[49] There is also a possibility of cross-reactivity with targets that are not part of the test. For example, when testing for the Zika virus alone, a false positive result is possible when a patient has been previously infected by a closely related virus such as dengue, yellow fever or West Nile, making it difficult to interpret results.[50]
- Precision, which evaluates the repeatability or reproducibility of the test across different variables, such as pathogen targets across a range of analyte concentrations spanning the detection range of the test, and among testing sites, such as different laboratories.

FDA requirements and guidance do not require that a particular MPOCT report all performance characteristics during the clearance or review process. FDA uses information from a clinical study to gauge how the MPOCT would operate if it were cleared or approved. FDA officials told us they have rejected MPOCTs for poor performance and poor results from clinical studies, such as low sensitivity or specificity. However, officials added they may also provide approval or clearance with limitations when

[48]Department of Health and Human Services, Food and Drug Administration, *Highly Multiplexed Microbiological/Medical Countermeasure* In Vitro *Nucleic Acid Based Diagnostic Devices: Guidance for Industry and Food and Drug Administration Staff* (Rockville, MD: August 27, 2014).

[49]Cross-reactivity with the wrong strain of influenza A could prevent proper treatment and identification of an avian or novel strain that may have pandemic potential compared to seasonal influenza A. However, cross-reactivity between seasonal influenza A and B may be less important clinically, because treatment of seasonal influenza A and B can be the same.

[50]These viruses are found in some of the same geographic areas and can have similar symptoms. This particular example is more of a problem for antibody, or serological, tests but not molecular, or PCR, tests. GAO, *Emerging Infectious Diseases: Actions Needed to Address the Challenges of Responding to Zika Virus Disease Outbreaks*, GAO-17-445 (Washington, D.C.: May 23, 2017).

there are specific performance issues. For example, even if an MPOCT exhibited high cross-reactivity during clinical studies, FDA officials told us that while they would be concerned, the MPOCT may be cleared or approved with certain limitations placed on it for use.

According to FDA officials, they evaluate performance characteristics on a case-by-case basis because, among other things, the intended use of MPOCTs influences the importance of certain performance characteristics over others. For example, screening tests need higher clinical sensitivity (low false negative rates) in order to identify as many patients as possible who have a disease, at the cost of including some of those without the disease (false positives). In this case, a follow-up test with higher clinical specificity can rule out those who truly do not have the disease. FDA officials also told us MPOCTs may be cleared with certain pathogens masked if acceptable performance has not been demonstrated (that is, the device may be cleared, but not for all the pathogens the developer requested), and often subsequent studies are done to add new pathogens to an existing panel or improve performance against a specific pathogen.

2.2 Developers also consider additional performance characteristics for designing and marketing MPOCTs

In addition to the characteristics considered by FDA in evaluating MPOCTs, key performance characteristics that developers consider in designing and marketing their MPOCTs to users are panel size, time to test result, throughput, and usability.

2.2.1 Panel size

The panel size, or number of pathogen targets that can be tested in one run is an essential performance characteristic. During our review of product inserts for performance characteristics in disease panels that contained influenza A, those panels ranged in size from 2 to 20 pathogens per test. According to experts at our two-day meeting and others we interviewed, more targets can be better in MPOCT panels for two reasons: (1) more targets on one pathogen could increase the sensitivity or specificity for detecting that pathogen and (2) targets against multiple pathogens on a panel could increase the range of possibly correct diagnoses. One developer at our meeting told us that, in theory, panels could be designed with an arbitrarily large number of diseases, because the science underlying the MPOCT is well-developed with respect to adding new pathogens.

A developer and users also told us that larger panels offer the opportunity to catch diseases that a user may not consider. Furthermore, a developer and users at our meeting consider opportunities to provide information on specific characteristics of pathogens, such as resistance against a specific antibiotic, which might improve patient outcomes by identifying the need for different antibiotics.

A developer at our meeting also identified the ability to detect coinfections—situations where a patient may be infected with more than one type of pathogen—because a positive result in a singleplex test might

dissuade a user from exploring the possibility of coinfection.[51] In contrast, another developer told us they have generally limited their MPOCT panels to targets that produce similar or related symptoms, because users preferred to limit targets to diseases more likely to be present in the patient, given factors such as the season and ability to treat (that is, not all pathogens have a treatment path).[52]

2.2.2 Time to test result

Developers design MPOCTs to provide users with test results quickly. Developers at the meeting told us they designed their MPOCTs to take about an hour or less, which is fast compared to conventional testing, such as cell culture. According to product inserts we reviewed, the time to test result ranged from 20 minutes to over 2 hours. However, we also determined that what constitutes the "time to test result" differed, based on the specific test setting. For example, when a sample is sent to a laboratory in an inpatient setting, the test result may not be seen by the physician for hours, even though the testing was conducted in the same hospital and the result is ready in a short amount of time, according to users at our meeting.[53] In an outpatient setting, patients may not want to wait for a result; therefore, getting results quickly may increase in importance. For example, for sexually transmitted infections, patients may be lost to follow-up for a variety of reasons including reluctance to return to the clinic for their results. This in turn may lead to untreated infections, resulting in the potential for sexually transmitted infections to spread. According to users and a developer at our meeting, shorter times, in the range of 15-30 minutes, were preferred in a small office or commercial setting, such as a pharmacy, in order to prevent a backlog of patients taking up space.

2.2.3 Throughput

Throughput is the number of patient samples that can be run simultaneously in an MPOCT. Developers told us that MPOCTs can be designed with low throughput, usually one sample at a time, for some settings such as doctor's offices, but that their MPOCTs can also be used by hospital laboratories. A few developers we talked with designed their MPOCTs to run tens to almost 100 samples at a time, but other developers stated that because high throughput was possible with automated systems, it was unnecessary to design their MPOCTs to run that many samples (figure 2). A user at our meeting was concerned about technologies that could only run one, or a few samples, at a time. For example, for a small clinic, if there is low throughput on a technology, such as one sample at a time, then the patients waiting for a test result on the same MPOCT could be taking up space in waiting or examination rooms, which could be used to see other patients. In order to increase throughput, more MPOCTs would be needed, which may lead to inefficient use of space within a laboratory.[54]

[51] In contrast to multiplex tests, singleplex tests detect one disease pathogen at a time.

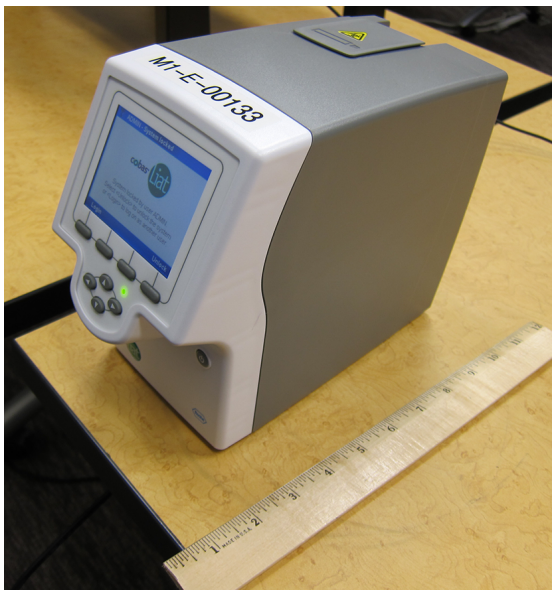
[52] According to FDA officials, a panel with more pathogens increases the likelihood of a false positive result as certain pathogens become less and less likely. In other words, the PPV for a pathogen goes down as prevalence decreases.

[53] According to CMS officials, test results may be prioritized for those patients that need treatment urgently in an inpatient setting, so not all delays are due to the availability of the test result.

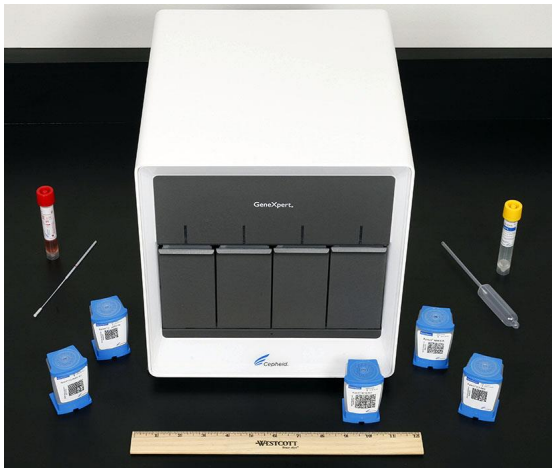
[54] One developer from the meeting told us that the goal of the development process for many POC tests is to generate a result within the typical contact time with the patient, and there is

Figure 2: MPOCTs differ in throughput and sizes

MPOCT showing small, 1-sample equipment (approximately 4 inches across).



MPOCT showing larger, 4-sample equipment (approximately 12 inches across).



Source: GAO and Cepheid| GAO-17-347.

2.2.4 Usability

Developers design MPOCTs with different usability characteristics. For example, developers designed some MPOCTs for ease of use. Developers and users said the way the technology provides a diagnostic result is important because a "yes or no" result would be much easier to understand, compared to other relative indications of disease. For example, interpreting displayed data curves and concluding whether a sample was positive for the pathogen can be challenging.

Developers also design some MPOCTs to be all-inclusive technologies that need no peripheral devices such as external computers. A user at our meeting considers compatibility with existing equipment when weighing whether to use an MPOCT, because additional equipment can incur further cost and space needs.

often strong emphasis on producing a result in 10 minutes or less. If this can be done for a test which is run patient-side, then throughput as a concept could become a non-issue for true POC tests.

3 MPOCT procurement and operation costs vary and are based on several factors

3.1 Procurement and operation costs charged by the eight developers vary

Two major types of user MPOCT costs are procurement and operational.[55] For the purposes of this report, we define procurement as the costs to buy the technology itself, and operational as the costs to run a single test, typically using consumables or cartridges. Procurement costs and operational costs are generally set by the developer and incurred by the user.[56]

Of the eight developers we interviewed, six have MPOCTs available on the market. These developers sell their MPOCTs at prices ranging from $25,000 to $530,000, with operational costs ranging from $20 to $200 per multiplex test. The remaining two developers do not have MPOCTs available yet on the market. They project setting procurement costs ranging from $1,000 to $5,000 per MPOCT and operational costs ranging from $5 to $50 per multiplex test. Table 2 displays the procurement and operation list costs and service contract prices across the eight developers. In addition, most developers we spoke to offer, or intend to offer, service contracts for maintenance and support of their device; users also generally incur these costs if they opt for the service contract.

[55]Other costs associated with MPOCT include disposal of associated medical waste, maintenance, personnel, and space; however, we did not examine these costs in our review.

[56]In some instances, developers provided list prices, which may deviate from actual procurement costs, as noted in Table 2 below.

Table 2: Variation in MPOCT costs across the eight developers in GAO's review

	Cost to Users[a]		
Developer	**Procurement**	**Operation (consumables)[b]**	**Service contract**
MPOCTs on the market[c]			
1	$26,000–$530,000	In bulk: $20–$75 per test cartridge	$5,000–$60,000 per year depending on instrument type, contract term, and service options the laboratory requires
2	$40,000	$50 per test (sold in batches of 24 test kits)	$7,500 per year per unit
3	• $40,000 for one-sample unit • $15,000 for basic expandable unit, plus $70,000 per every 2 expansion modules. Each module increases the throughput by a sample.	$100–$200	No
4	$25,000–$30,000	$35–$150	$1,800–$8,725 per year
5	$25,000	$60–$75	$5,500 per year
6	$40,000–$190,000	N/A[d]	$3,200–$22,800 per year
MPOCTs not yet on the market [c,e]			
7	$2,500	$25 per single-sample cartridge that can contain (up to 50 multiplexed tests)	No
8	$1,000–$5,000	$5–$50	Will offer a service contract but price has not been determined

Source: GAO analysis of developer-provided data. | GAO-17-347

[a]Average costs actually paid by users may be substantially different than reported list prices.

[b]Costs of controls needed to run the tests may not be included.

[c]All technologies listed in this table are molecular.

[d]This developer did not develop its own consumables.

[e]Costs for two developers that did not have MPOCTs on the market are projected.

Developers identified additional MPOCT costs incurred by users including training, technology maintenance, infrastructure costs—such as space, personnel, and accessory costs (materials not included in the consumable, such as swabs)—and disposal costs.[57] One developer noted that some MPOCTs create a lot of waste material, such as packaging waste, that must be disposed.[58] MPOCT costs could also vary based on discounts offered by the developer or the type of institution purchasing the tests. For example, one developer said that large-volume laboratories could potentially negotiate a volume discount when purchasing technologies or consumables.

3.2 Numerous factors affect MPOCT procurement and operation costs

Developers said that a number of factors contribute to the procurement and operation costs they charge users, such as the intended use of the technology, ease of use, and turnaround time. For example, in terms of ease of use, an MPOCT that requires minimal operator involvement may be more expensive to develop than one that requires more operator involvement. Additionally, some developers told us that test complexity—which increases in MPOCTs detecting more targets or offering increased throughput—can affect cost. For example, a technology with a list price of $500,000 may be able to detect more targets and have high throughput, compared to a technology with a list price of $1,000 that is able to identify fewer targets and can only process one sample at a time.[59] Developers also told us that other factors affecting cost include market potential and demand for the technology, and other competitors on the market.

Different business strategies used by developers can also affect costs. For example, a few developers said their business strategy for developing MPOCT is to develop the platform, or basic instrumentation, for the MPOCT and then partner with other companies to develop the assay for the test panels. This strategy removes some of the regulatory burden and cost from the platform vendors. While a platform vendor needs to get regulatory approval or clearance for the instrument for use with a panel, the partnered company developing a particular multiplex assay must obtain regulatory approval or clearance for the panel itself. Another developer likened its business model to a "printer ink" model whereby the developer sells the technology inexpensively but profits off the operational cost they charge—that is, the cost of the consumable used during a test—while using very low-cost materials (such as mass manufactured plastic components) to keep their manufacturing costs low.

Developers consider different factors in deciding whether to offer service contracts and what to charge if they do offer such contracts. One developer said that its service contract prices depend on the technology type, contract term, and level of service option required by the laboratory. However, another developer said that their low-cost

[57]Some of these costs, such as technology maintenance, may be covered under service contracts.

[58]Certain medical wastes must be disposed as hazardous materials, which require special containers, handling, and disposal procedures.

[59]Multiple low-throughput MPOCTs can be deployed simultaneously to increase overall throughput.

technologies would not require a service contract, adding that such a contract would require a more complex and costly infrastructure for service personnel and travel.

According to some developers, constraints on MPOCT costs are important considerations when deciding whether to develop a technology. For example, a developer at our meeting told us the payment rate paid to users, by private insurance or Medicare, for the cost of a test is an important consideration. This developer said that payments are limited by the constraints on potential users as well as the willingness of potential users to adopt a technology. Another developer at our meeting added that investors in these technologies want to know their return on their investment, which is tied to how clinicians using the test get paid, which in turn is tied to payment. Finally, a developer at our meeting said that revenue from service contract payments is a way to recover research and development costs, but there is customer resistance to such contracts.

4 Technical challenges in developing and validating multiplex assays can delay MPOCT implementation

MPOCT developers identified three challenges associated with the development and validation of multiplex assays that could hinder MPOCT development and raise development costs:

1. Lack of resources needed for developing tests.
2. Sample processing and panel modification.
3. Overcoming multiplex panel limitations.[60]

4.1 The lack of resources needed to develop multiplex assays

MPOCT developers identified uneven access to samples and lack of reliable genetic databases as challenges that can increase assay development costs and delay development. Additionally, MPOCT developers identified biocontainment resource requirements as a challenge that could slow assay development for select agents.

First, lack of sample access leads to delays and increased costs in developing assays and may hinder rapid responses to emerging infectious diseases. Samples can be used to help determine the performance of the MPOCT.[61] Access to samples is uneven, with some developers having little difficulty obtaining samples, while other developers told us they struggle to get samples. Samples can be procured though repositories, such as those run by CDC, or purchased from commercial vendors, with reported prices ranging from $50 to $1,000 per sample.[62] Obtaining samples for emerging or select agent diseases is difficult, according to developers, due in part to their rarity. Some developers told us they had to wait to get samples, use non-human animal samples in lieu of human patient samples, or use spiked samples.[63] One developer added that compliance with licensures and certifications for handling biohazardous materials—including some types of samples—is time consuming and costly.

[60]Some of these issues and challenges can also affect singleplex assays, but they were identified in the context of multiplex technologies.

[61]Some developers told us that for some diseases, FDA requires prospective samples. Retrospective samples could be used for rarer disease. Thus, for some diseases, a developer may have to wait for people to get sick before being able to test their assay. Additionally, a developer told us it is rare to obtain samples with simultaneous multiple pathogens. FDA officials told us there are various strategies developers can use to ensure sufficient numbers of samples for FDA review submission.

[62]One way of obtaining samples from CDC is through a principal investigator contact. CDC does not list these principal investigators, but told us that principal investigator names can be obtained through the CDC Technology Transfer Office. CDC also told us that each principal investigator has specific criteria for evaluating sample requests. According to CDC officials, these criteria include ethical reasons or the actual availability of samples.

[63]Spiked samples do not have a pathogen; a controlled amount of pathogen is subsequently added to emulate a diseased sample. One developer told us it took almost 4 years to collect sufficient samples for testing.

Obtaining samples internationally has additional challenges –dealing with countries' reluctance to ship samples and more limited utility from data from foreign samples, among others. One developer told us that for Zika, U.S. samples were scarce because of the small size of the outbreak and international samples were often not acquired in a manner necessary for molecular testing.[64] Developers added that they faced challenges gaining access to Zika samples, such as from Puerto Rico, in part resulting in an uneven distribution of samples. Scientists in the field have also reported that limited availability of clinical samples is perhaps the greatest impediment to test development.[65]

Developers at our meeting told us of a lack of reliable genomic databases for designing diagnostic assays. For assays that require information about the genome of pathogens, such as PCR, the lack of reliable databases can hinder assay design. The databases help in the design of probes—short fragments of genetic material that help identify the presence of the target—and ensure their suitability. One developer at our meeting told us that genomic databases are not updated quickly enough to address recent disease outbreaks, such as Ebola and Zika.[66] Further, another developer at our meeting told us of problems with existing databases, such as errors that cause delays resulting from having to recheck the data.[67]

Genomic databases support MPOCT development

Genomic databases are repositories for biological sequence information, including nucleic acid (such as DNA, or deoxyribonucleic acid) sequences for genes and entire genomes of microbes and other organisms. One such database is called Genbank, a National Institutes of Health genetic sequence database, which describes itself as containing an annotated collection of all publicly available DNA sequences. The National Institute of Allergy and Infectious Diseases also supports the Bioinformatics Resource Centers, which stores and provides a variety of research data on pathogens, which can be accessed via different publicly-available sequence databases. Databases can be used, among other things, to help design pathogen detection DNA components, called primers, needed for the polymerase chain reaction (PCR) that certain MPOCTs use. Public domain software tools such as Primer BLAST can check the primers against these databases to check for specificity – to help make sure the primers will not result in a false positive – and can also check that the primers will not result in a false negative result.

Source: GAO analysis based on literature | GAO-17-347

Second, developers told us of additional resource challenges with developing and testing assays for select agents. For such work, they would require special biocontainment facilities to handle such

[64]Molecular testing relies on detecting nucleic acids within a sample.

[65]Caliendo and others, "Better Tests."

[66]For example, this developer told us that parts of the Ebola genome originating from Spring 2014 were not released until mid-November, 2014.

[67]A developer from our meeting used GenBank, a public genomic database, as an example. One study, among others, of errors in Genbank can be found in Samier Merchant, Derrick E. Wood, and Steven L. Salzberg, "Unexpected cross-species contamination in genome sequencing projects." *PeerJ* Nov. 20, 2014. A regulatory expert from our meeting noted that the FDA is establishing a publicly available database called FDA-ARGOS (dAtabase for Reference Grade micrObial Sequences), which may help address this issue.

agents. One developer told us that biothreat agent detection has only one customer—the U.S. government—putting any such program subject to availability of the program's funding, which would make it a high-risk prospect if the developers invest in biocontainment facilities. This developer told us that select agent work often moves more slowly because of biosafety requirements. Test development under such circumstances takes time, they said, and will not be sufficient for fast responses. As a result, developers may be reluctant to invest in such efforts, leading to slower progress in MPOCT development for select agent applications.

4.2 Technical challenges with sample processing and panel modification can hinder development

Two types of technical challenges can hinder assay development: (1) challenges associated with collecting and processing samples, and (2) challenges associated with modifying panels.

Developers identified two technical challenges for developing assays associated with collecting and preparing samples.[68] First, preventing contamination while collecting and handling patient samples is a challenge. Contamination may lead to false positive results by incorrectly identifying the presence of some pathogen that was introduced into an otherwise uninfected sample. Second, engineering the purification and extraction step is challenging because of variability in the physical properties of the samples and pathogens being processed. For example, certain non-liquid tissue samples may need to be liquefied, necessitating an extra step before the assay. If the pathogen being processed is known to generate spores, such as *Bacillus anthracis*, more extensive lysis may be required.[69]

Developers must determine whether modifying an existing panel—for example, to include new diseases or to update existing diseases, such as new influenza strains—is worth the effort. Developers told us that when an FDA-approved or FDA-cleared panel is modified by changing an existing target or adding a new target, the panel is considered a new test and must go through the FDA review process again before it can be marketed, with new labeling, documentation and training associated with the test. While not all steps for the review need to be repeated, developers told us they have to consider possible new interactions based on the test modification. A developer told us that as the size of the panel increases, the complexity of assessing such interactions increases as well.[70] Another developer told us that such interactions in a multiplex panel cannot be analytically predicted to determine how such interactions may affect the sensitivity and specificity of the panel; experimentation with clinical samples is necessary, which takes time and resources. Another developer told us that

[68]The sample collection and preparation process includes acquiring a sample of a patient's tissue, loading the sample into the device, and isolating or extracting the components for the assay to detect.

[69]Lysis is the process of removing the cell membrane or cell wall so that the interior components of the cell can be manipulated with chemical reactions.

[70]For example, adding an additional disease target to an existing 3-disease panel may involve examining up to 3 new direct interactions, whereas adding an additional disease target to an existing 20-disease panel may involve examining up to 20 new direct interactions. FDA officials told us the risk of modifying a panel is generally lower than that associated with creation of an analogous panel.

similar challenges apply to changes in the type of sample—such as using blood instead of saliva for the test.[71] One developer told us that it resists modifications to cleared test panels to avoid having to restart testing and validation.[72] This challenge may be a barrier to strategies that involve developing MPOCTs for marketable application, then modifying the technologies to include select agent or emerging infectious disease targets.

4.3 Developers face technical challenges to overcome multiplex panel limitations

Developers identified two challenges that limit the capabilities of multiplex panels: (1) overcoming practical limits to the number of targets that can be detected within a small sample volume, and (2) identifying targets used for detecting pathogens. Developers told us of a practical limit to the number of targets that can be uniquely detected in a single-reaction volume. For example, they told us that for certain types of technologies, a maximum of six to eight fluorescent colors can be reliably distinguished, representing an upper limit for the number of targets for each assay. Technical workarounds exist, such as by using small chambers, each containing its own reaction, or by customizing dyes that can be read with special equipment that can bypass this maximum. However, implementing these strategies has challenges. For example, segregating the sample into small chambers reduces the effective sample volume; developers using this approach may use up to three separate chambers to detect a single target. The use of customized dyes requires special instrumentation to differentiate between the colors—which can require trained personnel to operate.

Another challenge in developing multiplex assays is identifying genetic targets that can be used for detecting the pathogen. One developer at our meeting told us that, for example, viruses have much smaller genomes compared to bacteria. As a result, if a multiplex panel is being designed to detect viral genomes, developers are more constrained in the number of available targets they can generate compared with pathogens with larger genomes. Additionally, the ability to select targets to address cross-reactivity is constrained. Another developer told us that it uses multiple targets for a given pathogen—in essence providing multiple opportunities to detect the same pathogen, which may increase test sensitivity. However, having limited available targets means that this strategy cannot be readily implemented, limiting the potential performance of such assays. One developer added that for select agents, the targets may be classified which poses additional challenges for developers.

[71]This developer estimated $500,000 for testing costs incurred for a new type of sample. FDA officials stated that changing the sample type is a fundamental change, rather than a challenge, for most assays.

[72]Creating a new test for which no existing test can be used as a comparison can be very expensive because such tests may need to go through a more intensive FDA approval review—Premarket Authorization (PMA)—according to a developer. An article states that the PMA approval process is 10-fold more expensive than the 510(k) pathway. The latter allows developers to compare their test to an existing legally marketed test that is not subject to premarket approval.

5 MPOCTs have potential benefits for patient care, but face implementation challenges

The ability of MPOCT to provide fast results, simultaneously detect more than one pathogen, and offer ease-of-use features, has the potential to improve patient outcomes across different care settings. However, we found conflicting views among developers and users—including laboratory users of the tests and physicians who use the test results to make decisions—on the extent to which these MPOCT abilities improve patient outcomes. Further, we identified three challenges associated with MPOCTs that could affect their widespread adoption. Additionally, developers told us that they face challenges with the FDA review process, as well as FDA's process for obtaining CLIA waivers, while users told us they are concerned about the implications of using CLIA-waived technologies.

5.1 Potential benefits of MPOCTs can improve patient outcomes across different care settings, but opinions differ on the extent of such benefits

We identified several potential benefits associated with MPOCTs, including:

- Improving health care management for the patient;
- optimizing antibiotic usage;
- limiting the spread of disease, including via surveillance of select agents;
- decreasing health costs; and
- increasing access to testing in remote or low-resource settings.[73]

5.1.1 MPOCTs can improve health care management for the patient

Developers, users, and regulatory experts we spoke to said that the ability of this technology to provide rapid results can potentially lead to better management of patient care. For example, some users explained that when test samples have to be sent out of their point of care for testing, patient care management can become challenging. One reason for this challenge is that it takes additional time and resources to track down patients if they leave the point of care before the test results are available. A physician who can obtain results quickly while the patient is present can begin targeted treatment immediately, which could help prevent losing some patients to follow-up.[74] A scientific article reinforces this by stating that MPOCT's ability to provide fast results can help increase the likelihood of patient follow-up, such as for repeat care, which in

[73]Some users we spoke to said that the potential benefits of multiplex testing are separate from those of POC testing. For example, one user said that some potential benefits of multiplex testing, such as faster time to diagnosis, are already being seen in a non-POC setting, such as in hospitalized settings. Further, the configurations and performance characteristics of the MPOCTs we reviewed are not generalizable to all MPOCTs.

[74]Follow-up occurs when actions are taken after a positive or ambiguous test result to ensure appropriate test evaluation occurs, such as when a patient and health care provider arrange to make contact in the future to re-assess the patient's condition.

turn can improve the level of care provided.[75] Users added that some diseases take 3 to 4 days to diagnose, but if a test can provide results within 3 to 6 hours, then there can be benefits to the patient by starting treatment earlier.

Physicians we spoke to said that MPOCTs can quickly provide information about a patient's condition, which they can use to make actionable clinical decisions. For example, results from this technology can, depending on whether the infection is viral or bacterial, inform treatment decisions that would entail patient hospitalization or discharge from the hospital. One physician added that obtaining timely results that allow him to take action on clinical decisions regarding a patient, is a key factor in his decision on whether to adopt MPOCTs. The ability to obtain results quickly can also help educate and reassure patients about their condition. According to an article, MPOCT testing has been shown to reduce the physician's decision-making time for patient management.[76]

Additionally, some users said that MPOCTs can facilitate clinical decision-making because one test may provide much more information, compared to "serial" or "sequential" testing after a negative result.[77] According to users, MPOCT is good for syndromic diseases where the patient is presenting with a set of symptoms common to different illnesses. Similarly, one developer who described their MPOCT approach as "syndromic-based," said that for diseases like Zika, it makes sense to use a multiplex test that includes dengue and chikungunya, given the similarity of their symptoms. Moreover, some users we spoke to said that the ability to test for more than one disease can be valuable in immediate care settings, such as emergency rooms, where rapid turnaround time is needed for clinical decision-making.

5.1.2 MPOCTs can improve antibiotic stewardship

Some developers and users said that faster time to diagnosis could also improve antibiotic stewardship. Users we spoke to said that MPOCT can avoid unnecessary antibiotic use because a physician can show patients a result indicating a viral rather than bacterial infection, tell them they do not need antibiotics, and provide an expectation for their recovery. Users also agreed that MPOCTs can target treatment and noted that such results could help decrease antibiotic resistance by limiting the use of antibiotics. When used appropriately, use of antibiotics can improve health outcomes, and therefore reduce health care costs.

According to one article, antimicrobial stewardship—the optimization of antimicrobial use in clinical settings—is enhanced by test panels that are able to detect antimicrobial resistance genes.[78] As stated previously, MPOCT panels that can provide information on antibiotic-resistant strains of bacteria may help identify the need

[75]Samantha Spindel and Kim E. Sapsford, "Evaluation of Optical Detection Platforms for Multiplexed Detection of Proteins and the Need for Point-of-Care Biosensors for Clinical Use" *Sensors*, Vol. 14 (2014).

[76]Spindel and others, "Optical Multiplexed Detection of Proteins" *Sensors*, Vol. 14 (2014)

[77]Serial or sequential testing is performed when the results of one test are used to help decide subsequent tests to run. MPOCT may still require serial testing—for example, to confirm a given negative detection—but can reduce the number of serial tests.

[78]Caliendo and others, "Better Tests."

for different antibiotics. Additionally, according to one article:

> "Prompt initiation of appropriate antimicrobial therapy has led to dramatic reductions in infection-associated morbidity and mortality; however, antibiotic overuse may cause considerable harm as a result of unintended drug toxicity, and the development of resistance."[79]

Studies have also reported that the majority of patients in outpatient settings who present with upper respiratory infections receive antibiotics even though their illnesses are likely caused by viruses.[80] Using antibiotics in such situations may be partly a result of the inability to identify bacterial or viral pathogens quickly.[81]

5.1.3 MPOCTs can help limit the spread of disease

Developers, users, and regulatory experts also noted that a faster time to diagnosis can help prevent the spread of disease, such as by facilitating outbreak containment. For example, utilization of MPOCTs could avoid sending a contagious person back into the community or could lead to changes in behavior if patients know they have a communicable illness, such as a sexually transmitted infection. One user at our meeting noted that MPOCTs can provide practitioners with a better understanding of disease persistence and circulation in the community.[82]

For human infectious diseases, some users we spoke to said there is a desire in public health to minimize disease outbreaks, and the development of MPOCTs could further the understanding of disease prevalence in the community and minimize outbreaks by providing rapid results. For example, according to an article, MPOCTs are becoming increasingly important in response to outbreaks of respiratory tract infections that may have potential to become epidemic.[83] Another article stated that MPOCT value was demonstrated during the Ebola outbreak in 2014 by ensuring timely patient test results in such infectious disease outbreaks.[84] According to a developer from our meeting, MPOCTs can help prevent outbreaks that could have adverse economic impacts on a country. Further, this developer stated that in addition to enabling diagnosis, MPOCTs can support critical care for sick patients held in isolation. Physicians we spoke to said that MPOCT results could inform infection control precautions, such as isolation and public safety measures.

MPOCTs could also help with the surveillance of select agents. A DHS official said that since many such infections start out similar to influenza, multiplex screening can test for many agents at once, including select agents

[79]Caliendo and others, "Better Tests."

[80]Caliendo and others, "Better Tests."

[81]Caliendo and others, "Better Tests."

[82]A user from our expert meeting also noted that information about disease circulation in the community can also be extremely beneficial to pharmaceutical companies. Understanding disease prevalence will encourage them to invest in the development of new drugs in response to market needs.

[83]Alimuddin Zumla and others, "Rapid point of care diagnostic tests for viral and bacterial respiratory tract infections—needs, advances, and future prospects" *The Lancet Infectious Diseases*, Vol. 14 (2014)

[84]Gerald Kost and others, "The Ebola Spatial Care Path™: Accelerating point-of-care diagnosis, decision making, and community resilience in outbreaks" *American Journal of Disaster Medicine*, Vol. 10 (2015).

such as *Bacillus anthracis*.[85] This official added that the ability to rapidly screen for multiple agents is important because a patient who has anthrax disease needs treatment as soon as possible. Some users agreed that in a bio-attack scenario there may be benefit to testing for many possibilities, such as select agents. However, other users we spoke to cited concerns with the screening of select agents. For example, they told us false positives, which may be more prevalent when PPVs are low, could cause a public health emergency for no reason.

5.1.4 MPOCTs can help decrease health care costs

MPOCTs can lead to health care cost savings. Some users commented that treatment without a definitive diagnosis can cost more because such treatment might be contrary to what should be done, such as providing potentially costly, but ineffective, antibiotics for a viral infection. Moreover, one regulatory expert stated that patients lost to follow-up may incur significant costs. Such patients may not seek care until very sick or complications develop, which can increase health care costs. Similarly, some users told us that in situations in which multiple pathogens can cause the same observed or reported symptoms, such as influenza virus and respiratory syncytial virus, combining tests into a multiplex panel can save time and make the laboratory running the tests more efficient.[86]

The scientific literature also reported on MPOCT's potential to provide cost savings, but stated that more studies are needed to assess the overall cost-effectiveness of MPOCTs. Cost savings, to both patients and insurers, may be achieved by preventing unnecessary treatments, secondary visits to the doctor, or long hospital stays. For example, community-acquired pneumonia (CAP) accounts for enormous health care costs, at an estimated $17 billion annually in the United States.[87] Rapid identification of the pathogens that cause CAP can facilitate timely, effective use of therapeutics, reduce costs, and ultimately shorten hospital stays.[88] Additionally, a study reported on the cost-effectiveness of an MPOCT, relative to conventional testing strategies, in the detection of influenza among pediatric patients in an emergency department. The authors found that incorporating MPOCTs was the most effective strategy for pediatric patients, in terms of quality-adjusted life years, but it was also the most expensive.[89]

5.1.5 MPOCTs can increase access to care in remote or low-resource areas

Developers, users, and regulatory experts we spoke to identified various MPOCT features that contribute to its ease of use, which may help make MPOCTs suitable for a wide range

[85] *Bacillus anthracis* is a bacterial select agent that can cause anthrax disease.

[86] One user noted that from a laboratory perspective it is easier to use one test rather than a variety of tests having different methodologies, especially for a respiratory panel that requires significant preparatory work.

[87] Charlotte A. Gaydos, "What Is the Role of Newer Molecular Tests in the Management of CAP?" *Infectious Disease Clinics of North America*, 27 (2013).

[88] Gaydos, "What Is the Role of Newer Molecular Tests in the Management of CAP?" *Infectious Disease Clinics of North America*, 27 (2013).

[89] Richard E. Nelson and others, 2015; "Economic Analysis of Rapid and Sensitive Polymerase Chain Reaction Testing in the Emergency Department for Influenza Infections in Children," *Pediatric Infectious Disease Journal,* Vol. 34, no. 6 (2015): 577–82. Quality-adjusted life years is a measure of test effectiveness that accounts for both the duration and the quality of life.

of care settings, such as remote or low-resource areas. Such features include:

- low technology maintenance or little required troubleshooting;
- small sizes (ranging from a microwave to a shoebox);[90]
- customization for panels of different disease combinations; and
- minimal training required for use.[91]

These ease-of-use features allow MPOCT use in settings, such as physician offices, and hospitals, and use by health care providers with varying degrees of training. Scientific literature stated that the ideal MPOCT should be easy to use, portable, affordable, and fast and accurate in providing results (figure 3). For example, developers and users said that such an MPOCT could be used by personnel, such as military personnel, with minimal medical training, by local health care workers in remote areas, by a nurse in an emergency room setting, or by personnel inside a retail pharmacy.

Figure 3: MPOCTs can be compact and easy to use

An MPOCT can be used by pressing buttons on a touchscreen and inserting a cartridge containing the patient sample.

Source: GAO | GAO -17-347

Developers told us that MPOCTs can have multiple applications due to their customizable nature. For example, MPOCTs can be adjusted to test for different types of disease or syndromes based on users' needs, while the technical operation of the MPOCT remains the same.[92] As another example, one developer said that beyond detecting human infectious diseases, MPOCTs could be used in a shipping port to survey goods coming into the United States,[93] as part of airport screening, or to help identify bacteria with antibiotic resistance on hospital room surfaces. Other developers also noted that MPOCT could be used for biosurveillance, such as for detection of aerial pathogens, a key capability of interest to DHS.

According to scientific literature, ease-of-use features may also increase access to care in remote or low-resource areas. Most deaths by infectious diseases occur in developing

[90]One developer at our meeting noted that a multiplexed lateral flow assay can be the size of a pen.

[91]Some of these features overlap with the "usability" performance characteristics discussed previously. Other features include technology weight, for example.

[92]As previously noted, such adjustments may need to go through testing and FDA review before being marketed.

[93]For example, such a technology could be used to survey imported grains for genetic modification.

countries because of the lack of medical facilities and services, and MPOCTs can enable disease diagnosis by rapidly providing results and by making the test available at patient bedsides or at local care centers otherwise lacking in testing facilities.[94] According to an article, advances in MPOCTs may enable sample collection and testing to be done in remote settings, such as those far from hospitals or testing laboratories.[95] By performing diagnostic tests and obtaining results closer to the patients, MPOCTs in remote areas may confer improved public health by enabling the rapid diagnosis and subsequent treatment of patients, which in turn could reduce disease transmission in remote communities.[96]

5.1.6 Developers and users vary in their assessment of MPOCT utility

Developers and users we spoke to expressed different opinions on the extent to which MPOCTs improve patient outcomes. Some developers based their assessment of MPOCTs in terms of their value-added potential to patient care, such as their ability to aid in clinical decision-making by providing rapid results. Other developers also based their assessment of MPOCTs on their market potential, which includes some health outcome factors. Moreover, a few developers at our meeting told us that investors would invest in the development of an MPOCT for which potential demand and profitability—and thus utility to users—are clear.[97] Another developer at our meeting said there is demand for MPOCTs, adding that health care providers want health care that is better, cheaper, and faster, and that MPOCTs can provide those capabilities. Another developer described obtaining feedback from potential commercial customers that showed a need for MPOCT development due to the convenience and time-saving capabilities of such technologies.

A market-based approach may limit the potential utility of MPOCTs, however. For example, some users said that MPOCTs could be used for surveillance of potential exposure to select agents, but some developers said that they are not developing MPOCTs for the detection of select agents because there is no significant market potential for their development, and potentially little return on investment. As a result, certain MPOCT screening benefits may not be realized by relying only on market incentives.

Developers and users disagreed on the strength of evidence showing MPOCT improvement on patient outcomes. Some developers said MPOCTs have been shown to improve patient outcomes. For example, two developers told us that some studies reported that the use of MPOCTs overseas has increased access to care, improved health outcomes, and reduced mortality rates.[98]

[94]Jong-Hwan Lee et al., "Multiplex diagnosis of viral infectious diseases (AIDS, hepatitis C, and hepatitis A) based on point of care lateral flow assay using engineered proteinticles" *Biosensors and Bioelectronics*, Vol. 69 (2015) and Chen-zhong Li et al., "Paper based point-of-care testing disc for multiplex whole cell bacteria analysis" in *Biosensors and Bioelectronics*, Vol. 26 (2011).

[95]Caliendo and others, "Better Tests."

[96]Chen-zhong Li and others, "Paper based point-of-care testing disc for multiplex whole cell bacteria analysis" *Biosensors and Bioelectronics*, Vol. 26 (2011) and Louise M. Causer and others, "A field evaluation of a new molecular-based point-of-care test for chlamydia and gonorrhea in remote Aboriginal health" *Sexual Health*, Vol. 12 (2015).

[97]However, such utility is not necessarily directly related to patient outcomes.

[98]Some studies in the U.S. have identified benefits such as reduced duration of antibiotic use, early treatment of disease, and decreased length of inpatient stay on a positive test result.

However, some users disagreed. Some users we spoke to based their assessment on available evidence of the technologies' impact on patient outcomes, stating that the benefits of these technologies have not been well-established. Some users described MPOCT benefits as hypothetical because proof of such impact is lacking, adding that most studies have not shown a difference in length of hospital stay, mortality, and hospital readmission rates. Furthermore, one user said that while proof of MPOCT impact on health outcomes can be established through studies, such work requires years to provide suitable data. Additionally, this user argued that MPOCTs may not provide added value because they may cost more compared to currently available tests, such as those conducted in a central laboratory.

One regulatory expert at our meeting commented that even if the benefits of MPOCT have not been well established, the additional information provided by the technologies is beneficial. For example, he said that an MPOCT test that informs a treatment path can lead to health benefits. However, users we spoke to emphasized that some benefits of MPOCT testing manifest only if it can provide timely information that can be used to make actionable clinical decisions, such as prescribing treatment or admitting to a hospital. One physician added that if a patient has already been sick at home with influenza for a few days, rapid diagnosis does not provide information that can be used to inform treatment.

Beverly B. Rogers and others. "Impact of a Rapid Respiratory Panel Test on Patient Outcomes." *Arch Pathol Lab Med* Vol. 139 (May, 2015) and Min Xu and others. "Implementation of FilmArray Respiratory Viral Panel in a Core Laboratory Improves Testing Turnaround Time and Patient Care." *Am J Clin Pathol* Vol. 139 (2013)

There is a lack of published clinical performance data on MPOCT devices. According to scientific literature, more research and clinical studies would be needed to show how the use of MPOCTs in making treatment decisions impacts patient outcomes. For example, some studies reported that MPOCTs have similar sensitivity and specificity compared to conventional laboratory testing, so one may expect that benefits from laboratory testing should extend to MPOCTs. However, other studies stated that some types of MPOCTs, such as those using lateral flow assay technologies, are limited by poor performance results compared to traditional laboratory testing. Despite potentially poor performance, some articles reported that MPOCTs could be used for screening, when used in conjunction with confirmatory testing or in situations where early or immediate information is crucial to help make clinical decisions.

5.2 Several challenges associated with MPOCTs may affect user adoption

Developers and users we spoke to identified three challenges associated with MPOCTs that could affect their widespread adoption: (1) user reluctance, (2) user perception of MPOCT value, and (3) affordability of, and additional resources required.

5.2.1 User reluctance to use MPOCTs

We identified four reasons why users may not want to use MPOCTs based on our discussions with developers, users, and regulatory experts. First, users told us that adoption is affected by physicians' knowledge of MPOCTs and preferences for conducting or ordering clinical tests. Some users said that physician

education and training on MPOCT is necessary to properly order the test and understand the results. Additionally, users said that some physicians are not aware of new MPOCTs or prefer using existing tests. Further, one user at our meeting said that despite receiving education on MPOCTs, some physicians still choose the least expensive test even if MPOCTs can outperform such tests. Moreover, one physician said that physician education is very important when introducing new tests to the market. Physicians need to learn about the new test, to trust it, and finally to incorporate it into their clinical decision-making. According to this physician, information sources such as formal education, web resources, and notices from a hospital or laboratory about the availability of new tests are important information sources for physicians.

Second, some users and regulatory experts expressed concern that physicians may not know how to interpret results provided by some MPOCTs, and that not fully understanding test results could impact treatment decisions. For example, some users said that the results from an MPOCT could provide more information than the physician wants and misinterpretation of results could lead to liability issues. One physician agreed that results interpretation may be challenging, saying that a test with a "yes" or "no" response is simpler to interpret than a more complex result requiring analysis. According to this physician, the easier the test is to use, the quicker is its adoption. Moreover, this physician said that there are challenges associated with positive test results lacking a treatment path, adding that there is little a physician can do with such information, so it is hard to see how the test could have much utility. He reiterated that for a test to be useful, it has to provide information that can be acted on. Additionally, scientific literature reported that interpretation of test results can be complicated by a patient's clinical status, for example, whether patients may be taking antibiotics at the time of testing or the extent to which an infection has run its course in the patient.

In asking FDA about potential difficulty in interpreting results from MPOCTs, officials told us that some MPOCTs are CLIA-waived tests. Such tests have been approved by FDA as simple tests with a low risk for an incorrect result, or as tests that could be used at home. FDA officials said they did not see any issues with physician use of CLIA-waived tests. They added that MPOCTs intended for professional use are labeled appropriately so that a physician can understand a test result.

Third, some users want to avoid unfocused testing that can result from using an MPOCT. For example, a few users told us that they are concerned about using MPOCTs without the ability to select and test specific diseases. Some users said that "shotgunning," or ordering numerous tests to chase numerous potential diagnoses, is frowned on by their colleagues and contrary to how doctors are currently trained to diagnose. Other users preferred limiting targets to diseases more likely to be present in the patient, given factors such as the season (for example, influenza season) and ability to treat the patient based on test results. Users also told us they are concerned about the utility of MPOCT testing for diseases that have no treatment path. For example, positive results for the presence of coronavirus have no

action potential—that is no treatment is currently known.[99]

Users told us they would prefer syndromic panels, such as a panel detecting respiratory disease targets that have similar symptoms, over a panel of many targets for diseases that lack common symptoms. For example, a panel that distinguishes among diseases causing runny nose and coughing would be more useful than a panel that distinguishes among diseases, some of which cause runny noses and others which cause diarrhea. However, others noted that a syndromic approach may still have potential problems. For example, one user noted that a situation where positive detection of a pathogen causes a doctor to halt testing and subsequently miss another—potentially more dangerous—disease would be undesirable. Other users noted that syndromic panels may not be useful when there are unusual combinations of symptoms.[100]

Challenges in adding emerging infectious diseases to existing panels

Adding emerging infectious diseases, such as Ebola or Zika, to existing panels presents challenges. Developers adding a new disease target to a panel have to consider interactions between the new target and existing targets on the panel. Additionally, users may be reluctant to use a panel for diseases with disparate symptoms. For example, a developer at a meeting of experts told us Zika panels should include certain viruses—such as dengue, which can cause the same symptoms. However, a user told us he doesn't see Zika tests being multiplexed with a wide variety of other viruses because it would be an unnecessary cost and add confusion. Further, another user expressed concern over false positives and negatives from certain emerging infectious disease testing, if widely used. As a result, it is not clear that developing an MPOCT panel with the intention to gradually expand the panel, by adding new disease targets as they appear, will be accepted by users.

Source: GAO analysis of interviews | GAO-17-347

Some users also desire the ability to "black out" certain test results on multiplex panels, meaning that the user does not see, and may not be charged for, a subset of tests on the panel. One user at our meeting questioned the need for large panels that test for things the physician may not want and the legal issues that could result if the clinician did not act on a given test result. For example, users told us they can sometimes rule out, or exclude, certain diseases based on other patient indications and would not want to see MPOCT results associated with those diseases. One user indicated a reluctance to adopt MPOCTs that require use of the entire

[99]According to CDC, human coronaviruses usually cause mild to moderate upper-respiratory tract illnesses, like the common cold. Currently, no vaccines protect people against human coronavirus infection, and no specific treatments for illnesses caused by human coronaviruses are available.

[100]FDA officials told us there are currently no FDA-cleared MPOCTs that are not syndromic, indicating that such technologies may have limited clinical utility.

panel. According to another user at our meeting, the ability to "black out" some tests is something users want in MPOCTs, but is not always offered.

CDC officials said some analysis may be required with results from complex test panels. They told us a physician might not know what to do with a particular result when making treatment decisions, which may make some MPOCTs less useful in a clinical environment.[101]

However, a few developers at our meeting expressed surprise that users wanted smaller panels. They questioned the rationale in not receiving a result, indicating that even if no action could be taken, at least information had been gained that could be used for other purposes. Some users agreed, saying that sometimes just satisfying a patient's curiosity about why they were or were not getting a particular treatment may be worthwhile.

Fourth, users were also concerned with adopting MPOCT panels that test for rare diseases, but particularly for a panel that would test for the presence of select agents, because they may be likely to result in false positives and have mandatory reporting requirements to public health laboratories. For example, one user at our meeting said that many patients may be coming into an emergency room with "fevers of unknown origin" without having a disease associated with select agents, like anthrax or tularemia. However, because positive test results for rare diseases are more likely to be false positives, systematic testing for such diseases may result in wasted resources to address all patients who test positive, through additional confirmatory testing, quarantine, and unnecessary prophylaxis.[102]

5.2.2 User perception of MPOCT value

Several users do not yet see the value of new MPOCTs due to a lack of trust in the technology and limited peer-review studies. Physicians told us that they need to have confidence in a test before they use it. For example, one physician stated that building confidence in a new test requires that the test demonstrate the capacity to assist in clinical decision-making with consistent results. This physician would not be willing to adopt MPOCTs that lack these features. Another physician said that sometimes physicians run an older test in conjunction with a newer test to ensure confidence in the results of the new test. Running such dual testing can be expensive, with potential problems if the different tests provide conflicting results, thus some users may not be willing to make an investment in newer technologies, such as MPOCTs.

Some users described challenges in establishing the performance of MPOCT testing. For example, users commented that validation studies required to test the technology are expensive and difficult to do because of multiple pathogens in the test panel that must be validated. One user at our meeting commented that she would not want to use a test with a large panel of diseases because of the difficulty in validating certain disease pathogens. Scientific literature also

[101]In addition to detecting the presence of pathogens, MPOCTs can also be designed to provide information on characteristics of the pathogen, such as virulence or antibiotic resistance.

[102]An agency expert at our meeting noted that one approach could be to mask results from select agents except under emergency situations.

reported that the poor performance of some MPOCT and the lack of published clinical data on patient outcomes may hamper its widespread adoption. Thus, evidence users want to see may be lacking, resulting in difficulties evaluating or comparing the effectiveness of MPOCTs, which may ultimately affect the technology's adoption.

5.2.3 Affordability of MPOCTs, and additional resources needed for implementation

Users expressed concerns with the affordability of MPOCTs and anticipate requiring additional expenses and resources for their use. Developers, users, and regulatory experts identified MPOCT costs as a challenge and said that the cost of MPOCT must be low for users' adoption.[103] One user said that high-throughput central laboratory systems will usually cost much less than low-throughput systems, such as MPOCTs. However, we did not perform a cost-comparison analysis over the lifetime of a technology versus alternative testing modes such as central laboratories. A developer added that some users would not utilize a $100 test, even if the test had perfect sensitivity and specificity and took only 10 minutes. Further, one developer questioned the need for big test panels that cost $500–$700, saying such tests could lead to potential for abuse by ordering unnecessary tests. A developer told us that physicians are suspicious of running large panels and that he has received comments from physicians saying that with these test panels, they pay for many results that are negative instead of one result that is positive.

Capital costs may limit how many MPOCTs a physician buys, according to some developers. However, some users told us that cost did not have much impact on their use of MPOCT. Further, one user said that cost has less impact if an institution decides to purchase the technology, so that ultimately whether a test is ordered or not depends on the likelihood that it will significantly change the care of patients and improve outcomes. Additionally, while an MPOCT may unnecessarily test for some pathogens, its use may provide indirect cost savings. For example, MPOCT costs could be compared against the benefits of shortening a patient's stay in the hospital or time in isolation. However, while a multiplex test may save time because many tests are run with one multiplex rather than one singleplex test, multiplex testing may be more expensive, if additional confirmatory tests are needed.

Furthermore, users said that adoption of MPOCTs may be limited if there are not enough patients whose care could be informed by a MPOCT test. For example, users said that MPOCTs that can test only for one panel of diseases could impact users' adoption because there may not be enough patients with the syndrome covered by the panel to support the cost of the technology. However, cost savings might result from being able to definitely rule out pathogens, such as for rare diseases. Scientific literature reported affordability to be a critical attribute that MPOCT technologies must have for widespread implementation.

A few users and developers told us that integrating MPOCTs into the workflow of an office or department can affect adoption of

[103]Technology prices may decrease with increasing adoption, due to factors such as gains in mass production efficiency. We did not examine such factors in our report.

such technology because of the personnel, training, and resources needed to handle the technology. One user at our meeting said that MPOCTs could change the work and patient flow of an office or clinic. Further, implementing MPOCTs could force space allocation changes, require additional staff to handle the equipment, and change the number of patients a physician could see in a day. Moreover, some physicians told us that MPOCTs can be a burden and distract staff from other patient care duties. For example, one physician said that the nurse who actually conducts the test must be trained and credentialed. The time spent on training and maintaining this credential detracts from time spent on clinical duties and caring for patients. Another physician stated that in addition to the time it takes to run a test, quality control and documentation issues (documenting batch numbers and reagents, for example) related to tests can take away from providing patient care.

6 Developers and others discussed implementation challenges they faced in the regulatory review process

6.1 Developers reported challenges with FDA's review process

Developers we spoke to identified three challenges associated with the FDA review process. First, as described previously, FDA has discretion in the type of information it deems necessary for MPOCT approval or clearance. Some developers told us that the specific tests and data to meet such requirements are not explicit, which makes it challenging to determine which experiments to perform to pass the review process.[104] Other developers said the clearance or approval review process can be complicated, due to the challenge of satisfying FDA's requirements. For example, one developer said that to obtain FDA clearance or approval for new MPOCTs,[105] they must establish a link between the diagnosis and treatment, not only showing that they can detect or diagnose the disease correctly, but that it also leads to a clinical outcome.[106] As a result, it will take longer for FDA to review all the data.

In an effort to provide information about the FDA review process, FDA officials said they offer a program for pre-submission in which they meet with companies before a test is submitted for review. According to FDA officials, pre-submission is an opportunity for developers to discuss the technology with the reviewer and ask questions before the review process begins.[107] By communicating with FDA during pre-submission, FDA said developers are able to design studies appropriately and are therefore less likely to have to redo them. While pre-submission is not required, FDA believes it can lead to a better submission process. However, one developer we spoke to stated that while the pre-submission process is meant to answer questions, nothing is solid in these pre-submission agreements and there is potential

[104]In 2012, we reported a number of issues related to FDA's review of medical device submissions. For example, interviewed stakeholders noted that FDA does not clearly communicate to stakeholders the regulatory standards that it uses to evaluate submissions. In particular, industry stakeholders noted problems with the regulatory guidance documents issued by FDA. These stakeholders noted that these guidance documents are often unclear, out of date, and not comprehensive. See GAO, *Medical Devices: FDA Has Met Most Performance Goals but Device Reviews Are Taking Longer*, GAO-12-418 (Washington, D.C.: Feb. 29, 2012).

[105]A new test would lack a substantially equivalent device to which it could be compared.

[106]FDA officials stated that FDA recommends using method comparison studies or comparison to standard of care testing to clinically validate such diagnostic tests. They also told us that, to date, all *de novo* petitions for nucleic acid tests for infectious diseases were granted using method comparison studies.

[107]FDA officials told us pre-submission can start at the earliest stages of device development, and that there are other developer resources. For example, FDA publishes previous decision summaries to guide developers on studies performed by previous successful applications. Summaries can be obtained by searching FDA databases at https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Databases/default.htm.

for pre-submission requirements to be different each time.[108]

Second, some developers commented that the FDA review process, which can take 4 to 6 months according to one developer, is costly, time-consuming, and delays return on investment. As a result, it can be difficult investing resources in long-term development, especially for smaller developers.[109] For example, one developer said the prospective sample collection required for a new test can slow the review process because the developer must wait for people to get sick.[110] The developer also told us that smaller companies cannot sustain test failures and therefore such a company must be careful about selecting MPOCTs to develop, given the time investment. According to FDA, the 510(k) clearance process takes on average about 125 days, with FDA spending on average 52–55 days reviewing the technology and the developer taking 70–75 days to respond to questions.

Third, one developer told us that it can be challenging if FDA reviewers change each time they go through the review process. This developer said that in such circumstances, the evidence required may also change, potentially delaying approval or clearance of the technology. FDA officials told us that their managers are responsible for ensuring consistency during review and that they conduct periodic audits to assess consistency, among other things. FDA officials added that they try to keep the same reviewer assigned through the entire review process but that it is not always possible because of reviewer workloads. Moreover, FDA officials said that the level of communication among reviewers is such that if a new reviewer is assigned, reviewers can still talk to one another. Often, there is a team of reviewers for multiplex tests because they take a multidisciplinary approach to review these tests. Finally, FDA officials believe that companies can leverage information from review memorandums on the agency's website, which contains information about how technologies are tested.[111]

FDA officials said that it does not issue guidance for every type of technology but, in general, releases a guidance document when it sees a particular need, such as multiplex technology, or for a particular disease. FDA officials added that they are happy to discuss the review process with developers, but they said the review process is necessarily complex in order to assure devices meet safety and effectiveness requirements. They added that FDA needs to understand the performance of the technology and any issues developers may have to address in labeling the technology. Because of the breadth of technologies and the scientific challenges in testing a technology, FDA officials stated they believe the requirements in the review process are necessary to ensure safe and effective diagnostic technologies.

[108]FDA officials told us that with rapidly changing technologies, it is impossible for FDA to list requirements for tests that are novel.

[109]The FDA review process can take longer during the premarket review process when a new panel needs to be developed for an MPOCT test that is class III and does not have an existing predicate device that FDA can compare to.

[110]FDA officials stated that sample collection and clinical studies precede the FDA review process.

[111]FDA officials noted that when developing a device under the 510(k) process, the most valuable step would be reviewing the clearance of the last device of this type cleared, which should be explicit about what tests were done for favorable FDA action.

6.2 Developers and regulatory experts identified challenges with the CLIA-waiver process

Developers and regulatory experts identified three challenges associated with the FDA CLIA-waiver process requirements. First, some regulatory experts said that CLIA guidance can be problematic in terms of the stringent study requirements that they believe are difficult to satisfy. For example, some regulatory experts were concerned that when developers apply for CLIA-waivers on a test that FDA has already approved or cleared, CLIA study requirements may require that an untrained user get a performance that nearly matches the "gold standard" of testing, which can be tests in central laboratories performed by trained users. A regulatory expert at our meeting said that the performance needed to obtain a CLIA-waiver must be within 95 percent of gold standard performance while the performance needed to obtain 510(k) clearance can be lower. Regulatory experts at our meeting expressed some frustration over these study requirements because, in certain cases, such requirements increase the level of performance needed for obtaining a CLIA-waiver status, for products that have already achieved FDA approval or clearance.[112]

A regulatory expert at our meeting said that these study requirements might prevent companies—especially smaller companies—from entering the MPOCT market. Regulatory experts at our meeting suggested that the CLIA-waiver guidance should be revised to focus more on whether an untrained user in a CLIA-waived setting can run the test and get comparable results to those of a trained user, and less on whether the results nearly match gold standard methods.

FDA officials confirmed that it is possible that the performance necessary for meeting the gold standard may need to exceed the performance needed to gain approval or clearance for marketing.[113] That is, a device intended for untrained users may need to outperform the same device intended for trained users to obtain CLIA-waived status. However, a regulatory expert at our meeting explained that a higher overall performance may be needed for a CLIA-waived device to protect against issues arising from the environment where such tests could be used. For example, increased accuracy was considered important for CLIA-waived tests to protect against potentially serious consequences that may arise in much less controlled environments, such as doctor's offices.

Second, a developer we spoke to indicated that the CLIA-waiver requirements can vary among MPOCTs, which could lead to confusion among developers. For example, this developer had a CLIA-waived device

[112]FDA officials stated that 95 percent is the initial target, but developers can make the case to lower the performance needed for approval or clearance based on assessment of risk and utility. Additionally, they told us that CLIA-waived tests must satisfy accuracy requirements (i.e. the tests must be simple and have an insignificant risk of an erroneous result), whereas 510(k) clearance does not have a similar requirement. 42 U.S.C. § 263a(d)(3). Thus, developers with cleared devices wishing to obtain a CLIA-waiver must demonstrate test accuracy.

[113]FDA officials noted that a gold standard is usually intended to mean viral or bacterial culture. Culture is considered a gold standard since this technique recovers the causative agent of disease in a live state. Any other diagnostic method—for example, PCR or immunoassay—is only detecting a surrogate marker of the causative agent and these methods are therefore not widely considered gold standard methods. A diagnostic device was recently CLIA-waived by comparing the assay to non-gold standard PCR assays and also contrived samples.

requiring no user intervention, but was unsure whether waiver requirements prohibited user intervention based on other similar devices that were also waived. A scientific article stated that the exact performance requirements for a waiver can be elusive.[114]

FDA officials acknowledged some variation in CLIA-wavier study requirements. For example, an FDA official said that depending on how studies for waiver designation are designed by the developer in cooperation with the FDA, and the claims of the intended use, one developer may need to run 900 replicates, while another developer may need to run much fewer replicates. This official added that devices submitted for CLIA-waiver may be different and there are no set requirements for getting a device waived. However, this official also added that submission and review of applications for waiver status is fully established in guidance documents. He said the most efficient way to get a device waived and cleared is through the dual-submission process for 510(k) clearance and CLIA-waiver.[115] He also said this process is designed to take advantage of efficiencies where the requirements of 510(k) and CLIA-waiver can overlap, such as in the clinical studies required for both designations.

Third, a developer said that the cost to do a clinical study for a CLIA-waiver is expensive, especially on top of the costs spent on the FDA approval process. One regulatory expert at our meeting said that the CLIA-waiver alone can cost $350,000, in addition to the millions of dollars already spent on FDA clearance or approval. Regulatory experts added that this issue may block companies—particularly small companies that can't afford to have a technology fail in the CLIA-waiver process—from entering the CLIA-waived market.[116]

6.3 Users expressed concern over the implications of MPOCTs being CLIA-waived

Users identified three concerns with MPOCTs being CLIA-waived. One concern raised by users is how to manage these technologies from a quality-assurance perspective. For example, one user said that laboratories have robust quality-assurance programs for their MPOCTs and it takes a lot of effort to ensure high-quality performance from these tests. In the hands of non-laboratory staff performing the testing, this quality assurance will be difficult to monitor and may result in inaccurate test results. Moreover, another user said that untrained users may not be aware of the nuances that go into running a quality test, which may result in undiagnosed or missed cases. To address this concern, some users emphasized the need for constant staff training so that users are reminded of the importance of attention to detail when using MPOCTs. Without such training, these

[114]Caliendo and others, "Better Tests."

[115]FDA officials told us CLIA-waiver studies can generate sufficient data for both CLIA-waiver and 510(k) approval. While the dual-submission pathway is currently available, the guidance for such submissions is not yet available.

[116]FDA officials noted that a developer could perform a study with a protocol which fulfills 510(k) and CLIA-waiver study recommendations simultaneously. If the study generated acceptable data the developer could get 510(k) and CLIA-waived concurrently without further data. If a device is already cleared, then some of the 510(k) data can be utilized for the CLIA-waiver study; however there are additional data needed for a CLIA-waiver study, such as flex studies and minimally trained users involved in the clinical study testing.

users said they have seen variation in test performance.[117]

A second concern raised by users is the potential for misinterpreting results from a CLIA-waived MPOCT. A few users said the nature of a CLIA-waived technology—simple and low-risk for erroneous results—may actually create a greater potential for misjudging or misinterpreting the results of the test by untrained users, which could in turn lead to incorrect treatment plans. One user at our meeting cautioned of the downstream effects of an incorrect diagnosis using a CLIA-waived MPOCT test and the harm it could cause to a patient. This consideration would be a factor in this user's decision to use the test. Another user at our meeting added that CLIA-waived MPOCTs may not contain raw quantitative data needed to provide further context to a positive or negative test result, which could be an interpretation barrier for these devices.

Third, a few users said the lack of oversight over how to use a CLIA-waived technology—following label instructions being one of the only requirements—may decrease test accuracy and lead to potential misinterpretation of test results. For example, one developer at our meeting expressed frustration that users in her CLIA-waived study didn't follow or read the instructions on the label. As a result, there was no way of explaining poor test performance or why a user may struggle with the test procedure.

However, a regulatory expert at the meeting noted that the CLIA-waiver is designed for what would happen in real-life, such as when users don't read instructions on the label.

FDA officials told us about recent changes in the CLIA-waiver process that they believe have improved it. For example, FDA now allows developers to submit their technology to the FDA premarket notification and CLIA-waiver process at the same time to streamline the two processes. However, FDA officials said the CLIA-waiver process is complex in order to ensure the simplicity and accuracy of waived tests, adding that the science of diagnostic tests can be complex, and FDA needs confidence in the simplicity and accuracy of the test to grant a CLIA-waiver. FDA officials said they were not concerned over the potential misuse of CLIA-waived MPOCTs due to the CLIA-waiver review process, adding that to become a CLIA-waived MPOCT, the technology must be studied under real-world conditions, including in the hands of users with varying technical skills. They acknowledged that these studies can be expensive and therefore, most developers will not submit a test to the CLIA-waiver process unless they are confident of its accuracy when used by untrained users.

However, despite some of these concerns, some developers and users we spoke to recognized the need for CLIA-waived MPOCT devices. Four of the developers we spoke to were developing or already developed CLIA-waived MPOCT devices. These developers said the ability to provide rapid results and ease of use make MPOCTs suitable for a CLIA-waived environment. Additionally, some developers said the development of CLIA-waived devices is an opportunity to expand upon diagnostics available in decentralized health settings, such as retail pharmacies,

[117]For example, in response to concern about Ebola virus, CDC issued biosafety guidance for U.S. laboratories for managing and testing clinical samples. Among other things, the guidance laid out safety and staff training recommendations for using point-of-care devices to test patients for Ebola. https://www.cdc.gov/vhf/ebola/healthcare-us/laboratories/safe-specimen-management.html (accessed April 19, 2017).

small hospitals, or by first responders in the field. Users also noted that MPOCTs can be useful in settings where a short time to diagnosis is needed to begin treatment. Further, some users at our meeting identified the increased role of MPOCTs in the growing decentralized care model, such as a retail pharmacy, where rapid results and immediate treatment are significant features. Finally, one user at our meeting said that users are not necessarily resistant to such decentralized testing; however, they want to see the performance data of these tests and an expansion of test panel offerings for MPOCT use.

7 Agency and expert comments

We provided a draft of this report to officials at the Department of Defense, Department of Energy, Department of Homeland Security, and the Department of Health and Human Services with a request for comments. We incorporated their technical comments received into this report, as appropriate.

We provided a draft of this report to all 18 experts from our meeting group. We requested they review it with respect to technical quality. Ten experts responded with technical comments that we incorporated as appropriate.

As agreed with your offices, unless you publicly announce the contents of this report earlier, we plan no further distribution until 30 days from the report date. At that time, we will send copies to interested congressional committees, the heads of the agencies identified above and other interested parties. In addition, the report will be available at no charge on the GAO website at http://www.gao.gov.

If you or your staff have any questions about this report, please contact Timothy M. Persons at (202) 512-6412 or personst@gao.gov or Elizabeth H. Curda at (202) 512-7215 or curdae@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of our report. Key contributors to this report are listed in appendix V.

Timothy M. Persons, Ph.D., Chief Scientist

Elizabeth H. Curda, Director, Health Care

Appendix I: Objectives, scope, and methodology

Our objectives were to:

1. Identify the reported performance characteristics and costs of MPOCTs.
2. Identify the technical challenges associated with multiplexing assays.
3. Identify the potential benefits and reported implementation challenges associated with MPOCTs.

Scope and methodology for assessing technologies

To address all of our objectives, we assessed certain medical technologies that could be used to help diagnose infectious disease in patients. These technologies – MPOCTs – can be (1) deployed at point-of-care settings and (2) test for the presence of pathogens associated with at least two diseases from a single patient sample. We focused on technology capability rather than how the technology was implemented. For example, some technologies we examined were not implemented at point-of-care settings, but could potentially be deployed there. Additionally, some technologies, while able to detect the presence of pathogens for at least two diseases, were sometimes used for detecting targets or pathogens for only one disease. We combine discussion of different contexts for MPOCT use, including routine clinical, emerging infectious disease and select agent detection excepting situations where the specific context was provided.

To address the first objective, we analyzed market surveys of MPOCTS from DOD and DHS published in 2012 and 2015, respectively. These market surveys identified existing MPOCTs and assessed them against each agency's listed program requirements.[118] From the DHS market survey, we selected for further review developers whose MPOCTs were identified as coming very close to meeting program requirements. From the DOD market survey, we selected all developers of MPOCTs listed because the agency did not identify which MPOCTs met or approached its requirements. We limited the scope of our study to these MPOCTs because these technologies were identified as being potentially suitable for federal agency application. At the expert meeting, MPOCTs were discussed broadly, without focusing on a specific developer, but were limited to U.S. applications.

To address all our objectives, we used information from agency documentation and scientific literature to enhance our understanding of MPOCTs and diagnostic testing, identify challenges associated with MPOCT assays and identify potential benefits, and challenges and costs and inform discussion at the expert meeting. We attended two relevant conferences on MPOCTs in Fall 2015 and 2016 (SelectBio Point-of-Care Diagnostics and Global World Congress 2015 and 2016). In addition, to address all of our reporting objectives, we: (1)

[118]These market surveys contain lists of candidate technologies, their developers, features, and discussion of the potential suitability of these technologies for purposes specified by each agency. The features described include technical specifications such as speed and number of targets.

conducted site visits to developers of MPOCTs, (2) convened a meeting of experts with the assistance of the National Academies of Sciences, Engineering, and Medicine (NAS), and (3) interviewed agency officials and national laboratory staff, academic, laboratory, and scientific and medical organization members, as discussed below.

Site visits

We contacted nine developers identified in the market surveys as described in the Scope and Methodology, and arranged for site visits to interview their staff and observe their facilities, including the developers' MPOCTs. These site visits were used to gather information about MPOCTS selected for review for all objectives. We also asked the developers about their procurement costs, which are the costs to buy the technology itself – also referred to as system or unit costs – and operational costs, which are the costs to run a single test, typically using consumables or cartridges. Although all the developers accepted our request for site visits, some developers differed from whom we initially identified, because of mergers or other business arrangements. Not all developers had commercially-available technologies, and some focused on the technology, leaving the assay to business partners. One developer left MPOCT development and thus we limited ourselves to the remaining 8 developers in our report. The developers we visited and additional information are listed in appendix IV.

We also visited the Lawrence Livermore National Laboratory in Livermore, California to discuss its ongoing work in MPOCT development.

Expert meeting

With the assistance of the NAS, we convened a 2-day meeting of 18 experts on MPOCTs. We worked with the NAS to identify and recruit a list of experts from academia, industry, laboratory, scientific and medical professional organizations, and federal government agencies covering significant areas of our review. We included among the experts (1) those who develop or help develop MPOCTs, (2) those who use MPOCTs to guide patient care, including laboratory users as well as physicians who use results to make clinical decisions, and (3) those who work with regulatory aspects of MPOCTs. These experts were identified by NAS as having sufficient knowledge and/or experience in these technologies to discuss the issues addressed in this report, and they expressed a willingness to participate in this meeting. We asked experts at our meeting to identify any potential conflicts of interest, which were considered to be any current financial or other interest that might conflict with the service of an individual because it could impair objectivity. The group of experts as a whole was judged to have no inappropriate biases. The experts are listed in appendix III.

During this meeting, we solicited input from the experts on the topics of our work for all objectives. In particular, we moderated discussion on the objectives listed above, as well as on discussion of technical terminology and issues such as the ethics associated with the development and use of MPOCTs. The meeting was recorded and transcribed to ensure that we accurately captured the experts' statements. After the meeting, we used the transcripts to characterize their statements. Following the meeting, we

continued to seek the experts' advice to clarify and expand on what we had heard. Consistent with our quality assurance framework, we provided the experts with a draft of our report and solicited their comments, which we incorporated as appropriate.

Additional interviews

To gather information for all objectives, we interviewed:

- Federal agency officials from the Department of Homeland Security, the Department of Defense, the Department of Energy, including the Pacific Northwest National Laboratory, Sandia National Laboratories, and the Lawrence Livermore National Laboratory, and the Department of Health and Human Services, including the Centers for Disease Control and Prevention, the Food and Drug Administration, and the Centers for Medicare and Medicaid Services.
- Nine representative health care organizations or academic organizations who were users of MPOCTs, including the American Medical Association, the American Society for Microbiology, the American Association for Clinical Chemistry, the Association of Public Health Laboratories, Stanford University, the American Association of Bioanalysts, the Infectious Diseases Society of America, the American College of Emergency Physicians, and the American Society for Clinical Laboratory Science.

Limitations to scope for assessment of technologies

We did not assess all available or developing technologies. For example, all of the MPOCTs identified by the market surveys for which we based site visits were PCR-based technologies. Other technologies, such as lateral flow assays, were discussed during the expert meeting as well as at conferences we attended. However, our report primarily focused on PCR technologies identified by the market surveys. Some additional technologies were presented in scientific literature and conferences but were technologically immature (for example, at the proof-of-concept stage) and were excluded from our analysis. We also excluded MPOCTs developed outside the United States or intended primarily for deployment outside the country.

We grouped all PCR-based technologies together. PCR was modified among the different MPOCTs we assessed. We did not distinguish among the different types of modification of PCR in our analysis.

Information communicated to us by developers and users we spoke to were reported as provided. For example, cost information consisted of list prices and may not account for factors such as academic or volume discounts or other contractual adjustments. Additionally, given the rapid pace of development of MPOCTs, information provided to us may change. Further, after the people we talked to provided responses to our questions, we analyzed the responses and grouped them into key categories that are presented in this report. The categories we chose are not the only way the information could be organized and are not necessarily

exhaustive. Finally, the findings based on our interviews and site visits should not be considered generalizable to all MPOCT development and usage.

We conducted our work from September 2015 to August 2017 in accordance with all sections of GAO's quality assurance framework that are relevant to technology assessments. The framework requires that we plan and perform the engagement to obtain sufficient and appropriate evidence to meet our stated objectives and to discuss any limitations to our work. We believe that the information and data obtained, and the analysis conducted, provide a reasonable basis for any findings and conclusions in this product.

Appendix II: Technologies in the pipeline include next-generation sequencing and microarrays

Developers identified diagnostic testing technologies that are in the development pipeline, including next-generation sequencing and microarray technology, which may complement or replace current MPOCTs.

Next-generation sequencing is a method for sequencing the genome of an organism (or multiple organisms) by cutting strands of DNA into short fragments and sequencing large numbers of fragments at the same time. The sequences of the fragments are then aligned using a reference genome to reproduce the genomic sequence of the original DNA strands. This method increases the length of the genome that can be sequenced in a single reaction and can reduce the sequencing cost per unit length of DNA. Scientific articles have described studies that used next-generation sequencing technologies for mapping the human and bacterial diversity present on rider contact surfaces in the New York City subway system as well as providing evidence that Ebola virus can be sexually transmitted.[119]

One user at our meeting told us next-generation sequencing is less likely to be implemented for diagnostic testing as it will be for examining how different communities of microbes affects diseases. A developer at our meeting told us that next-generation sequencing may be the next method to replace multiplex PCR.[120] A developer working on next-generation sequencing technology told us it takes 2-3 days to obtain a sequence and that they don't foresee this technology being available at the point of care within 5 years. However, a user at our meeting mentioned that there are such technologies currently moving into the point of care that can eventually examine every single pathogen in a patient.

Microarrays can use chips to detect short segments of target genome. One developer told us their microarrays are not point-of-care technologies because they are large instruments that are not particularly fast and are complicated to use. Another developer we spoke to told us that they are developing a fast platform—with a goal of under 2 hours from sample to result—that uses a cartridge containing reagents to perform the test. This developer told us microarrays can fill the gap between current nucleic acid testing methods (such as PCR) and sequencing technologies by detecting several hundred targets at once. A developer at our meeting told us that microarrays can allow a type of antibody test called "lateral flow tests" to go beyond the current 8-12 targets.[121] This developer noted that microarray approaches may increase the number of targets being detected.

[119]Ebrahim Afshinnekoo and others. "Geopsatial Resolution of Human and Bacterial Diversity with City-Scale Metagenomics." Cell Systems Vol. 1 (2015) and Suzanne Mate and others. "Molecular Evidence of Sexual Transmission of Ebola Virus." NEJM Vol. 373 (2015).

[120]One user at our meeting told us that PCR is required for next-generation sequencing, to amplify the initial genomic sample.

[121]Lateral flow assays are typically based on antibody-based detection of disease-causing organisms. Their configuration is similar to a home pregnancy test "dipstick," whereby a liquid sample is applied to an absorbent material that draws the sample across a detector. Positive detections can be indicated by the appearance of lines in the readout region.

Appendix III: Expert participation

We collaborated with the National Academies of the Sciences, Engineering, and Medicine to convene a two-day meeting of experts to inform our work on multiplex point-of-care technologies; the meeting was held on October 26-27, 2016. The experts who participated in our study are listed below. Many of these experts gave us additional assistance throughout our work, including by providing additional technical expertise and answering questions, and 10 who reviewed our draft report for technical accuracy.

Nazneen Aziz

Executive Director
Kaiser Permanente Research Bank
Oakland, CA

James Boiani

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Washington, DC

Hong Cai

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Appendix IV: Site Visits

We made site visits to developers of MPOCTs to inform our work on multiplex point-of-care technologies during the summer and fall of 2016. The developers we visited are listed below. Many of the developers gave us additional assistance throughout our work, including by providing additional technical expertise, answering questions, and reviewing excerpts of our draft report for technical accuracy.

BioFire Diagnostics, LLC

Salt Lake City, UT

Cepheid

Sunnyvale, CA

Focus Diagnostics/Diasorin

Cypress, CA

Illumina Inc.

San Diego, CA

Luminex Corporation

Austin, TX

NVS Technologies

Menlo Park, CA

PositiveID Corporation

Pleasanton, CA

Roche

Pleasanton, CA

Thermo Fisher Scientific

South San Francisco, CA

Appendix V: GAO contact and staff acknowledgments

GAO contact

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Staff acknowledgements

In addition to the contact named above, Sushil Sharma, Dr.PH, Ph.D. (Assistant Director), Geri Redican-Bigott (Assistant Director), Hayden Huang, Ph.D. (Analyst-In-Charge), Maggie G. Holihan, Rebecca Parkhurst, Ph.D., and Katrina Pekar-Carpenter, Ph.D. made key contributions to this report.

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