April 24, 2020

Q&A: *In Vitro* Diagnostic COVID-19 Testing – Part 1

AdvaMedDx and its member companies are supporting the public health response to the 2019 novel coronavirus (COVID-19) pandemic by expanding the availability of and patient access to diagnostic testing. As of April 24, over thirty commercial diagnostic tests for COVID-19, including rapid, point-of-care tests, have received Emergency Use Authorization (EUA) from the U.S. FDA since the first commercial test received EUA on March 12.

Q. Who are AdvaMedDx's members?

A. AdvaMedDx member companies produce advanced, *in vitro* diagnostic (IVD) tests that facilitate the early detection of disease and guiding of appropriate treatments to improve the quality of patient care and public health. These include tests that are front-line tools in the fight against COVID-19, from diagnosing the infection to guiding treatment decisions for those diagnosed and determining if individuals exposed have potentially developed immunity to the virus. FDA plays in important role, providing oversight of IVD manufacturer test development and manufacturing.

Q. How are AdvaMedDx member companies increasing access to coronavirus testing?

A. IVD manufacturers and laboratories are working around the clock to produce more tests as quickly as possible. Many AdvaMedDx member companies have rapidly developed IVD tests to detect the novel coronavirus, as well as to determine if individuals have been exposed to the virus and potentially have developed immunity. They are continuing to work closely with FDA and other government departments and agencies to facilitate patient access to these tests. To date, there are over 30 commercially available COVID-19 IVDs that have received Emergency Use Authorization from FDA – permitting these tests to be deployed to laboratories, hospitals, and other testing sites. These commercial tests will increase coronavirus testing capacity, speed, and throughput to guide patient care and protect public health.

A current list of diagnostic tests that have received FDA EUAs to detect the COVID-19 virus can be found here: https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations

Q. Will IVD manufacturer COVID-19 tests that have received FDA Emergency Use Authorization (EUA) to diagnose symptomatic patients facilitate faster testing from when the outbreak began?

A. Yes. Commercial IVD tests authorized by FDA include those that run on automated systems – platforms manufactured by IVD companies capable of processing high volumes of tests per day. Most of these commercially available IVD tests provide results in 1 to 4 hours at hospitals and labs; commercially available point-of-care tests produce results in as little as 5 minutes. These commercial IVD test methodologies are in contrast to the initially available, manual lab testing performed in lower volumes, and generally taking much longer to run. The new tests are helping fill an urgent need across the U.S. for laboratories and other facilities to access easy-to-use, faster-to-result diagnostic tests to screen patients for COVID-19. These tests complement one another, running on various manufacturer platforms already

in place in hospitals and labs across the country and around the world. IVD manufacturers are part of a larger testing ecosystem that includes hospital, public health and reference laboratories – all critically needed to increase testing capacity.

Q: How many commercial COVID-19 IVDs are currently available?

A: IVD manufacturers are doing all they can to scale up as quickly as possible. As of April 24, collectively, IVD manufacturing capacity for EUA tests shipped to hospitals, laboratories and other health care settings is expected to reach: over 28 million tests to diagnose symptomatic patients, per month, or over 7 million tests per week, by the end of April (for companies reporting production data).

IVD manufacturers' tests are complementary of one another. That is, IVD tests are delivered to hospital laboratories, reference laboratories – and, for rapid point of care tests, to physician offices and other care setting – across the continuum of care. More tests are coming on line every week as manufacturers ramp up capacity.

Q. Will there be enough tests to meet demand?

A. Demand is unprecedented, and AdvaMedDx members are continuing their work to help meet that demand. Our member companies are striving to innovate, developing more tests that can be offered and performed quickly – including at the point of care, where results can be delivered in just minutes. More and more of these technologies will be coming into the market in the weeks and months ahead, and as production volumes continue to accelerate for existing tests.

Q. If the test is not available in all major cities and all 50 states, how does it help people in places without the test?

A. Distance from a laboratory is not a barrier to testing. To complete any type of medical test, it is routine for a sample taken at a doctor's office, hospital or other health care facility to be sent to a laboratory for testing – often at a distance. The transfer of samples occurs rapidly, using courier and logistics services if necessary. And the results of tests are sent back to the health care provider by phone or electronically, regardless of location.

Q. How are AdvaMedDx members' *in vitro* diagnostic tests different than laboratory-developed tests?

A. *In vitro* diagnostic tests are developed by manufacturers for the commercial market for use by laboratories, providers and other users. Manufacturers develop IVD tests and the instruments on which the tests are performed, as well as the collection devices used to collect the specimens tested. IVDs can be performed in labs on site, often producing results in 1 to 4 hours, or in as little as 5 minutes in the case of point-of-care tests. Laboratory-developed COVID-19 tests, in contrast, are developed in hospital labs, reference labs, or public health labs where patient specimens are shipped or brought in for analysis. These lab-developed tests are generally performed manually, not on automated systems or instruments, and usually require more time to return an actionable result.

Q. How can I learn more about commercial COVID-19 tests?

A. To learn more about IVDs for COVID-19 that have received Emergency Use Authorization from FDA and their availability, please visit the AdvaMedDx web site to access links directing you to each IVD manufacturer's COVID-19 test information portal. For more information, you can also access a related FDA site here.

Q. Have changes to FDA's emergency use regulations accelerated development and access to commercial diagnostic tests?

A. Yes. AdvaMedDx and our member companies have been working closely with FDA officials to increase patient access to COVID-19 testing. FDA in recent weeks has implemented streamlined emergency use authorization policies that have allowed commercial manufacturers to rapidly distribute quality tests to laboratories, hospitals and other health care settings across the country.

Q. How much do commercial COVID-19 tests cost for patients?

A. Individual laboratories and hospitals determine the price of the tests they offer. The Families First Coronavirus Response Act, now law, requires all insurers to cover the cost of the tests with zero copayments. Additionally, the law provides special coverage for the testing costs for uninsured individuals. Congress has recently appropriated funds to help cover the cost of testing uninsured individuals.

Q. What are PCR tests? Antigen detection tests? Serology tests?

A. *Real-Time Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) Tests:* Currently, the vast majority of COVID-19 testing uses the RT-PCR method. This method of testing detects the presence of the COVID-19 virus in a patient sample by detecting the virus' genetic material (RNA or DNA).

Antigen Detection Tests: These are tests that detect unique proteins or other molecular structures ("antigens") found on the surface of the COVID-19 virus. Many antigen tests can be designed to be rapid and used at the point of care.

Serology Tests: These are blood-based tests that can be used to identify whether individuals have been exposed to pathogens, such as COVID-19, by examining the presence of antibodies to the pathogen, providing an indication of potential immunity. The hope is that people who have been exposed to COVID-19 develop antibodies in their bloodstream that may help them to fight off and diminish the chances of re-infection. Performed both in labs and at the point of care, serology testing likely will be an important tool to begin the critical work of determining how and when Americans can get back to work, building on the success of physical distancing that has helped limit COVID-19 exposure to date. This testing will be particularly useful for essential functions such as health care, first responders, and food service. Manufacturers and laboratories are developing serology tests that are currently in use, under FDA's Policy for Diagnostic Tests for Coronavirus Disease-2019, to provide more information to clinicians about who may have been exposed to COVID-19.

Under the FDA's policy, the agency allows commercial manufacturers or laboratories to develop, market, and use serology tests once they have evaluated and determined their tests to be accurate and reliable, provided notification to the FDA, and met certain other conditions. As of April 24, FDA has been notified of over 100 serology tests currently being offered in the U.S.

Importantly, serology test developers have the option to submit their test to FDA for Emergency Use Authorization, allowing the agency to review the test's validation data prior to authorizing its use for COVID-19 response. As of April 24, the FDA, after reviewing supporting data that has been submitted, has granted EUAs for three serology IVDs to aid in the diagnosis of COVID-19, and more are on the way.

Q. What are Point-of-Care tests? CLIA-waived tests?

A. Developed and manufactured by IVD companies, point-of-care tests are performed at or near the site of patient care, at the hospital bedside, and in physician offices or clinics, for example, and often providing results in minutes. Point-of-care refers to the location where the tests are performed, meaning outside of a central laboratory and closer to the patient.

Many tests which are performed at the point of care are also CLIA-waived. (CLIA stands for the Clinical Laboratory Improvement Amendments, which regulate laboratory testing.) As defined by CLIA, waived tests are categorized as "simple laboratory examinations and procedures that have an insignificant risk of an erroneous result." Point-of-care tests approved for home use, for example, are also CLIA-waived. CLIA-waived tests *must* be designed to reduce the likelihood of error when used by untrained users.

As of April 24, three point-of-care IVDs have received FDA EUAs for COVID-19 and are also deemed CLIA-waived. Additional point-of-care IVD EUAs for COVID-19 will be entering the market in the coming weeks.

Q. How else are IVD manufacturers assisting with the COVID-19 pandemic response?

A. Manufacturers of *in vitro* diagnostics play a central role in the health care system in America and around the world. To address the COVID-19 pandemic, IVD makers don't just provide tests essential to diagnosing this illness. They also provide a range of tests to help treat coronavirus patients, such as blood gas tests to help care for patients who may require ventilators to help them breathe. IVD makers are also working to ensure continued access to all the diagnostics that patients and physicians rely on every day to provide the right treatment for every condition.

Q. What can we do to support IVD manufacturers as they work to produce more COVID-19 tests to meet public health need during the current "sheltering in place" timeframe?

A. During the current "shelter in place" policies in most states and other policies to help limit spread of the disease and fight the coronavirus, it is necessary to ensure that critical employees at diagnostics and other medtech companies – who are on the front lines and so essential to providing tests and other critical supplies – can continue to do their work. This need extends beyond just COVID-19. Medical technology manufacturing businesses will continue to do everything they can to continue to do what they do best – provide the medical technologies essential to maintaining our health care infrastructure, and saving and improving patients' lives.

Q. What is AdvaMedDx and what is its role?

A. Functioning as a division of the Advanced Medical Technology Association (AdvaMed), AdvaMedDx is the only advocacy organization exclusively addressing policy issues facing diagnostics manufacturers both domestically in the United States and abroad. AdvaMedDx member companies produce innovative diagnostic tests performed in laboratories, at the hospital bedside, in doctor's offices, in medical clinics, and even in the home.

Test Production, Supply Chain and Allocation – Part 2

Q. With more tests being manufactured, why are there still not enough tests to meet demand?

A. Demand is unprecedented, and AdvaMedDx members will continue their work to help address that demand. The enormity of the demand requires the full efforts of IVD manufacturers and suppliers,

public health laboratories, hospital laboratories, and reference laboratories – the entire testing ecosystem – to address the testing needs in this pandemic.

AdvaMedDx members with COVID-19 tests are literally running manufacturing shifts around the clock and will continue to innovate and develop more tests that can be offered – including at the point of care, where results can be delivered in just minutes. More and more of these technologies will be coming into the market in the weeks and months ahead as production volumes continue to accelerate for existing tests.

AdvaMedDx encourages policy makers to work with IVD manufacturers, laboratories, hospitals, and all elements of the diagnostic testing ecosystem, to bolster laboratory infrastructure and ease challenges to maximizing laboratory capacity, to strive toward greater widespread testing availability. Importantly, Congress has recently taken steps to provide support to states to augment laboratory infrastructure.

Q. GM is helping manufacture ventilators. Why not encourage other manufacturers to develop IVDs in new facilities to scale up production?

A. Diagnostic tests and test kits are highly specialized products that are manufactured and assembled under tightly controlled conditions, meeting rigorous standards for operations and quality. Transferring or retrofitting existing manufacturing processes to non-IVD production facilities to increase production under the Defense Production Act (DPA) would take many months or even years. And the level of ramp-up of the IVD industry has been remarkable. Supporting the IVD industry as it continues ramping-up is the most meaningful and efficient way to continue to grow the manufacturing of testing and testing supplies.

In addition, IVD instruments – the platforms on which tests are run in laboratories – are highly-specialized and complex instruments built by hand in controlled manufacturing environments inspected by FDA and other regulatory entities. For large, high-throughput platforms, the typically time between placement of an order and delivery and installation of the platform is 4-6 months. For modernize sized platforms and point-of-care platforms, many manufacturers do presently have supply.

Q. How do IVD supply chains work to ensure COVID-19 test availability?

A. IVD manufacturers and suppliers are taking significant measures to maximize operations to allow for continuity of supplies during the pandemic, striving to meet unprecedented demand. IVD tests and test kits (that range from 25-1,000 tests, per kit, with an average comprising about 100 individual tests) are made up of numerous highly specialized materials and components that are specifically sourced from suppliers across the globe. The IVD supply chain is intricate and complex. Manufacturers strive to have redundancies built into their supply chains.

Because of the extraordinary need for testing during the COVID-19 pandemic, there has been some stresses to the supply chain. Many IVD manufacturers, are conferring with state and federal governments as they strive to maximize operations. Ensuring IVD manufacturer capacity to manage the the IVD supply chain at this critical time limits the potential for supply chain interruptions that could decrease test availability.

Q. What are the potential negative impacts of requiring an IVD test manufacturer to only produce COVID-19 tests?

A. IVD manufacturers produce many types of diagnostic tests that are essential to patient care, and are relied upon by patients and providers each day. Replacing the production of one manufacturing line that

may be producing oncology, cardiac, sepsis or blood gas tests, for example, in favor of a COVID-19 test, would cause a shortage in these other essential tests. Such a mandate on diagnostic test manufacturers could even hamper providers' ability to care for patients diagnosed with COVID-19. Ventilator patients, for example, require frequent blood-gas testing to properly calibrate the ventilator. And COVID-19 patients are susceptible to bacterial infections that could become septic, requiring appropriate testing.

Q. What is the best method to ensure allocation of COVID-19 IVDs is supporting the public health response?

A. Many IVD manufacturers are working closely with the federal government, and state governments to inform IVD allocation decisions. The CDC and White House Coronavirus Task Force has emphasized the importance of prioritizing testing for health care workers, for inpatient care, and for those most at risk, particularly in areas where the incidence of transmission is highest.

When making IVD production scale-up and test allocation decisions, it is critical to consider the current placement of large scale IVD instruments in reference labs and hospital laboratories needed to run the tests across the U.S. IVD tests must be allocated to where instruments that match with those tests are located. While not universally the case, commercial tests typically have technical features and biochemistry unique to each manufacturer, so that specialized tests developed by a single manufacturer generally are suited to run on platforms also developed by that same manufacturer. The tests on these platforms all complement one another, because platform placement in hospitals and labs across the country and around the world is widespread.

Point-of-care testing, can be made widely available, virtually anywhere that patients seek care, from emergency departments, doctor's offices, clinics and often in pharmacies. These tests compliment testing done in laboratories and helps make access to testing more widely available.

Q. How quickly can serology test production be scaled up?

A. Serology tests are generally made up of several key components: antibodies and antigens. Antibodies are molecules naturally made by our immune systems to recognize specific components of pathogens, or antigens. Antibodies that are used in serology testing must be highly specific. Production of these highly specific antibodies requires live animals and tissue-culture techniques that can make the production process long and expensive. Similarly, serology tests also require production of COVID-19 specific antigens that are typically produced in mammalian or bacterial cell lines. To mass produce COVID-19 serology tests, specific antibodies and antigens must be produced in large quantities, which can be complex, and resource and time consuming. To date, 3 IVD companies have serology tests on the market, authorized by the FDA under an EUA.

Q: How does China's export regulation on certain diagnostics tests impact availability in the U.S.?

A: As of April 1, China's regulatory authority, the National Medical Products Administration (NMPA), has required its approval for certain COVID-19 related products, including tests (PPE, ventilators, and tests). NMPA's stated objective is to stop products they deem inferior from reaching outside of China. Several AdvaMedDx member companies are working with partners in China to export from China to the U.S. COVID-19 antibody, or serology tests. China is continuing to insist that NMPA approval is required, regardless of AdvaMedDx member's intent to bring their tests through the FDA for Emergency Use Authorization and not sell in China. Senior levels in both governments have been considering ways to address this regulation. The impact of China's export regulation is the limitation of these serology tests in the U.S.

Q. What steps have been taken to increase the availability of sample collection materials and supplies, such as swabs, to support broader COVID-19 testing?

A. Initially, only nasopharyngeal (upper throat) swabs and viral transport media were authorized by the FDA for COVID-19 specimen collection and transport. Since then, FDA has taken key steps by providing guidance on alternate collection methods, including broadening the range of swabs and specimen types that can be validated and used with FDA Emergency Use Authorized tests. In addition to nasopharyngeal swabs, FDA has deemed the following specimen types as acceptable: oropharyngeal (throat) specimens, mid-turbinate (nasal passageway) specimens using a flocked tapered swab, or anterior nares (nostrils) specimens using a round foam, polyester, or spun rayon swab. The agency has also not ruled out other specimen types such as tongue swabs, saliva, or sputum samples, although more data is needed.

Similarly, for transporting patient specimens, FDA prefers the use of viral transport media (VTM) or universal transport media (UTM). If VTM/UTM are not available, the use of alternate transport media, such as liquid Aimes or phosphate-buffered and normal saline, is acceptable if the best available evidence indicates that these transport media will stabilize the patient sample without meaningful degradation.

In light of the supply challenges, traditional manufacturers have taken critical steps to rapidly scale up production of swabs and other supplies to meet demand – more than doubling capacity in some cases. Further, a number of non-traditional manufacturers have adapted their infrastructure and technologies to manufacture swabs (which requires validation prior to use) adding to the national supply. Increased manufacturing capacity and availability of alternatives has led to increased access to swabs and other collection supplies across the board.

Additional Background – Part 3

This section is intended to provide the following additional information:

- Describe IVD manufacturers and the products they produce;
- Define key terms associated with IVD testing – such as the difference between "test," and "test kits";
- Describe where tests are performed; and
- Provide a sample workflow required to run an IVD test from patient sample collection to reporting the diagnostic test results to a health care provider.

In Vitro Diagnostic Manufacturers

IVD Manufacturers – Manufacturers develop and manufacture *in vitro* diagnostic (IVD) tests, platforms/instruments on which tests are performed, and the collection devices used to collect the patient specimens (samples) tested. It is important to note that tests are typically packaged as "test kits." Test kits might typically contain 100 tests or more. (See below for more on the distinction between tests and test kits.) FDA provides oversight of IVD manufacturers' test development and manufacturing.

Key Terms Associated with IVD Testing

***In Vitro* Diagnostic (IVD) Tests –** An IVD is a medical test, developed by manufacturers for the commercial market, that examines specimens (e.g., blood, tissue, nasal mucus, etc.) taken from the human body, as well as data derived from specimens, in order to screen or diagnose patients for

diseases or other conditions, monitor and prevent disease, and help determine appropriate treatments and cures.

IVD Instruments or Platforms – IVD tests are run in laboratories on instruments/platforms. Unlike manual tests developed by laboratories (see below) that may take significantly longer to return a result, IVD tests generally can return results in 1-4 hours or less. Platforms/instruments are devices that can be designed for use in small and large clinical labs, and even at the point-of-care, often with easy to follow and automated workflows and integrated software to perform accurate, reliable diagnostic testing.

> **While not universally the case, commercial tests typically have technical features and biochemistry unique to each manufacturer, so that specialized tests developed by a single manufacturer generally are suited to run on platforms also developed by that same manufacturer. The tests on these platforms all complement one another, because platform placement in hospitals and labs across the country and around the world is widespread.*

***In Vitro* Diagnostic Test Kit –** An IVD test kit consists of components and materials that are used to perform the diagnostic on an IVD instrument or platform*. While test kits may contain small numbers of tests, others contain up to 1,000 tests*. **In general, a single IVD test kit supports an average of 100 tests.**

An IVD test kit for COVID-19 testing generally consists of the following components:

- **Extraction Reagents** – These are the specialized materials used to extract the pathogen's RNA or DNA from the patient sample. These reagents are not specific to any particular pathogen.
- **Amplification Reagents –** These particular reagents and associated materials (probes, primers, enzymes) can allow for the replication of pathogen's RNA or DNA so that it can be detected. Amplification reagents are very specific to the pathogen a test seeks to detect.
- **Antibodies (for serology tests)** – Serology tests require synthetic antibodies made to detect human antibodies against COVID-19 virus and produce a signal that can be read by an instrument.
- **Internal Controls** – Materials or solutions used to verify that the instrument and reagents are functioning properly.
- **Other required materials that may not be included in an IVD kit:**
  - IVD instrument or platform to perform the test.
  - Patient specimen collection devices (such as swabs) and transport medium.
  - External Controls – to ensure the system, including specimen processing, functions properly.

Sourcing of IVD Platform/Instruments and IVD Tests and Test Kits: IVD supply chains are global, complex and interdependent. The many components of IVD instruments/platforms and IVD test kits are sourced from a multitude of entities across the U.S. and globally. Interruptions of the supply chain for one manufacturer or supplier can have an immediate, cascading impact on many other manufacturers and their customers.

Real-Time Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) Tests – Currently, the vast majority of COVID-19 testing uses the RT-PCR method. This method of testing detects the presence of the COVID-19 virus in a patient sample by detecting the virus' genetic material. (See more info above.)

Serology Tests – These are blood-based tests that can be used to identify whether individuals have been exposed to pathogens, such as COVID-19, by examining the presence of antibodies to the pathogen. (See additional info above.)

Antigen Detection Tests – These are tests that detect unique proteins or other molecular structures ("antigens") found on the surface of the COVID-19 virus. Many antigen tests can be designed to be rapid and used at the point-of-care.

Where IVD Tests are Performed

Medical Laboratory (or Clinical Laboratory) – Laboratory where, using IVD manufacturer platforms/instruments, clinical tests are carried out on specimens to obtain information about the health of a patient to aid in diagnosis, treatment, and prevention of disease. These labs can be found in hospitals, physician offices, clinics, and as standalone laboratories.

- Laboratories may develop their own tests, known as laboratory-developed tests (LDTs). These tests, performed on patient specimens that are shipped or brought in for analysis, are performed manually, generally significantly increasing the time it takes to return an actionable result. LDTs can only be developed and performed in labs with highly trained clinicians (e.g., PhD-level clinical microbiologists). Conversely, commercial IVDs that run on high throughput instruments can be performed in labs on site, often producing results in 1 to 4 hours, or in as little as 5 minutes in the case of point-of-care tests.

Reference laboratory – These are freestanding medical laboratories that are capable of performing more complex testing in larger volumes.

- These laboratories may also develop LDTs, as explained above.

Point-of-Care Testing – Developed and manufactured by IVD companies, these tests are performed at or near the site of patient care, wherever medical care is needed, including in physician offices, at the hospital bedside, clinic, or even the patient's home, and often providing results in minutes. (See additional info above.)

CLIA-Waived Testing – Developed and manufactured by IVD companies, these tests can be performed outside of the laboratory, directly at the point-of-care (e.g., a physician's office). (See more info above.)

How an IVD Test is Run: COVID-19

Sample Workflow for Performing an *In Vitro* Diagnostic RT-PCR Test to Detect the SARS-CoV-2 Virus:

Most COVID-19 diagnostics use the RT-PCR method and sample workflow below, where the patient sample is collected via a nasal or oral swab. Workflows may vary, including for point-of-care tests.

1. **Collect patient specimen** – may be done using a nasal or oral swab, depending upon the test.
2. **Put the specimen in transport media or test cartridge** to be transferred to a hospital laboratory or shipped or delivered to the laboratory or testing site.
3. **Place specimen in instrument**: After removing the patient specimen from the transport media, the specimen or cartridge with specimen is placed into the instrument for processing/testing.
4. **Prepare instrument**: Load the general reagents, primers/probes, extraction reagents and controls onto the IVD instrument.
5. **Run the test** to amplify the target RNA and report the results to the lab. (As noted above, IVD instruments are automated. Lab-developed tests are complex and require many manual steps.)
6. **Instrument produces results** that first have to be confirmed by the lab, showing that the test was processed without errors.
7. **Results are reported to health care providers to guide patient care**.