Regulatory Approach to Point-of-Care/At-Home Testing in the United States

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KEYWORDS

- Point-of-care testing • CMS (Centers for Medicare and Medicaid Services)
- COVID-19 testing • CLIA (Clinical Laboratory Improvement Amendments)
- Guidelines • Waived and home testing

KEY POINTS

- A huge benefit to laboratory testing occurred in 1988 and the 1990s resulting in more rapid results and improving patient care.
- Classification of laboratory tests as waived, moderate, and high complexity allowing for personnel responsible for performing tests, regulations including testing, oversight, and levels of complex and simplified testing laboratory classifications.
- Performing waived testing in the near patient setting with appropriate oversight to ensure accurate results.
- Modification of regulations to allow home-based testing and appropriate confirmatory testing.
- Consequences of failing to follow testing guidelines and possible effect on patient well-being.

INTRODUCTION

Laboratory testing is extremely important in diagnosing diseases and treating patients. It is arguably involved in 70% of medical diagnoses.[1–5] The accuracy and speed of results is important to accurately treat patients.[4,5] Until recently many nonlaboratory health care providers did not realize how important laboratory tests were and did not follow up with quality control, quality assurance, and training. Therefore the results were often questionable and could result in putting patients at risk.[1,5] During the most recent pandemic (COVID-19) it has become apparent that laboratory testing and accurate results are paramount to good patient care.[6] Results of important laboratory tests are often delayed because of the transport of samples to the core laboratory or reference laboratory. A multidisciplinary team is needed to institute laboratory testing, and it is important for the laboratory to lead and be part of this team.[5–9] These teams should discuss the advantages and disadvantages of performing tests either in the main laboratory or in

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the point of care (near patient testing) (POC).[5,7–10] Many things must be considered before approving tests for the laboratory: adequately trained technologists, directors that have expertise and knowledge in the laboratory of the new tests, the technology that is currently available, and support of nonlaboratory health care workers and physicians. Administration should also be on board with the testing offered. In particular, when complex testing, such as molecular testing, is being brought on board, several things mentioned previously must be considered.[4,5,8] This is an important task but is even more difficult when the testing is only approved by Emergency Use Authorization (EUA) and there are no standard Food and Drug Administration (FDA) comparisons and guidelines for preuse evaluation and comparisons with standard methods. This would mean that no standard approval or complex evaluation of the tests are performed as required by FDA before the pandemic.

HISTORY

POC testing has been active since ancient Egyptian times.[1,2] In the last 30 years it has become an important part of diagnosing diseases.[5] In particular, in 1988 the Clinical Laboratory Improvement Amendments (CLIA) were outlined to help classify laboratory tests and also to oversee the testing process.[1,3–5] Before this amendment, testing outside of the core laboratory was not regulated, which led to inaccurate results that put patients at risk.[1,4–8] Even after the institution of these guidelines, the testing personnel and laboratory directors did not follow testing guidelines and therefore many errors occurred in the results.[1,5] Following the waived testing study[1] the institution of inspections and following quality guidelines and manufacturer's instructions for waived testing as outlined by the companies that manufactured the tests was determined to be a problem in inaccurate testing.[1,5,8] Although it was concerning that health care workers and physicians would not follow laboratory guidelines and manufacturer's procedures, the general public with "at-home" testing may or may not follow good laboratory testing.[1,4,5]

The evaluation of waived laboratory testing over the years has proven that many testing sites do not follow guidelines, perform required QC/QA, or training or oversight of the testing personnel.[1,4] The waived laboratories must follow the most stringent requirements by either the state that they are in or the federal requirements. Some states accept federal requirements and others have more stringent guidelines. However, until laboratory inspections occurred in waived laboratories, errors were rampant and the process did not improve.[1,4]

During the worldwide COVID-19 pandemic the need for laboratory tests and availability for testing was off the charts. Testing started in the federal and state government laboratories and then went to academic medical centers. The need became so great that testing was increased across the United States with many sites performing testing including reference laboratories, small hospitals, physician offices, and drive-through sites for collection. The need was so great that millions of tests were being done and approval of new tests was required. The EUA was instituted during the COVID-19 pandemic and a total of 439 EUA tests were approved for use. This stimulated a concern about proper testing and training became a legitimate problem because many medical laboratory scientists became overworked and exhausted. With the numbers of laboratory workers already becoming difficult to recruit, POC and at-home testing became an option. Accuracy of testing is also of concern with at-home testing and testing at multiple sites in the population.

The number of laboratories and the numbers of waived tests have increased dramatically (**Fig. 1**). Waived testing laboratories are by far the highest number of laboratories in

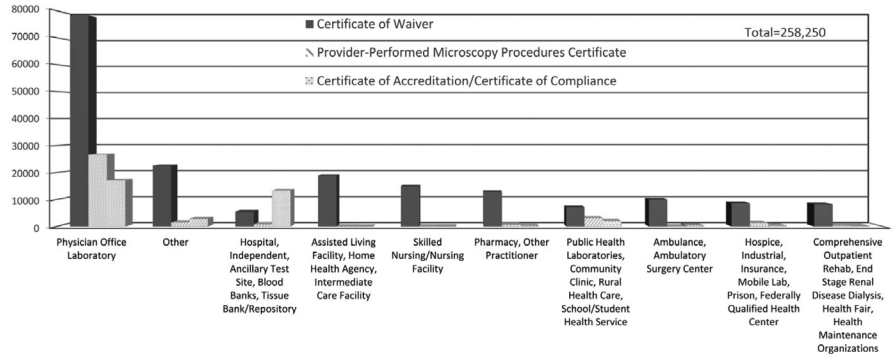

Fig. 1. US laboratory demographics, June 2017. (Data obtained from CMS Quality Improvement & evaluation System (QIES) database, 06/27/2017. Laboratory types in QIES data are self-reported. Numbers included laboratories in CLIA-exempt states of NY and WA. Data do not include CLIA certificate of registration laboratories. Anderson N, Stang H. Promoting good laboratory practices for waived infectious disease and provide-performed microscopy testing. Clin Microbiol Newsl 2017; 39:183-8.).

the United States with most of them having a CLIA waived certificate (see **Fig. 1**; **Fig. 2**).[1,5] They have grown immensely over the years.[1,4,5,10] The federal guidelines for testing in waived laboratories are much less stringent than nonwaived laboratories (**Table 1**). In addition, the number of analytes has also grown.[1,4,5,10]

Most waived laboratories use rapid antigen detection tests (RADT) for detection of infectious diseases. Typically these rapid tests are not sensitive and are typically dependent on and more reliable when the patient is demonstrating symptoms of the disease.[11] If they are tested without symptoms, the positive predictive value of their results is less than 50% even if the specificity of the test is 98%.[12] They are also dependent on the incidence of the disease in the population tested; with an incidence of 1% and a specificity of 98%, the positive predictive value would be 28.8%. This means that out of every 100 positive samples, close to 71.2% would be false positives.[11] This outlines why these positive tests should be confirmed with a more accurate test, such as molecular tests. If the incidence of the disease is high in the population and the patient has symptoms, the false-positive rate is much lower.[11]

Despite the nuances of mass testing, RADT used in Europe showed a decrease in active cases in spite of the parameters mentioned previously.[11] At-home testing of RADT was performed in the United Kingdom and the United States. Data from at-home testing show a significant decrease in sensitivity determined during testing by health care workers and the untrained performing testing, 70% to 77.8% in research and health care workers compared with 57.7% of untrained at-home testers.[11] At-home collection of swabs showed that only 80% of those collected were performed by clinicians.[13,14] The storage of the test kits can affect the sensitivity of the results.[11]

With the need for high-capacity testing during the COVID-19 pandemic, molecular testing has been approved for POC testing and possibly at-home testing. A more sensitive alternative, rapid molecular testing, is a possibility with high throughput. Rapid COVID waived testing does not really have a rapid throughput with a large number of samples and usually only tests for COVID.

Centers for Medicare and Medicaid Services (CMS) updated their guidance (October 7, 2022) on some of these concerning POC or inpatient care settings molecular and antigen testing requirements for certified laboratories performing FDA-approved EUA tests.[15] These antigen and molecular tests were approved under the

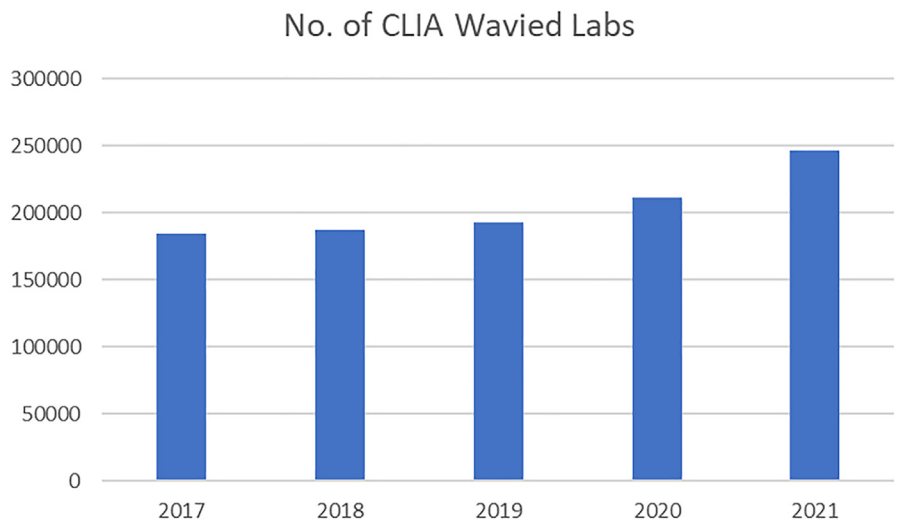

Fig. 2. The rise of certified waived laboratories and analytes "The Rise of POC Testing". (*Data from* CMS on the number of CLIA waived laboratories in the United States. https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/2021-1993_Historical_Numbers.pdf.)

EUA to be performed and requested by health care providers after onset of symptoms. CMS does not approve testing of patients that does not follow these guidelines, in particular those laboratories under the CLIA 1988 certificates and testing patients that are asymptomatic.[15] They must follow the instructions for use by the manufacturer.[15] Also, nonwaived laboratories must establish performance of the system before reporting patient results.[15]

COVID POINT-OF-CARE AND HOME TESTING

During the COVID pandemic testing had begun under EUA approved by the FDA. This outbreak was classified as COVID-19 and was caused by COVID-2 released from Wuhan, China. Many tests used in state and federal laboratories and core and reference laboratories were laboratory-developed tests. In a short period of time tests were

Table 1
The regulations for waived and nonwaived laboratories for POC and at-home testing[3]

Requirement	Waived	Nonwaived
Personnel	No requirement	Testing and leadership must have appropriate degree and training
Quality	Must follow manufactures' instructions	The laboratory must have a quality program
Proficiency testing	No requirement	External or alternative proficiency testing for all tests
Safety	No requirement	Safety procedures are required
Validation and verification	No requirement	Requirement
Enforcement	None	Biennial inspections
At-home testing	With approval	NA (Not Applicable)

available for other smaller laboratories and they were available from manufacturers, the numbers of which have exploded and EUA approval for COVID testing happened quickly. Millions of tests were performed in certified and accredited laboratories.[13,14] The testing was divided by the methods and analytes were approved to be used in high complexity, moderate complexity, and waived laboratories.[14,16] The total number of laboratories has increased. In September of 2022, the laboratory types are: certificate type (nonexempt only) compliance 17,708; waiver 243,951; provider performed microscopy 27,257; and accreditation 16,039.[17]

As of September 27, 2022, more than 430 COVID-19 tests have been approved for EUAs.[18] In this communication the director of the federal center for devices and radiologic health, stated that laboratory testing is key to combating the COVID-19 pandemic and if further methods of testing is required, that instead of approving them through EUA they should be approved using traditional premarket approval of these tests. "All tests for covid with molecular, antigen testing, and serology were approved for use in the laboratories in the United States."[18]

However, it also states that,[18]

"Moving forward, the FDA generally intends to focus its review on EUA requests and supplemental EUA requests from experienced developers for and not focus on at home testing but rather focus on the items below.

- Diagnostic tests that are likely to have a significant benefit to public health (such as those that employ new technologies);
- Diagnostic tests that are likely to fulfill an unmet need (such as diagnosing infection with a new variant or subvariant);
- Supplemental EUA requests for previously authorized tests when the request is intended to fulfill a condition of authorization or includes a modification that will significantly benefit public health or fulfill an unmet need; and
- Tests for which the EUA request is from (or supported by) a U.S. government stakeholder, such as tests funded by the Biomedical Advanced Research and Development Authority (BARDA) or the National Institutes of Health's Rapid Acceleration of Diagnostics (RADx)."

The federal administration has made available 350 million COVID tests to the public and delivered to their homes.[19] Although this allows most Americans access to testing, it does not do anything to ensure these tests will be done accurately.[1,4,5] There is no need for a physician's order for the test, no training of the testing individuals, no follow-up for either positive or negative tests, no capture of data to track the test results, and no pretest probability for the reliability of the test results. Although at-home tests do offer an avenue for the public to get testing done, it may not give accurate data to the family, their physician, or infection control and epidemiology.

Positives in Health Care for Doing Point-of-Care Testing

Some of the obvious advantages to POC testing are (1) rapid results, laboratory results available while the patient is evaluated by care givers; (2) current testing methods (NAAT [Nucleic Acid Amplification Test] and improved antigen testing) are robust and are sensitive and accurate; (3) some NAAT POC testing methods are now comparable with those methods offered in the core laboratory (https://www.cdc.gov/cliac/past-meetings.html); and (4) these are similar tests to sexually transmissible diseases, group A streptococcus, and some urine tests that clinics and physician's offices are used to running.[20]

Home test advantages are they allow families to test those that are sick and then distance them from their families if positive and if negative to not modify their activities, and

they give caregivers reason to expedite office visits for a positive patient. Negative antigen tests in symptomatic patients and positive antigen tests in asymptomatic patients are recommended to be confirmed with a NAAT test "Given rapid tests' lower sensitivities and specificities, it's a good idea to use a PCR tests to confirm positive antigen tests in asymptomatic individuals and negative antigen tests in symptomatic individuals, as well as close contacts of positive cases. A PCR test can act as a 'second opinion'." [21]

Possible Negatives of Performing Point-of-Care Testing

There some obvious negatives of performing COVID testing at the POC.[20] The overall cost of performing testing at the POC is a negative. Both reagent cost and the cost of instrumentation is high. This is why administration must be behind bringing the testing to multiple sites because the cost of running multiple sites with the same testing is large, so confirmation of the need to do this is extremely important. Another negative is that most of the testing at POC contains limited analytes.

Some challenges with POC include test performance by nonlaboratory personnel without training and guidance.[4] Quality concerns for waived laboratory testing includes: lack of training in testing and quality assessment, constant turnover of employees, and a total lack of personnel training. Strategies to address these concerns include administrative structure for organization and oversight before instituting testing. A laboratory stewardship team to oversee POC testing for good quality results is of utmost importance.[4,5,9] This is extremely important to address, training, constant oversight, following procedures, and maintaining procedure manuals (manufactures procedures), taking into account preanalytical, analytical, and postanalytical parameters to allow good samples, testing, and data management.[4,5] The flu variant of 2009 H1N1 actually was detected with higher sensitivity using DFA (Direct Flourescent Antibody) and polymerase chain reaction when respiratory cells were detected in the sample at levels of greater than 60.[22,23]

At-home testing during COVID showed a rise in the numbers tested and also opens up questions about its reliability and future of testing and diagnosing infectious diseases (discussed next).

THE FUTURE OF POINT-OF-CARE, NEAR PATIENT TESTING, AND AT-HOME TESTING

The future of POC and near patient testing is using evaluated test methods and following the guidelines for waived, moderate, and high complexity testing depending on the laboratory classification. Under the waived CLIA certificate, these sites will be following guidelines from state and federal guidelines. Those testing in laboratories will adhere to the current guidelines. Some things that must be concentrated on are found in Sautter and colleagues[5]:

- Managing College of American Pathologists, The Joint Commission, COLA, and CLIA inspections at the POC
- Turning nonlaboratorians into testing personnel
- Competency assessment and education
- Quality control, handling failures and review
- Managing outpatient clinics and family practice centers
- Gaining physician and nursing allies
- Evaluating new instrumentation and justification
- Controlling how POC testing gets into the facility
- Challenges of data management

In particular the management of testing during a pandemic is certainly contentious. We have seen this over the years; an example is the H1N1 outbreak of 2009, the largest viral pandemic outbreak in 40 years in 2009.[5,22]

An evaluation of testing done during the H1N1 outbreak in New York showed that the sensitivity of antigen tests for the variant flu virus was 17.8%.[11,24] The current testing for flu at the time was not adequate to detect the organism. Also questions about the sample type ideal for detection of the virus was also raised.[22] It is not unusual for pathogenic viruses to change with an antigenic drift that changes the virus minimally, this occurs with flu viruses and can change them enough that second infections can occur in a person that was previously infected.[25] However antigenic drift can also occur and is mostly associated with pandemic flu, such as H1N1.[25]

During the COVID-19 pandemic five waves and three variants occurred over time and resulted in changes in infectivity and severity. These changes are called lineages of the virus (genetic variations).[26]

At-home testing opens many questions about reliability and concerns of the need and whether they will help the patient (eg, did they have symptoms, did their caregiver suggest testing, and many others). However, the White House memo discussed later seems much more reasonable. Including education of patients and providers has expanded the testing for COVID.

The institution of sending millions of COVID tests out to the public and not requiring potential patients to report the result can be worrisome. During this time of many hundred types of tests approved by EUA, it is almost impossible to capture the results of POC and home testing to assess the incidence of disease. Putting the testing results, immunology rates, and mortality rates into data files and sharing this with government leaders and health care professionals while keeping staff safe during these pandemics is an extremely important postanalytical phase of testing.[9]

One laboratory-developed test from the Centers for Disease Control and Prevention was available in about 2 months from the start of the outbreak and available to state health departments and large health care organizations; manufacturers' testing was available many months later. There were no EUA approvals for testing in health care settings or home testing, such as was available for the COVID outbreak. Evaluation of other viral detection methods (DFA, antigen testing, culture, and others) had to be evaluated by the laboratories to make sure they could detect the H1N1 variant.[27]

With the start of laboratory testing for COVID-19 many tests were EUA-approved and also some were approved for POC and in-home testing. Antigen tests are not as sensitive and robust as molecular tests. As the virus mutated and produced other variants, the likelihood of being able to detect the disease was in question.[11]

SUMMARY

The COVID-19 outbreak and pandemic resulted in many more deaths and infections across the world compared with recent viral infections. It became and still is a danger during a contentious time in the world in general. Testing was brought to laboratories in the United States as soon as possible with no manufacturer's approval from standard FDA evaluations. The speed at which testing was done was amazing and eventually resulted in hundreds of tests available for serology, antigen testing, and molecular NAAT. Under the previous and current White House leadership COVID testing and vaccinations became available much faster than previous H1N1 vaccines and testing.[22] This was achieved using an EUA and was done when no approved alternatives were available.[9] The Centers for Disease Control and Prevention and state

public health laboratories, as they did for H1N1 testing, began testing for COVID-19. Unlike the H1N1 outbreak, where no EUA approval was instituted, testing for COVID was started following EUA by large reference laboratories, academic centers, and private large hospital systems.[7] This testing expanded into hundreds of thousands of tests each day, in addition to many POC sites across the country. It is clear now the importance of laboratory tests and medical laboratory scientists in making disease diagnosis.[9,17] Good laboratory practices must be followed, especially during a deadly pandemic, such as COVID. Diagnostic management teams, laboratory stewardship, and laboratory technology teams are needed to choose accurate testing methods.[1,5] Some of the most important parameters are the preanalytical, analytical, and postanalytical test phases.[5] There is a need to focus on all phases of testing. Of concern is that 70% of laboratory errors are associated with preanalytical errors.[1,3,5,6,8,9]

Testing in the future is discussed in an FDA news release.[18] Although the FDA is suggesting review of new tests using a 510K evaluation, they also think that some EUA approvals may also occur. When changes in the wave of infections with variants of the virus occur then new testing may be needed. To date five waves of infections have occurred and three variants have been seen in the United States. The most transmissible variant is the Omicron variant. Fortunately, the Omicron variant does not have the high mortality rate that previous variants had but is very communicable and has quickly spread throughout the United States. The institution of vaccines, therapy, and laboratory testing has aided the health care field in battling this pandemic.

A recent White House memo states that: "The nation's testing supply has increased dramatically. We now have free testing sites at 21,500 locations around the country. In January 2021, there were no rapid, at-home tests on the market available to Americans; during January 2022, there were more than 480 million at-home tests available to Americans on top of all other testing options."[28] In addition, in-home testing must be regulated and not be done with millions of tests sent to the general public for use. This was and is a concerning approach to testing and monitoring the population. No control or training was done and no data were available from most of this testing. The Federal government and administration has mentioned that updates and guidance will be available. "The Administration will put forth new educational efforts for the public and providers so that Americans can rapidly access treatments. The Administration will establish 'One-Stop Test to Treat' locations at pharmacy-based clinics, community health centers, Long-Term Care Facilities, and the U.S. Department of Veterans Affairs (VA) facilities across the country. 'One-stop' sites will be operational by March."[28]

It is unclear what will be available in the future for COVID testing or reacting to another pandemic. However, after going through two enormous pandemics over the last 10 to 13 years (H1N1 and COVID-19) we are much more prepared for another outbreak and could respond in several different ways. As the White House memo states, "As the country emerges from the Omicron wave, our path forward relies on maintaining and continually enhancing the numerous tools we now have to protect ourselves and our loved ones–from vaccines, to tests, to treatments, to masks, and more."

One can only hope that we will be prepared for any new viral pandemic or for variants of the COVID-19 infections. We must learn from our history (quick testing platforms, vaccinations manufactured, distribution of vaccines, and recruiting and listening to laboratorians about the critical needs for this specialty)[29]; we must remember from 2009 to the present to protect our population from serious infections.

CLINICS CARE POINTS

- Follow Best Practices During Testing: The Pre-analytic phase, Test orders, Patient identification, Pretest instructions and information, Specimen collection and handling.
- The Analytic Phase, Quality Control (QC), Test Performance, Results Interpretation.
- Resolving problems; The Post-analytic phase :Reporting Test Results, Confirmatory testing, Maintaining records of referred testing [22].

DISCLOSURE

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