CDC Advisory Committee to the Director (ACD) Laboratory Workgroup (LW)

Review of the Shortcomings of CDC's First COVID-19 Test and Recommendations for the Policies, Practices, and Systems to Mitigate Future Issues

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I. Introduction

In January 2020, the Centers for Disease Control and Prevention (CDC) worked swiftly to develop and distribute a laboratory diagnostic test for the novel coronavirus then spreading around the globe. Unfortunately, the CDC failed at this task. The test as initially sent to state and local public health laboratories could not be used.

For several critical weeks, CDC was the only laboratory in the nation able to perform COVID-19 testing. Lacking awareness of how rapidly and widely the virus was spreading, public health agencies were slow to recommend behavior changes or implement protective measures. While peer nations dramatically increased their testing capacity, the US remained well below the testing capacity needed to understand the situation and begin to identify infected individuals to slow disease spread.

The failure of the CDC's diagnostic test for the virus, later named SARS-CoV-2, was far from the only significant misstep in the federal government's overall response. But it was one of the first and most consequential.

Our charge in this report is based on the following language from the [2021] report of the Labor-HHS Appropriations Committee: The language states:

> *The agreement includes direction in the Office of the Secretary to establish a Task Force, including participation from outside stakeholders and subject matter experts, to evaluate what contributed to the shortcomings of the first COVID-19 tests, including laboratory irregularities, and what policies, practices and systems should be established to address these issues in the future.*
>
> *The Task Force shall also examine CDC's processes for the development and deployment of diagnostics and its ongoing operations, including communications and electronic laboratory reporting with clinical, commercial reference, and State and local public health laboratories.*

We appreciate the CDC for convening our group to examine the processes, policies and systems that led to the failure of the SARS-CoV-2 test.

II. Methods

The Advisory Committee to the Director appointed a laboratory workgroup after a solicitation published in the Federal Register on May 4, 2022. The workgroup includes 12 subject matter experts, including three full-time academic faculty members, three directors of large clinical laboratories, one senior scientific director of a large commercial reference laboratory, one regulatory expert, one senior scientist representing a major diagnostic manufacturing company, four directors of state public health laboratories, one state epidemiologist and an executive officer of the Council of State and Territorial Epidemiologists, and one science advisor from the Association of Public Health Laboratories.

To address the task for this report, the workgroup requested and received briefings from CDC officials, reviewed documents, and met three times – virtually on October 18, 2022, in person on

December 1 and 2, 2022 to discuss findings and recommendations, and again virtually on January 12, 2023. The December 1 meeting included a tour of the CDC's laboratories. As part of its meeting on December 2, the Workgroup convened an external panel of subject matter experts to explore issues involving reporting of laboratory results to state laboratories and the CDC.

The CDC provided extensive briefings and documents to the Workgroup for its review. The CDC did not make available the former director of the Respiratory Virus Diagnostics Laboratory, but the workgroup was able to review the report of the Senate Governmental Affairs Committee,[1] which did interview him.

III. What Contributed to the Shortcomings of the First COVID-19 Tests

On February 6, 2020, just weeks after the emergence of SARS-CoV-2, CDC began shipping test kits to state and some local public health laboratories. These tests were polymerase chain reaction, or PCR, tests containing oligonucleotide primers and probes to bind to and identify the virus.

The CDC's original test kits included three primer/probe sets that match to different parts of the genome of SARS-CoV-2: N1, N2, and N3. N1 and N2 were designed to match to SARS-CoV-2 uniquely. N3 was designed to match to sequences found in all sarbecoviruses (the family to which SARS-CoV-1 and SARS-CoV-2 belong), including SARS-CoV-1, the virus that caused the 2003 SARS outbreak.

Within two days, however, multiple laboratories reported problems with both N1 and N3 components. On February 10, the CDC announced an investigation into the cause of the problems. On February 26, 2020, the FDA gave permission for the CDC test kits to be used without the N3 component. The CDC began to re-manufacture the kits containing both N1 and N2 probes and permitted public health laboratories to move forward with testing. By March 3, 2020, 46 public health laboratories were able to use the new tests. Delays in the launch and scale-up of accurate laboratory testing contributed to the initial failures in the pandemic response, particularly in New York City.[2]

In published articles and statements, the CDC has publicly identified three major causes of its failure with the initial COVID test: contamination of the N1 probe, poor design of the N3 probe, and inadequate quality control prior to distribution of the test.

Contamination of the N1 probe. To determine whether a test works, developers generally apply the test to samples that contain the pathogen itself. For SARS-CoV-2, however, the CDC needed to make a diagnostic test quickly -- even before the agency had in its possession an actual sample of the virus. To do so, the agency used the published genetic sequence of the virus to manufacture its own

[1]Historically Unprepared Examination of the Federal Government's Pandemic Preparedness and Initial COVID-19 Response. A HSGAC Majority Staff Report. December 2022. https://www.hsgac.senate.gov/imo/media/doc/221208_HSGACMajorityReport_Covid-19.pdf.

[2] Pei S, Kandula S, Shaman J. Differential effects of intervention timing on COVID-19 spread in the United States. Sci Adv. 2020 Dec 4;6(49):eabd6370. doi: 10.1126/sciadv.abd6370. PMID: 33158911; PMCID: PMC7821895.

version of viral material, which we will refer to as the "CDC-manufactured positive control." CDC officials were aware that if even minute amounts of the CDC-manufactured positive control were to contaminate test kits, then the test kits would be unusable because there would be "false positives" due to detection of the CDC-manufactured positive control material.[3]

After problems with the tests emerged, the CDC found that contamination did in fact occur, for the N1 probe portion of the test kits. The CDC believes the contamination occurred in the laboratory that played a key role in both designing and assembling the test kits, known as the Respiratory Virus Diagnostics Lab, or RVD lab.[4] The former director of the RVD lab, however, provided Senate investigators his view that the contamination occurred in a different laboratory, known as the Core Lab. This is the laboratory that manufactured both the CDC-manufactured positive control and the N1 probe.[5] We did not investigate further to distinguish between these possible sites of contamination; it is our view that the implications for policy are similar regardless of where the contamination occurred.

Poor design of the N3 probe. A review by CDC scientists found the N3 probe had defects in design that led it to yield positive results when results should have been negative.[6] The evidence for this conclusion includes computer modeling that indicates the potential for the probe to bind to the 3' end of the N3 reverse primer and generate this false positive error, and the identification through sequencing of primers binding together. Evidence also includes the high failure rate of N3 across multiple laboratories -- without evidence of contamination with the CDC-manufactured positive control. Nonetheless, the former director of the RVD laboratory told Senate investigators his view that N3 was well-designed, and that contamination was the likely reason for its failure. In our view, the CDC's published explanation is more consistent with available evidence.

Failure of quality control. Prior to releasing test kits to state public health laboratories, the RVD laboratory performed a test for quality. The CDC found that the first round of quality control testing "used an 'incorrect' testing procedure," and that during a second round of quality control testing using

[3] This "false positive" would occur during the quality control of the test, rendering it unusable. The problem would be identified before patient samples would be reported, so there would not be "false positive" patient results.

[4] Lee JS, Goldstein JM, Moon JL, Herzegh O, Bagarozzi DA, Jr., Oberste MS, et al. (2021) Analysis of the initial lot of the CDC 2019-Novel Coronavirus (2019-nCoV) real-time RT-PCR diagnostic panel. PLoS ONE 16(12): e0260487. https://doi.org/10.1371/journal.pone.0260487

[5] Historically Unprepared Examination of the Federal Government's Pandemic Preparedness and Initial COVID-19 Response. A HSGAC Majority Staff Report. December 2022. https://www.hsgac.senate.gov/imo/media/doc/221208_HSGACMajorityReport_Covid-19.pdf.

[6] Similar to the N1 problem, this "false positive" would occur during the quality control of the test, rendering it unusable. The problem would be identified before patient samples would be reported, so there would not be "false positive" patient results. Lee JS, Goldstein JM, Moon JL, Herzegh O, Bagarozzi DA, Jr., Oberste MS, et al. (2021) Analysis of the initial lot of the CDC 2019-Novel Coronavirus (2019-nCoV) real-time RT-PCR diagnostic panel. PLoS ONE 16(12): e0260487. https://doi.org/10.1371/journal.pone.0260487

a correct procedure, 1 of 3 kits failed. Yet this finding "did not result in a kit recall or performance alert to …Test Kit recipients, and the faulty tests were distributed."[7]

Consistent with our charge, we evaluated contributions to these shortcomings – focusing on the "causes of the causes." We found four major issues.

A. Inadequate Planning

Timely development of a laboratory test for an emerging infectious agent requires a dedicated plan that encompasses all activities, from test design through distribution. However, in early 2020, the CDC did not have a comprehensive plan in place for rapid development, validation, manufacture, and distribution of a test for a novel pathogen.[8]

In response to our request for planning documents that existed in January 2020, the CDC provided an existing plan for "graduated response" – which was intended to allow for the scale up of efforts at the Center level without a full agency-wide response.[9] The CDC's planning document explained that "most responses do not warrant a CDC activation," and introduced the concept of graduated responses to help "differentiate between normal program work and Center responses."

The "graduated response" plan lacked key details relevant to test development. It did not set out a governance structure, timing, a plan for redundancy in test development, engagement of the private sector or other essential elements of a laboratory response plan for a novel pathogen threatening the entire US population. It also did not contemplate a transition from "graduated response" to agency activation.

As a result, the CDC lacked a useful plan for test development and deployment as the early days of what would become the COVID-19 pandemic unfolded.

One example of the failure of planning relates to the contamination of the N1 probe with the CDC-manufactured positive control. There was controversy within the CDC over whether to use the Core Laboratory -- where the probes for the test kits would be manufactured – to also make the CDC-manufactured positive control. It was known that manufacturing both components in the same physical space would increase the risk of contamination of the final product. Because of the perception that there was no reasonable alternative approach to quickly gain access to positive control material, the Core

[7] Office of Laboratory Science and Safety. Root-Cause Analysis: Unanticipated Failure of the 'CDC 2019-Novel Coronavirus (2019NCoV) Real-Time RT-PCR Diagnostic Panel. Issue Date 24 March 2020. Updated 5 October 2020. The director of the RVD laboratory told Senate investigators that the individual failure rates of the components were lower than the failure rate of the kit itself. However, it is our view that the individual failure rates were still far higher than would be expected for a successful test, and the high failure rate of the kit itself was a major indication of a problem with the test.

[8] This inadequate planning is surprising as lack of planning was previously identified as a point of failure in establishing and rapidly deploying a Zika test in 2015.

[9] CDC, Framework for a Graduated Public Health Emergency Response. 7 May 2019.

Laboratory did manufacture the positive controls (taking what its staff considered extra precautions against contamination) despite the known risk.

Regardless of where contamination happened, the use of the laboratory to manufacture the positive control introduced an unnecessary risk. With better planning, the CDC could have been ready to utilize an alternative laboratory altogether for manufacturing the positive control quickly either elsewhere on campus or in the private sector.

B. Ineffective Governance

Effective governance, fundamental to laboratory operations at all times, is especially critical during public health emergencies, when collaborations across laboratories are required to design, validate, manufacture, and distribute a new test.

Three labs at the CDC -- the Respiratory Virus Diagnostics Laboratory (RVD), the Core Lab, and the Reagent and Diagnostic Services Branch (RDSB) – were all involved in manufacturing the SARS-CoV-2 test. The RVD laboratory designed the test and assembled key components. The Core laboratory made the test materials. The Reagent and Diagnostic Services Branch did the final packaging.

At no point, however, were these three laboratories brought together under unified leadership to develop the SARS-CoV-2 test.

Before the pandemic. The three laboratories reported to different Centers within CDC, with the RVD laboratory reporting to the Division of Viral Diseases within the National Center for Immunization and Respiratory Diseases (NCIRD), and the RDSB and Core Laboratory reporting to the Division of Scientific Resources within the National Center for Emerging and Zoonotic Infectious Diseases (NCEZID). There was no strong cross-cutting laboratory leader or other governance process in place. This gap may have contributed to the absence of a plan for events like the pandemic.

The first weeks of the response. The CDC laboratories implemented the "graduated response plan," which brought more staff resources to the laboratories. This period covered the vital early days of test development at CDC. It also saw the beginning of challenges with the SARS-CoV-2 test, including:

- *No single point of coordination between the three involved laboratories as to how an accurate test would be designed, validated, manufactured, and distributed.* This lack of coordination appears to have created multiple opportunities for contamination.
- *Difficulty implementing a quality management system for test development*. As described in more detail in Section 3 below, the "graduated response" apparently did not adopt a proven quality management system across the involved laboratories.

- *Errors in test design.* As described in more detail below, the lack of a well-defined governance process or use of best-practice software to help to design the test during this phase appears to have contributed to an insufficiently deliberative test design process, leading to errors.

During this phase, those in charge of test development in the RVD laboratory reported to non-laboratory specialists who may have lacked the expertise to critically evaluate technical laboratory processes and complex data sets.

Incident Management. On January 20, 2020, the CDC established an agency wide incident management system, or IMS, to respond to the COVID-19 pandemic. The purpose of an IMS is to establish clear and effective leadership, as well as to ensure that agency leadership is regularly informed of potential challenges which might impact the response.

With respect to the development of the SARS-CoV-2 test, the IMS structure included an Associate Deputy Incident Manager responsible for the laboratory effort. This leader oversaw the Laboratory Task Force, which included a diagnostic testing component, led by the RVD director.[10]

In practice, however, this incident management structure failed to work effectively. The IMS did not include the Core laboratory, so even with agency-wide mobilization, there was no unified leadership for all three involved laboratories. In addition, the Associate Deputy Incident Manager stated that she was not empowered to oversee test development. The RVD laboratory director reportedly utilized usual chains of command or circumvented the chain of command within the IMS to speak to senior leaders directly.

These IMS failures led to delays in understanding the scale and cause of the test problem across the CDC. For example, the Associate Deputy Incident Manager and others responsible for the laboratory team stated that they did not learn quickly about complaints about the performance of the CDC-manufactured IVD test that were sent from state laboratories to the RVD lab. Similarly, these officials stated that they did not learn for months about the quality control failures that occurred just prior to distribution. Further, they indicated that understanding these issues earlier might have led to different decisions on test development, validation, and distribution inside and outside of CDC.

The failure of the IMS structure to understand challenges in the development of the SARS-CoV-2 test also impeded transparency with partners, including state and private laboratories, some of whom could have developed their own tests sooner had they known of the scale of the CDC's challenges.

C. Inadequate Quality Control, Quality Assurance and Regulatory Oversight

Quality control and quality assurance are essential to successful development, validation, and implementation of any laboratory test. In reviewing what went wrong, the CDC identified one failure in quality control that occurred just before release of the test kits. This was far from the only failure of

[10] CDC. 2019 NCoV Response Organizational Chart. 30 January 2020 (1030) No Names.

quality control. We identified the lack of an effective quality management process throughout the test development, validation, and manufacturing phases. Essentially, at the start of the pandemic, infectious disease clinical laboratories at CDC were not held to the same quality and regulatory standards that equivalent high-complexity public health, clinical and commercial reference laboratories in the United States are held. Also, CDC did not use good laboratory processes for the manufacture and distribution of its clinical diagnostic SARS-CoV-2 test.

During the early graduated response phase, rather than using an existing quality management system, CDC officials told us that a new approach was established. This approach was described as "difficult to stand-up" and lacked clarity regarding the critical aspects of test design, validation, and manufacture. It apparently drew upon elements from different programs; referring to the acronym for Quality Management System, CDC officials described it to us as a "Franken-QMS hybrid." In essence, there appears to have been no reliable quality management system in place to guide early response activities.

The failure to establish a strong quality approach to test development reflects failures in planning and failures in governance, as noted above. After the manufactured test was distributed to state and local public health laboratories, many did employ effective quality control processes before using the test. After public health laboratories reported quality control failures of the CDC-manufactured test, the CDC apparently suggested that the problem could be found in the public health laboratories' own quality systems. Instead, the failure was at the CDC.

The CDC's root cause analysis of the manufactured test's failure focused on the erroneous release of faulty tests for distribution. However, even this investigation did not follow best practices for such reviews within the CDC.[11] Typically, root cause analyses look for an underlying cause or causes, not only the proximate step before failure.

It is important to ask why external regulators did not identify the failures in quality control before distribution of the CDC test. There are two agencies that have relevant regulatory authority: the Centers for Medicare and Medicaid Services, under the Clinical Laboratory Improvement Amendments, or CLIA; and the U.S. Food and Drug Administration (FDA), under the Food, Drug, and Cosmetic Act.

CLIA applies only to the use of in-vitro diagnostic tests for patient care and not the manufacturing and distribution of in vitro diagnostic tests. Much of this manufacturing apparently occurred in laboratory spaces where CLIA-licensed testing was not performed (This is permitted by law).

The CDC submitted information about its SARS-CoV-2 in-vitro diagnostic test kit for emergency use authorization from the FDA prior to distribution. The submission occurred on February 3, 2020, and FDA granted the emergency use authorization the following day. The submission was

[11] National Center for Immunization and Respiratory Diseases (NCIRD). Root Cause Analysis (RCA) Tools Job Aid. 29 August 2018.

based on data from the test kit that CDC used internally, which did not show test failures in N1 or N3.[12] By the time the final quality control had taken place on the test kits that CDC was sending out to state laboratories, the FDA had already granted an emergency use authorization.[13]

D. Poor Processes for Test Design

If, as the CDC found and we are inclined to agree, there were design flaws in the N3 probe, the decision to include N3 in the SARS-CoV-2 test kit had substantial negative consequences. The N3 probe was not included in European tests; the justification for its use was to have a useful test in case mutations in the virus rendered the other probes ineffective.

It appears that the decision to include N3 probe was made by the RVD laboratory director, during the "graduated response" phase of the response. The Senate investigation reported:

> [The RVD laboratory director] told Senate Committee staff that he presented a plan to CDC officials on January 15, 2020 for developing both the in-house CDC test and a test to send state public health labs. According to [the RVD laboratory director], the purpose of the January 15 meeting was to inform CDC officials and obtain their approval, of the RVD lab's intended process for manufacturing the first test kits … [The RVD laboratory director] told the Committee that his superiors within CDC approved the plan.[14]

The nature of test review by "superiors at CDC" is not explained in the Senate report. We asked the CDC whether there was a design control process involving laboratory experts, with discussion, deliberation, and sign off. The CDC indicated that the agency did not have evidence of the use of such a process. Greater attention at this specific moment may have made an enormous difference, as,

[12] The reported non-failure of the N1 primer/probe in the CDC's internal test is not difficult to explain. It is attributable to the fact that there was no contamination in the batches of primers/probes used for the clinical testing conducted at CDC.

The reported non-failure of the N3 primer/probe is more complex issue. The CDC's PLoS study reported that "pre-EUA" lots of primers/probes did show problems with N3. The discrepancy between the PLoS study and the application for emergency use authorization could be due to the fact that fresher batches of the N3 primer/probe appear to have been less likely to experience problems. More investigation would be needed to fully understand the apparent non-failure of N3 in clinical testing conducted at the CDC, as reported in the application for emergency use authorization.

[13] The FDA's review focuses on the accuracy of the test, not quality control for individual lots of test materials. However, the absence of these data made it impossible for the FDA to spot the problem.

[14]Historically Unprepared Examination of the Federal Government's Pandemic Preparedness and Initial COVID-19 Response. A HSGAC Majority Staff Report. December 2022. https://www.hsgac.senate.gov/imo/media/doc/221208_HSGACMajorityReport_Covid-19.pdf. P155

according to the CDC, available computer models for probe design could have predicted the failure of the N3 component.[15] Using such models is a common practice in test design.

To be clear, the desire and decision to include a target that would react to all sarbecoviruses (the goal of N3) in the CDC test was not the point of failure. Rather, the design and validation of the N3 primer/probe is where the failure occurred. Detecting and preventing the poor performance of the N3 primer/probe did not occur before it was manufactured and distributed.

A related failure of test design was the lack of clearly defined pass/fail threshold criteria for test validation. This failure set the stage for the failure of quality control just before dissemination; despite 1 in 3 test kits failing, the CDC still sent the manufactured IVD test kits to public health laboratories.

IV. What Policies, Practices, and Systems Should Be Established to Address These Issues in the Future?

Our review finds that there was no single point of failure for the CDC's test for SARS-CoV-2. Rather, the inability to rapidly develop an effective test for a global pandemic reflected systematic failures across the agency – failures of planning, governance, quality control, and test development. It follows that major changes in policies, practices, and systems are needed for the CDC's laboratories to attain high quality standards.

Significantly, over the last several months, the CDC has made addressing challenges with its clinical laboratory enterprise an urgent priority. Some of our recommendations, detailed below, overlap with moves that CDC has proposed or is in the process of advancing. Others would go further.

Where these recommended changes require new resources, Congress should provide them. Once implemented, these changes should lead to far stronger and more effective laboratories at the CDC, supporting work against a broad range of threats to the American people.

A. Leadership and Management

Fundamentally, the failure of SARS-CoV-2 test development was a consequence of major gaps in leadership and management at the CDC. Leadership should plan for anticipated challenges. Management systems should assume that human error will occur and put in place mechanisms to catch and remediate errors before harm occurs. In January 2020, there was no clear leader responsible for emergency planning for laboratories, nor was there an effective management structure in place.

The current organizational structure has laboratory functions scattered across the agency, with more than 100 different laboratories reporting in various forms through multiple chains of command.

[15] Lee JS, Goldstein JM, Moon JL, Herzegh O, Bagarozzi DA, Jr., Oberste MS, et al. (2021) Analysis of the initial lot of the CDC 2019-Novel Coronavirus (2019-nCoV) real-time RT-PCR diagnostic panel. PLoS ONE 16(12): e0260487 https://doi.org/10.1371/journal.pone.0260487

Our recommendations are intended to support the key people and functions necessary for clinical laboratories at the CDC to fully support the agency's mission.

Recommendation 1: There should be a senior leader for laboratories, reporting to the CDC Director, with major responsibility and authority for laboratories at the agency. This position should be a deputy director or equivalent position within the CDC's organization.

The laboratory leader should have the authority and responsibility to:

- set policy for the CDC's clinical laboratory functions, including quality, efficiency, and timeliness in both the CDC's laboratory response to emergencies and in day-to-day laboratory operation;
- develop a cross-Agency plan for the initial design and development of a test for a novel pathogen that threatens the population; and
- oversee safety across all basic research and clinical laboratories.

The person in this position should also, on behalf of the CDC, lead the development of a national laboratory system. Until now, the CDC has primarily viewed itself as just one part of a complex set of organizations and companies that produces diagnostic tests. The pandemic, however, revealed that greater organization of this system is needed for the nation to have ready and equitable access to a sufficient supply of diagnostic tests for novel threats. The role will involve working with the FDA, state and local public health laboratories, hospital and academic laboratories, diagnostic manufacturers, and commercial reference laboratories to plan and operationalize the ability to rapidly develop, scale and deploy needed tests. It will involve engaging with critical gaps in the supply chain that became evident during the pandemic.

An additional role for this senior leader is to head CDC's engagement in national research and development efforts in laboratory science. There are enormous opportunities in developing new technologies through partnerships with the National Institutes of Health, Biomedical Advanced Research and Development Authority, and the new Advanced Research Projects Agency for Health.[16]

Recommendation 2: The CDC should consolidate key laboratory support functions into a new Center. This Center should focus on clinical laboratory quality, laboratory safety, workforce training, readiness and response, and manufacturing.

The new Center, which should report to the new laboratory leader, should bring together necessary laboratory leadership and support functions, including:

[16] During the COVID-19 pandemic, the National Institutes of Health launched RADx, a public–private innovation program which has provided manufacturers with incentives to develop new technologies, as well as guidance on what is needed in the field. BARDA works with manufacturers to develop diagnostic tests and purchase diagnostic tools, therapeutics, and preventative measures, such as vaccines. The Advanced Research Projects Agency for Health, a new agency within the National Institutes of Health, is expected to drive innovation for new generations of laboratory testing.

- The Office of Laboratory Science and Safety, which oversees quality management programs and laboratory safety across the Agency;
- The biological arm of the Laboratory Response Network Program, LRN-B, which brings together state and local public health laboratories across the country to deploy new laboratory tests for infectious diseases;
- The Division of Scientific Resources, which, among other functions, manufactures reagents used in emergency response testing, including primers and probes for PCR testing; and
- The Division of Laboratory Systems, which focuses on outbreak preparedness, communication with public health partners, laboratory quality and workforce training and development.

The new Center – acting through the authority of the senior laboratory leader and the Office of Laboratory Science and Safety -- should be able to set laboratory quality standards, enforce those standards, audit for compliance with the standards, and oversee the quality assurance program for all laboratories at the CDC. This coordinated oversight will enable better communication and drive the needed culture change around laboratory quality. The Center should serve as a clear point of responsibility and organized structure for major laboratory decisions and provide a structure to communicate with CDC leadership on a regular basis.

The formation of a Center will require careful attention to organizational change management on a clear and reasonable timeline. This Center would also assure that laboratory quality and manufacturing decisions are coordinated and consistent throughout the agency and be a source of expertise for clinical laboratory directors across the agency.

Recommendation 3: The CDC should create and exercise plans for developing tests for novel public health challenges that include the governance structure to be utilized in an emergency.

During the COVID-19 pandemic, neither the "graduated response" nor the IMS functioned as needed for the development of SARS-CoV-2 tests. The new laboratory leader, working through the new laboratory Center, should address this problem by creating and exercising plans for the development of tests for any novel threat, including infectious, toxic, or environmental. The plans should:

- specify the governance structures to be used across CDC laboratories, providing a clear point of responsibility for all related tests at every stage of emergency response, building on changes that have been made in emergency lab governance in the last year;[17]
- integrate with the actions of state and local public health laboratories and health departments, hospital and academic clinical laboratories, commercial reference laboratories, and diagnostic test manufacturers, so that tests are not just developed quickly and effectively, but also able to be scaled and distributed;

[17] Centers for Disease Control and Prevention. Guidelines for Standing-up CDC Laboratory Functions During an Emergency Response. 14 July 2022.

- ensure that the expertise, standardized processes and established relationships of the Laboratory Response Network are made fit-for-current-purpose and utilized as part of an emergency response plan;
- provide the CDC leadership and external partners with information regarding laboratory issues during an emergency response;
- assure that, in advance of clinical testing, a validation plan, including criteria for acceptance and non-acceptance, is developed; for pathogens of pandemic potential, a generic validation plan could be pre-developed, so as not to lose time during a pandemic.[18]

The plans should address other critical steps in test development, including:

- incorporation of appropriate controls;
- assessment of test sensitivity, specificity, inter-assay reproducibility, intra-assay reproducibility and accuracy;
- development of a detailed standard operating procedure addressing acceptable specimen types, specimen stability, safe specimen handling, sources of reagents and equipment;
- an algorithm for defining possible results;
- definitions of test failure and how these should be handled
- a description of workflow;
- the strategy used for minimizing assay contamination; and
- and assessment of proficiency testing.

For nucleic acid amplification tests, the plans should make sure that there is adequate attention paid to the selection of target gene region(s) to be amplified and primer and probe binding sites, by both *in silico* and *in vitro* studies. The CDC should also develop plans for other testing modalities (e.g. serology) in the case that such testing modalities would be most appropriate for the yet-to-emerge novel pathogen. For all tests, the plan should require that a document control process be used.

The plan should specify the agency's approach to regulatory oversight in emergency circumstances. Under federal law, all CDC-manufactured test kits sent must be reviewed by the FDA.

B. Quality

Today, if the CDC director were to convene all the people directly responsible for clinical laboratories at the agency, more than 100 people would attend the meeting. That is because clinical

[18] The FDA website provides clear examples of templates that specify the information and data that are required for FDA-authorization under an EUA. These templates would provide an excellent model for a generic validation plan. https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas

laboratories exist in multiple divisions and branches, often reporting to non-laboratory experts. This diffuse structure reflects the fact that laboratories at the CDC perform many different functions, including diagnostic testing, clinical test development, public health surveillance, and basic science research. Many of these activities are comingled in the same laboratory spaces and are performed by the same laboratory scientists. It has been described that a scientist at the CDC may perform basic science research or test development in the morning and then perform CLIA-regulated diagnostic laboratory testing in the afternoon.

Unfortunately, this structure leads to inconsistent and ineffective oversight, intermingling of research and clinical laboratory testing, and clinical laboratory decisions being made by experts in basic science research (or non-laboratory experts) rather than by certified clinical laboratory professionals.

Moreover, it is difficult to correct critical quality issues in the current structure. It would be nearly impossible for the CDC to hire enough clinical laboratory directors and technical experts to meet personnel requirements under CLIA for all of its laboratory teams.

While clinical and basic research sciences can, and should be collaborative, cooperative, and complementary, these scientific domains have inherently different goals and requirements for success. Success in a clinical diagnostic laboratory is driven by adherence to strict regulatory requirements that support high-quality testing of human diagnostic specimens. Success in a research laboratory is driven by exploration, creativity, and the ability for the research scientist to make changes to processes, workflows, and methods on a frequent basis and without regulatory hurdles. The CDC needs a structure that supports the rigorous quality management required for clinical testing, while permitting the exploratory and constantly adaptive environment of a research laboratory.

Recommendation 4: Across the CDC, clinical laboratories should be consolidated, ideally at the Division level, with cross-Center strategies to encourage collaboration with epidemiologists and basic science research laboratories. Laboratories that follow a clinical quality management system should have separate technical staff and space from those that do not follow such a system, such as certain research laboratories.

We recommend that all clinical diagnostic laboratories be brought together organizationally – ideally at the Division level, but at least at the Branch level. These laboratories should be responsible for all clinical testing, public health surveillance, and laboratory test design, development, and validation. Each Division (or Branch) should have a laboratory director and a technical supervisor who meet the CLIA personnel requirements, be familiar with CDC and FDA requirements, and have clinical diagnostic laboratory experience.

These laboratory professionals should receive support from the newly formed Center discussed in Recommendation 2 above. Once this recommendation is put into practice, when the CDC director convenes the people directly responsible for clinical laboratories at the agency, fewer than 10 people would attend (with consolidation at the Division level), or fewer than 30 people would attend (with consolidation at the Branch level), much more manageable structures.

The CDC should maintain a strict separation of laboratory space and technical staff between laboratories that do and do not follow a clinical quality management system . Laboratories performing public health surveillance on clinical samples should work under the same quality standards as clinical diagnostic laboratories. To the extent practicable, laboratories should be designated as single use with respect to function – either clinical or basic research. Where by the unusual nature of their work, laboratories must do both research and clinical testing, the laboratories should adopt a clinical quality management system. The basic research laboratories that do not follow a clinical quality management system should not move organizationally to the new clinical laboratory units but should remain within their current organizational structure.[19] We recognize that this recommendation will require additional space and resources to implement.

To support alignment and interaction between clinical laboratories, basic research laboratories and epidemiologists, clinical laboratory directors will work closely with other divisions in their centers. Subject matter experts in both basic research and clinical testing should contribute to test design. However, the clinical laboratory directors should be responsible for test development, and validation, as well as the quality assurance program for clinical testing performed within each Division.

During a pandemic or other public health emergency, these clinical laboratory professionals should be part of an emergency response structure that ensures appropriate test design and validation of testing for use within the CDC, as well as effective manufacturing and distributing in-vitro diagnostic assays outside of the CDC.

Recommendation 5: The CDC should create and train a robust, diverse workforce for clinical laboratories, comprised of scientists who have the education, skills, and qualifications to support and lead high-complexity laboratories.

Our proposal to consolidate clinical laboratories at the division level for clinical testing, public health surveillance, and test design and development will require the CDC to develop a larger workforce of laboratory scientists.

The CDC needs more laboratory scientists trained to work in high-complexity clinical laboratories. CLIA requirements include a relevant college degree and coursework, extensive training in clinical laboratory practices, demonstrated annual competency, participation in external proficiency testing or alternative proficiency testing, and continuing education to maintain clinical certification.

The CDC also needs more senior clinical diagnostic laboratory leaders. CLIA and its implementing regulations require that oversight of high-complexity clinical laboratories be performed by experts with advanced education, training, and board-certification.[20] An advanced degree alone,

[19] Scientists who do both basic research and clinical laboratory work would still be able to do so. However, the laboratory spaces for this work would be separate, with separate technical staff, and under the jurisdiction of different divisions. These scientists could have a primary role in one division with an appointment in a second division, similar to how academic departments work in universities.

[20] 42 CFR 493.1443(b)(3)(i).

such as a doctoral degree in a basic science discipline or epidemiology, is not sufficient to oversee and direct high-complexity patient testing in a CLIA-licensed laboratory.

The CDC currently lacks sufficient experts with these qualifications to staff its clinical laboratories with the responsibilities that we envision. Developing this workforce starts with the human resources capability to hire, promote and retain these laboratory leaders. The CDC should review its hiring and promotion policies to make sure that clinical laboratory professionals find the agency an attractive place to work. Consolidating the clinical laboratories will help, as doing so will create many more paths to advancement within the same structure than exist today.

The CDC should also create training and career development pipelines, with an emphasis on increasing racial and ethnic diversity among clinical laboratory scientists and leaders. The agency should engage the American Society for Microbiology, Association of Public Health Laboratories, American Society for Clinical Pathology, Association for Molecular Pathology, and American Society for Clinical Laboratory Science, among others, to collaboratively build workforce development pipelines to feed the CDC's growing need for a highly qualified clinical laboratory workforce. For example, the CDC could develop a clinical laboratory fellowship program with the Committee on Postdoctoral Education Programs of the American Society for Microbiology.

Additionally, the CDC should redefine programs such as the CDC Laboratory Leadership Service to include more comprehensive clinical and public health laboratory training opportunities. Development of a Diagnostic Laboratory Leadership Service track that is based in clinical microbiology, quality management, and biosafety, and that leads to board eligibility would further expand the cadre of qualified clinical laboratory leaders.

Recommendation 6: The CDC should cultivate and foster a culture of laboratory quality through the adoption of a comprehensive clinical laboratory quality management system across the agency.

Quality management is the critical framework in a laboratory that performs clinical diagnostic testing. A robust quality management system that focuses on continuous and sustainable improvement is the bedrock of high-quality testing and accurate patient results. Successful quality management is more than just a series of laboratory processes or a comprehensive manual, it is a top-down culture that requires investment from both bench scientists and leadership. Quality management must exhaustively encompass pre-analytical, analytical, and post-analytical processes from test design and development to testing of human specimens and result reporting.

Quality management excellence begins with leadership and support, as outlined in Recommendations 1 and 2. Also essential is a highly trained clinical laboratory workforce whose education, training, and daily activities are built upon quality-in-practice, not just quality-in-principle, as outlined in Recommendation 5.

Also important are the tools to support a culture of quality. The CDC is now planning to use an eQMS system to track quality testing and other key metrics at all of the agency's laboratories. This is a promising effort that can be led by the new Center for laboratories discussed in Recommendation 2.

The CDC is also developing a Quality Manual for Microbiological Laboratories (QMML) to create consistency in microbiology laboratory functions across the agency. While we believe this is the right direction generally, we would point out that clinical and basic research laboratories have distinct needs for quality management. For clinical laboratories, an alternative to the QMML would be to adopt a standard, comprehensive quality management system used by high complexity clinical laboratories, such as the system developed by the College of American Pathologists, which has deemed status in the CLIA regulations. For basic science laboratories, we would note that researchers may find a QMML to be burdensome, restrictive, and of limited value.

C. Test Development

Effective test development begins with the science to develop a high-quality diagnostic test and ends with validation and implementation of that assay in laboratories across the country. The CDC sometimes also takes on the role of manufacturer and distributor of in vitro diagnostic tests, when needed. The CDC should focus not just on developing a test that can work for a few patients; it should lead the development of a broader national laboratory system that can provide testing at the scale required—from development through distribution. Tests that are not readily available, require unusual collection devices, use components that are difficult to manufacture at large scale, or suffer from slow turnaround times may cause harm, delay appropriate therapy or isolation, prolong unnecessary isolation, or delay initiation of public health mitigation measures. Moreover, tests that do not reach those in marginalized populations can exacerbate, rather than address, longstanding health inequities.

As soon as possible after a novel threat emerges, public health laboratories, hospital and academic laboratories, and commercial reference laboratories should be able to develop and deploy their own tests, with appropriate regulatory oversight and reporting requirements. These sectors play essential and complementary roles to the CDC as they have capability to sustain high throughput testing levels and diversify methods of testing. When feasible, diagnostic manufacturers should have access to data and materials required to develop tests for pre-existing instrument platforms, as well as to develop direct-to-consumer and over-the-counter tests.

Together, the CDC, public health laboratories, hospital and academic laboratories, and commercial reference laboratories constitute a national laboratory system. It therefore is essential for the CDC to work collaboratively with multiple partners, especially in the event of a major emergency.

Recommendation 7: To facilitate the rapid scale-up of testing, the CDC should involve external experts in its review and deployment process for clinical tests for pathogens with pandemic potential.

The consequences of failed IVD design or manufacture are severe, and both of these failures occurred at CDC in the SARS-CoV-2 response. Erroneous results may cause harm; falsely negative results can deny patients lifesaving treatment and risk spreading disease, with falsely positive results leading to unneeded treatment and/or isolation and missed diagnoses, in addition to anxiety.

Recently, the CDC has established a review board to quickly review the design of new tests for infectious diseases to reduce the chance of errors. This is an important step forward. As part of this process, the CDC should incorporate input from external subject matter experts from academic, commercial reference, and public health laboratories.[21] These experts can help shed light on key issues, including the potential for scale of different test options and the technology platforms on which the test should be validated. Up-front input will shorten the time required by such external laboratories to implement and scale use of these tests. The goal should be to add expertise in the design stage without adding delay or bureaucracy.

Recommendation 8: The CDC should incorporate redundancy into the national responsibility for test development.

The CDC should develop a "Centers of Excellence" program comprised of selected and pre-approved high functioning public health laboratories, hospital and academic laboratories, and commercial reference laboratories. This program could be modeled on the recent effort to create a Pathogen Genomics Centers of Excellence program. These centers should work with the CDC on collaborative design, development, and deployment of clinical diagnostic tests. We recognize that implementation of this recommendation will require additional resources.

This collaborative should eliminate the risk of a single point of failure for test design and validation. It would also provide redundancy and flexibility in case of pathogen genomic variation and supply chain issues, which have been widespread during the COVID-19 pandemic. The CDC should lead this effort and collaborate with its national laboratory partners and manufacturers of laboratory consumables and reagents.

The CDC has already moved in the direction of this recommendation, with a plan to involve two public health laboratories in making the same test. However, we would recommend considering the use of more than two laboratories, involving private clinical and commercial reference laboratories to support scale. Developing and deploying multiple successful versions of a test will allow for the greatest redundancy and flexibility.

Recommendation 9: To reduce the burden on the agency and support a high-quality laboratory network, the CDC should transfer the performance of selected rare tests to Centers of Excellence.

The CDC is the only testing site in the US for a number of rare tests for microorganisms, including nucleic acid amplification tests, serologic tests and culture-based tests.[22] Although available

[21] This external input will be valuable even for tests that are expected to be conducted solely at the CDC.

[22] CDC. 2023 Infectious Diseases Laboratory Test Directory.28 November 2022. https://www.cdc.gov/laboratory/specimen-submission/cdc-lab-tests.pdf

for free, turnaround times are often significantly longer than tests performed in hospital or commercial reference laboratories. To create greater reserve capacity at the CDC, improve service to individuals in need of testing, and strengthen laboratories around the country, the CDC should transfer the technology for some of these medically important but esoteric tests to commercial reference laboratories and academic laboratories. Doing so will strengthen the nation's laboratory system, while delivering rapid turnaround times with efficient extant systems for electronic test ordering and reporting. A model for this approach is the National Prion Disease Pathology Surveillance Center, the only CLIA-licensed laboratory that offers testing for prion disease diagnosis. A process to support access to these tests for people without the ability to pay should be an essential part of this plan. We recognize that implementation of this recommendation will require additional resources.

D. Electronic Laboratory Reporting

At the patient level, laboratory testing guides between 60% and 70% of clinical decisions. At the population level, laboratory results are used by federal, state and local public health agencies as part of public health surveillance and to guide public health response. Despite the importance of laboratory results, the US has struggled with efficient transfer of both patient and laboratory information between health care entities and public health agencies, including the CDC. These challenges were particularly evident during the COVID-19 pandemic, reflected in the difficulty sharing and aggregating laboratory data in real time.[23]

The full scope of laboratory data challenges across the country is beyond the scope of our review, and involves the resources, training, and electronic systems in use across the country, as well as important questions of legal authority. The CDC's Advancing Laboratory Data Exchange[24] project is an essential effort seeking to address many of the current issues and should be fully funded by Congress.

We focused on the challenging issue of the standardization of data elements and formats for laboratory testing. Especially at the beginning of an outbreak, maximizing rapid access to testing is essential to identify infected persons, initiate contact tracing, isolation and quarantine, and determine the geographical extent of the outbreak.

Under CDC oversight, the current workflow requires public health laboratories to contact the CDC to obtain a case identification number and provide answers to a specific list of questions -- before a patient specimen will be accepted for testing. This system frustrates patients and clinicians, causes delays, and limits access to testing.

[23]Historically Unprepared Examination of the Federal Government's Pandemic Preparedness and Initial COVID-19 Response. A HSGAC Majority Staff Report. December 2022. https://www.hsgac.senate.gov/imo/media/doc/221208_HSGACMajorityReport_Covid-19.pdf

[24] CDC. Expanding laboratory data exchange. 12 October 2021. https://www.cdc.gov/csels/dmi-support/expanding_laboratory_data_exchange.html

We also learned from subject matter experts that different programs at the CDC request different formats, forms, and message specifications. These requirements can also vary between local, state, and federal public health authorities. This complexity undermines the efficient collection and dissemination of laboratory data.

Recommendation 10: The CDC should lead the standardization of health data collection associated with laboratory tests to improve future public health responses.

To achieve this national goal, the CDC should work with the Council of State and Territorial Epidemiologists, the Association of Public Health Laboratories, and public health and private laboratory leaders to determine the minimum data set that should be required in an electronically transmissible format to initiate testing. While this sounds simple, coming to agreement with the many parties will require much negotiation and, potentially, a carrot and stick approach to support compliance. Fortunately, several groups of national health data experts, including the Advisory Committee to the Director of the CDC, have indicated the high level of need for this approach, and efforts have already been initiated. CDC should establish a timeline for its completion.

V. Responding to Questions

A. Will our recommendations undermine a culture of innovation at the CDC?

The CDC has long sought to foster innovation in infectious disease clinical laboratory science and practice. Such innovation has been critical to making the CDC a global reference facility for diagnosis and characterization of existing and novel pathogens and a leader in developing new laboratory methods to answer critical public health questions, such as estimating HIV incidence[25] or tracking outbreaks of foodborne diseases.[26] We do not believe that any of our recommendations for improving the rigor and quality of laboratory operations inside the CDC will impair the curiosity and practice-minded approach of laboratory scientists that has led to past innovation. If anything, we anticipate it will drive scientists to consistently strive for the highest quality, a pursuit which often leads to innovations that improve the accuracy and timeliness of testing. Moreover, we recommend that the CDC pursue stronger partnerships with public health, hospital and academic, and commercial reference laboratories, particularly when a new pathogen emerges. In such situations, we believe that having multiple laboratories using different methods to achieve the same endpoint (e.g., multiple high quality diagnostic tests) will benefit science and the public's health.

[25] Hall HI, Song R, Rhodes P, et al. Estimation of HIV Incidence in the United States. *JAMA.* 2008;300(5):520–529. doi:10.1001/jama.300.5.520

[26] CDC. About PulseNet. 29 September 2021. https://www.cdc.gov/pulsenet/about/index.html

B. Will changes make it difficult for epidemiologists at the CDC to work with clinical laboratories?

Public health practice only succeeds when there is close collaboration between epidemiologists and laboratory scientists. Our proposal maintains the connection between the CDC's epidemiologists and laboratory scientists who are working on the same pathogens and diseases. In addition, the adoption of remote working technologies during the pandemic has spurred greater collaboration, because it has helped remove the need to be physically present to have a face-to-face conversation. Moreover, the changes in governance that we propose should strengthen the integration of laboratory scientists into incident management systems, obligating epidemiologists and laboratory scientists to work together to track the development, evaluation, deployment, and performance of new, high quality laboratory tests when a new pathogen of pandemic potential emerges.

VI. List of Workgroup Members

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