Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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PERSPECTIVES

Responding to the Challenges of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

Perspectives from the Association for Molecular Pathology Infectious Disease Subdivision Leadership

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Clinical molecular laboratory professionals are at the frontline of the response to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, providing accurate, high-quality laboratory results to aid in diagnosis, treatment, and epidemiology. In this role, we have encountered numerous regulatory, reimbursement, supply-chain, logistical, and systems challenges that we have struggled to overcome to fulfill our calling to provide patient care. In this Perspective from the Association for Molecular Pathology Infectious Disease Subdivision Leadership team, we review how our members have risen to these challenges, provide recommendations for managing the current pandemic, and outline the steps we can take as a community to better prepare for future pandemics. *(J Mol Diagn 2020, 22: 968–974; https://doi.org/10.1016/j.jmoldx.2020.06.003)*

There are many factors as to why the response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the United States has been different from previous pandemic responses, and the goal herein is to document challenges to the SARS-CoV-2 response and provide initial recommendations to better prepare for the next pandemic. In 2009, the influenza A H1N1 pandemic was the first pandemic in the age of molecular diagnostics. The large network of academic and community hospital laboratories throughout the United States was able to develop and validate molecular tests in the first week of the outbreak to rule out H1N1 as the cause of a patient's illness, and this played a critical role in containing the H1N1 pandemic. For example, in Chicago, IL, during the

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Standard of practice is not defined by this article, and there may be alternatives. See *Disclaimer* for further details. This article reflects the consensus expert opinion of the Association for Molecular Pathology Infectious Disease Subdivision Leadership members, all authors contributed equally, and content does not necessarily represent the official position of their respective employers.

The 2019 to 2020 Infectious Disease Subdivision Leadership of the Association for Molecular Pathology is composed of Frederick S. Nolte (Chair), N. Esther Babady, Blake W. Buchan, Gerald A. Capraro, Daniel N. Cohen, Erin H. Graf, Amy L. Leber, Erin McElvania, and Joseph D.C. Yao.

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first month of the pandemic, 62% of the patients screened for H1N1 influenza were tested by community molecular diagnostics laboratories, with a typical turnaround time of 24 hours.[1] The clinical laboratory community rapidly provided widely available H1N1 influenza molecular testing, facilitating a swift pandemic response.[2–6]

Ten years later, laboratories are now responding to the SARS-CoV-2 pandemic.[7–10] As this article goes to press, the United States has surpassed all other countries in number of diagnosed infections and deaths (*https://coronavirus.jhu.edu/map.html*, last accessed April 28, 2020). The US federal government continues to recommend social distancing measures, and many states have taken significant public health measures to slow SARS-CoV-2 spread in their communities[11,12] (*https://www.kff.org/health-costs/issue-brief/state-data-and-policy-actions-to-address-coronavirus*, last accessed April 28, 2020). The highest rates of infection are currently observed in urban areas, consistent with patterns observed in seasonal flu outbreaks; however, community spread has been identified in all 50 states, and reported incidence has increased in areas with smaller population density as testing expands.[13] Experts believe that because of a number of factors, this is only the tip of the iceberg with regard to numbers of patients infected using current diagnostic test strategies, and the inability to identify asymptomatic yet SARS-CoV-2–positive patients rapidly complicates efforts to isolate and contain infections.[14–20] Despite these challenges, the CDC released guidance on how to safely reopen the United States in May 2020 (*https://www.cdc.gov/coronavirus/2019-ncov/downloads/php/CDC-Activities-Initiatives-for-COVID-19-Response.pdf*, last accessed May 27, 2020). Key to this guidance is building more testing capacity for both symptomatic and asymptomatic individuals.

Challenges to the SARS-COV-2 Pandemic Response in the United States

This new coronavirus has unique biological characteristics that would challenge any health care system's response, including high levels of infectivity[21] (*https://www.ncbi.nlm.nih.gov/books/NBK554776*). As a novel pathogen, existing clinical tests could not identify coronavirus disease 2019 (COVID-19) patients, and confirmation of diagnosis required molecular testing for SARS-CoV-2 viral RNA.[22,23] Once the genetic sequence of the virus became available in early January 2020 (*http://virological.org/t/genome-sequences-by-date-and-location/380*, last accessed April 28, 2020) and clinical tests could be developed and performed, reliance on a single assay production and test modality (ie, CDC test kit performed at CDC laboratories; *https://www.cdc.gov/coronavirus/2019-ncov/lab/rt-pcr-panel-primer-probes.html*, last accessed April 28, 2020) provided inadequate testing and SARS-CoV-2 detection capacity, ultimately hindering the public health system response (*https://www.nytimes.com/2020/03/28/us/testing-coronavirus-pandemic.html*, subscription required, last accessed April 28, 2020).

With the lack of access at local levels, high-complexity clinical diagnostic laboratories began appropriately developing their own tests but faced additional regulatory hurdles because of the invocation of Emergency Use Authorization (EUA) requirements by the US Food and Drug Administration (FDA; *https://www.gq.com/story/inside-americas-coronavirus-testing-crisis*, last accessed May 27, 2020). On February 4, 2020, the FDA granted EUA status for CDC's SARS-CoV-2 test kit, providing kit availability to US public health laboratories; however, this kit was subsequently found to have a manufacturing problem (*https://www.cnn.com/2020/04/18/politics/cdc-coronavirus-testing-contamination/index.html*, last accessed May 27, 2020). On February 24, the Association of Public Health Laboratories wrote a letter to the FDA, requesting enforcement discretion to allow state and local public health laboratories the ability to generate a laboratory-developed test for the detection of SARS-CoV-2, which was denied (*https://www.360dx.com/clinical-lab-management/aphl-asks-fda-make-own-tests-cdc-struggles-provide-sars-cov-2-test-kits#.Xp4d2chKiUl* and *https://www.360dx.com/regulatory-news-fda-approvals/fda-declines-aphl-request-make-own-sars-cov-2-test-kits#.XqLiUWhKiUk*, registration required, last accessed April 28, 2020). Once the remanufactured CDC test was available to public health laboratories on February 28, 2020, use of the test was initially restricted to specific reagent lots, extraction platforms, and real-time PCR instruments, which placed significant additional barriers on widespread implementation (*https://www.reuters.com/investigates/special-report/health-coronavirus-hospital-test*, last accessed May 27, 2020). The need for SARS-CoV-2 testing in the community resulted in the FDA changing its EUA policy and procedure at the end of February, allowing some academic laboratories to rapidly make their test available. It was not until March 12, 2020, that the FDA granted the first EUA for commercial test kits, and multiple molecular platforms became available for use by clinical diagnostic laboratories (*https://www.wsj.com/articles/how-washington-failed-to-build-a-robust-coronavirus-testing-system-11584552147?mod=article_inline*, subscription required, last accessed April 28, 2020).

Although clinical laboratories rapidly responded to make SARS-CoV-2 diagnostic testing available for patients, supply chain issues have limited testing capacity and led to bottlenecks that hindered widespread availability of these necessary tests (*https://abcnews.go.com/Health/wireStory/us-virus-testing-faces-headwind-lab-supply-shortages-69710161*, last accessed May 27, 2020). This situation resulted in the rationing of reagents, sample collection devices, and other testing resources (*https://oig.hhs.gov/oei/reports/oei-06-20-00300.pdf*, last accessed May 28, 2020). Because of these critical shortages and CDC recommendations providing specific clinical presentation and epidemiologic criteria to identify those eligible for diagnostic testing (*https://www.cdc.gov/coronavirus/2019-nCoV/hcp/clinical-criteria.html*, last accessed April 28, 2020), the initial data

set on the performance of SARS-CoV-2 diagnostics reflected only symptomatic patients biased toward the ill. Diagnostic data critical to determinations of mortality rate, infection rates, and other critical metrics—on which existing modeling and predictions are based—therefore potentially contain a testing bias that is not yet fully understood[24–26] (*https://www.statnews.com/2020/03/31/covid-19-overcoming-testing-challenges*, last accessed April 28, 2020). Full diagnostic testing capacity, to include serologic screening to identify individuals in the community who have been exposed and recovered from SARS-CoV-2, is only now becoming available, many months after the first confirmed US case of SARS-CoV-2.[23,27,28] Recent autopsy data indicate the earliest identified death was weeks earlier (*https://www.npr.org/sections/coronavirus-live-updates/2020/04/22/840836618/1st-known-u-s-covid-19-death-was-on-feb-6-a-post-mortem-test-reveals*, last accessed April 28, 2020). Only with additional testing and research on disease pathogenesis can the scope and pathogenicity of COVID-19 disease be fully understood.

Recommendations for Managing the Current Pandemic

The Association for Molecular Pathology (AMP) Infectious Diseases Subdivision Leadership is aware of and involved in multiple efforts to address SARS-CoV-2 testing development, test quality and interpretation, operation, and limited resource management. During the pandemic, guidance from AMP subject matter experts will continue to be provided in multiple formats. The authors anticipate providing additional communications as needed to document and to address emerging challenges. Throughout the course of the SARS-CoV-2 response, the AMP has continually maintained a website curating COVID-19–related scientific, regulatory, and reimbursement resources (*https://www.amp.org/clinical-practice/testing-resources-for-covid-19*, last accessed April 28, 2020). On February 20 and May 14, the AMP provided freely accessible online education regarding the COVID-19 pandemic (*https://educate.amp.org/local/catalog/view/product.php?productid=4*, last accessed May 5, 2020; and *https://educate.amp.org/local/catalog/view/product.php?productid=183*, last accessed May 27, 2020); additional webinars will provide periodic updates. The AMP has conducted a robust COVID-19 testing survey designed to identify and understand the laboratory community's challenges, with initial data from over 100 US-based laboratories available (*https://www.amp.org/advocacy/sars-cov-2-survey*, last accessed May 28, 2020). AMP member peer-to-peer listserv communications have been robust as colleagues rapidly shared concerns, challenges, knowledge, experience, and solutions to support the clinical laboratory community's COVID-19 testing response. Multiple AMP subject matter experts have been featured in media interviews and are interacting on social media outlets, effectively communicating laboratory community concerns and highlighting numerous success stories in spite of challenging conditions (*https://www.cnn.com/2020/04/09/politics/coronavirus-testing-cdc-fda-red-tape-invs/index.html*, last accessed April 28, 2020). We applaud the efforts of AMP members from all over the world, other professional societies, and laboratory professionals around the world for their leadership and dedication to patient care during this time of rapid change and instability.

Developing evidence-based recommendations in the midst of a rapidly evolving public health crisis poses multiple challenges. Reflecting on the experience and perspective of expert practitioners with available, high-quality data has identified topics where AMP can provide additional guidance to the diagnostic community, including the following:

- Recommendations for procedures and approaches for verification and rapid deployment of proficiency testing for molecular diagnostic tests for SARS-CoV-2;
- Recommendations for rapidly expanding molecular diagnostic testing capacity to improve overall disease recognition and control;
- Comparisons of the relative analytical and clinical performance characteristics of the various molecular diagnostic tests that have been granted EUA, to include root cause, prevalence, and significance of false negatives and false positives;
- Best practices for laboratory management and resource allocation in the face of supply chain disruptions;
- Recommendations for how academic institutions and community health systems can increase local testing capacity by leveraging resources available in research laboratories;
- Providing insight and commentary into the applicable regulations, standards, and proposed regulatory changes;
- Management of laboratory and health care worker staffing issues because of illness and quarantine.

The Important Role of the Molecular Laboratory Professional during a Pandemic

Molecular laboratory professionals, including molecular pathology physicians, doctoral professionals, and medical laboratory scientists, partner with ordering physicians to determine individual patient testing needs based on their clinical presentation. Testing for SARS-CoV-2, or any other emerging pathogen, should involve these board-certified professionals at every stage. This includes, but is not limited to, the following:

- Selecting appropriate molecular diagnostic testing procedures, including involvement in purchase decision making for manufactured products and instruments;

- Designing, verifying, and validating test performance characteristics;
- Determining appropriateness of specimens to be validated;
- Determining appropriateness of alternative collection devices to be validated;
- Determining appropriateness and prioritization of patient testing based on the clinical presentation (symptomatic versus asymptomatic) and multiple additional factors, including the patient exposure history, living facility, occupation, as well as the relevant data for disease incidence in the community;
- Interpreting the results in the context of other medical information.

These activities are within the scope of practice for our molecular diagnostic professionals. Involvement of the appropriately qualified molecular laboratory professional in every aspect of providing critical diagnostic testing services during the response to an emerging pathogen mitigates risks and promotes patient safety.

Much of the emerging published work on the development of new clinical tests for SARS-CoV-2 represents expertise and work arising from university medical center and hospital-based laboratories. This is not to neglect the impact of innovative testing developed in commercial referral laboratories, as well as the considerable impact of commercial development of new testing platforms. Referral laboratories play an important role in the development and performance of tests for infectious diseases, providing critical access to testing for community and smaller hospitals. Widespread availability of laboratory-developed and commercial assays can help accelerate provision of community-based clinical laboratory testing, ultimately shortening test result turnaround time and permitting rapid identification of and public health intervention with infected individuals. It is vital to have all stakeholders in the clinical laboratory community generate more opportunities for innovation in the design of new COVID-19 tests and testing strategies. In addition, public health laboratories play a critical role through contact tracing, epidemiologic data management and analysis, outbreak containment, and information dissemination to help curb the spread of infection. Ultimately, the success of the SARS-CoV-2 pandemic testing response requires ALL of us.

Steps to Better Prepare for the Next Pandemic

Even as clinical laboratories continue to make great strides in diagnostic capability and capacity related to SARS-CoV-2, a number of factors that have been developing in the health care delivery system for many years have been demonstrated to hinder the ability of clinical laboratories to provide adequate and timely results,[29] which may have hindered their ability to help guide patient care in this pandemic (*https://www.amp.org/AMP/assets/File/position-statements/2015/PerfectStorm-FINAL-CD.pdf?pass=34*, last accessed April 28, 2020). Regulatory requirements foisted on laboratory-developed testing procedures (LDPs) have proved to be inefficient and burdensome, and they impose shifting requirements on medical professionals and certified laboratories (*https://www.wsj.com/articles/how-washington-failed-to-build-a-robust-coronavirus-testing-system-11584552147?mod=article_inline*, last accessed April 28, 2020). Ongoing supply chain limitations have resulted in laboratories having validated diagnostic testing methods, but shortages and/or manufacturer prioritization of testing reagents, sample collection devices, and laboratory supplies needed to obtain and process patient samples has limited both test availability and laboratory testing capacity. Furthermore, these supply chain issues have resulted in molecular laboratories implementing several different SARS-CoV-2 laboratory-developed and FDA EUA tests to maintain and increase testing capacity. Running multiple molecular tests with different targets and varied limit of detection is a significant operational and technical challenge, requiring significant input from molecular experts to correctly interpret data for clinicians and patients.[30] These issues (among other factors) have led to rationing of testing, with the downstream consequence of severely limiting the ability to gather critical data needed to understand the characteristics of COVID-19 disease, and may have resulted in delays in design and implementation of time-sensitive public health management and mitigation efforts (*https://www.nytimes.com/2020/04/08/nyregion/new-york-coronavirus-response-delays.html*, subscription required, last accessed April 28, 2020).

Once the SARS-CoV-2 pandemic response becomes stable, AMP's clinical practice, education, regulatory, and reimbursement subject matter experts plan to perform an analysis of these challenges and provide recommendations based on lessons learned to improve response to future emerging pathogens. It is clear that rapid development and implementation of high-quality, widely available diagnostic testing for novel emerging pathogens is the lynchpin of mobilizing an effective public health response. The challenges to date of the COVID-19 pandemic have illustrated the incredible capacity for molecular diagnostic laboratories and their professional staff to respond quickly and effectively to unprecedented, multifaceted challenges. Our experience thus far in this pandemic underlines the critical importance of the role of dedicated medical and laboratory professionals in rapidly developing accurate, high-quality, and widely available clinical diagnostic testing during an outbreak to help serve patients, health care workers, and communities. Sustaining the capacity of these excellent laboratory testing services and professionals is in the best interests of patients and society. Early, robust, and collaborative engagement with the clinical laboratory professional community represented by AMP would positively contribute to future pandemic responses. Ensuring that effective networks of communication, coordination, and

response between the clinical laboratory community, public health laboratories, local, state, and federal agencies, and other stakeholders are developed, improved, and maintained is essential.

An appropriate regulatory framework should facilitate accurate and high-quality tests without hindering the application of recent discoveries or a robust response to emerging infectious disease. The FDA's EUA process is not an appropriate framework for LDPs (alias laboratory-developed tests). The agency's response to the emergence of COVID-19 confirms the best use of the FDA—to regulate test platforms manufactured by companies to be sold to testing laboratories. The model of laboratory oversight within the Clinical Laboratory Improvement Amendments of the Public Health Service Act has served as the engine of innovation in this space and rapid development and application of validated clinical discovery to patient care, and recognizes the central role that medical professionals play in the clinical laboratory (*https://www.govinfo.gov/content/pkg/USCODE-2011-title42/pdf/USCODE-2011-title42-chap6A-subchapII-partF-subpart2-sec263a.pdf*, last accessed April 28, 2020). This framework requires appropriate validation of diagnostic services, yet permits qualified regulated laboratories, and their medical leadership, flexibility to develop and validate laboratory tests appropriately and quickly.[29] This flexibility allows medical and scientific experts to implement LDPs for clinical use, and has facilitated the rapid application of new medical knowledge to respond to unmet public health needs, such as pandemic outbreaks of viral disease (eg, influenza A H1N1, SARS, and Middle East respiratory syndrome).[31] The Clinical Laboratory Improvement Amendments program, including applicable state laws and accreditation by deemed authorities (eg, College of American Pathologists), allows molecular pathology professionals to continually improve LDPs to reflect the most up-to-date scientific and medical understanding, providing the essential environment to mount a nimble response to place critical diagnostic tests into clinical practice (*http://www.amp.org/AMP/assets/File/advocacy/PrinciplesforOversightofLaboratoryDevelopedProcedures-FINAL.pdf?pass=72* and *http://www.amp.org/AMP/assets/File/advocacy/AMPCLIAmodernizationproposalFINAL8_14_15.pdf?pass=34*, last accessed April 28, 2020). To ensure that the laboratories can quickly respond to the next pandemic, it is imperative that oversight of LDPs remains with the Clinical Laboratory Improvement Amendments, especially during a public health emergency. In March 2020, in light of what was transpiring with COVID-19 testing, Senator Rand Paul introduced the Verified Innovative Testing in American Laboratories Act of 2020 (*https://www.congress.gov/bill/116th-congress/senate-bill/3512*, last accessed April 28, 2020). The AMP supports this legislation as its main provision clarifies that the regulation of LDPs rests with the Clinical Laboratory Improvement Amendments and not the FDA, including during a public health emergency. The Verified Innovative Testing in American Laboratories Act of 2020 will ensure that during the next public health emergency, barriers enacted by the FDA during the COVID-19 pandemic will not impede laboratories' ability to offer appropriate and accurate LDPs to patients.

Conclusions

Clinical laboratory physicians and professionals are in the vanguard of the response to the SARS-CoV-2 pandemic, providing accurate, high-quality laboratory results to aid in diagnosis, treatment, and epidemiology. In this role, we have encountered numerous regulatory, reimbursement, supply-chain, logistical, and systems problems that we have struggled to overcome to fulfill our calling to provide patient care. Despite the challenges and setbacks, the cadre of highly trained and dedicated molecular diagnostic professionals of the AMP has risen to the challenge and is providing the vital diagnostic intelligence needed for effective management of this pandemic. Although the current successes were achieved through determination and ingenuity, our experiences suggest that the hurdles and obstacles that have been encountered were not inevitable and certainly impaired our national recognition of and response to the pandemic. To prepare for the next unexpected challenges, thoughtful retrospection and intervention into key areas will improve our ability to care for patients and society when the next crisis arises.

On behalf of AMP, we recognize and thank our members and all members of the multidisciplinary medical teams for their expertise, dedication, and service. Organizationally, AMP will continue to proactively provide critical information and resources in support of all laboratory professionals involved in COVID-19 response activities. We will also continue to engage in, encourage, and support collaboration between all stakeholders to overcome SARS-CoV-2 and continue to put the care of patients first, every day.

Disclaimer

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