

How SARS-CoV-2 Transformed the Clinical Laboratory: Challenges and Lessons Learned

Jonathan M. Tsai MD PhD^{1,2, 3,†}, Nicole V. Tolan PhD^{1,2}, † Athena K. Petrides PhD^{1,2}, Sanjat Kanjilal MD MPH^{1,5}, Manfred Brigl MD PhD^{1,2}, Neal I. Lindeman MD^{1,2}, Yen-Der Li MD^{3, 4}, Milenko J. Tanasijevic MD MBA^{1,2}, Sankha S. Basu MD PhD^{1,2}, Stacy E.F. Melanson MD PhD^{1,2}

†Indicates equal contribution

Institutional Affiliations: ¹Department of Pathology, Brigham and Women's Hospital, Boston, MA, ²Harvard Medical School, Boston, MA, ³Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, ⁴Department of Molecular and Cellular Biology, Harvard University, Cambridge, MA, ⁵Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Healthcare Institute

Corresponding Author: Stacy E.F. Melanson, Brigham and Women's Hospital, 75 Francis Street, Amory 2, Boston, MA 02115, Tel: 617-732-6245,

Email: semelanson@bwh.harvard.edu Fax: 617-731-4872

Abbreviations: Brigham and Women's Hospital (BWH), Center Advanced Molecular Diagnostics (CAMD), Sunquest (SQ), Electronic Health Record (EHR), Mass General Brigham (MGB), Brigham Health (BH), coronavirus disease 2019 (COVID-19), Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), reverse-transcriptase polymerase chain reaction (RT-PCR), integrated DNA technologies (IDT), Emergency Use Authorization (EUA), research and development (R&D), Laboratory Developed Test

(LDT), turnaround time (TAT), anterior nares (AN), point of care testing (POCT), cycle threshold (Ct).

Running Title: SARS-CoV-2 and Laboratory Lessons Learned

Keywords: SARS-CoV-2 PCR testing, COVID-19, Clinical Laboratory, Lessons Learned, Informatics, Laboratory Management

Abstract: The COVID-19 pandemic has made a devastating impact on global health and continues to challenge healthcare infrastructure and delivery. The clinical laboratories were no exception as they are responsible for diagnostic testing that dictates many clinical, infection control and public health decisions. Information technology and laboratory management tools are critical assets for maintaining and adapting operations in response to crises and when utilized effectively, promote the integration between the clinical laboratory specialties (e.g., chemistry, hematology, microbiology, and molecular pathology). During the COVID-19 pandemic, our systems and processes were strained due to high testing volumes, demand for rapid turnaround times, supply chain constraints, and constantly evolving testing algorithms and result interpretations as our knowledge of the virus and of diagnostics increased over time. In this report, we describe those challenges and subsequent adaptations made by each clinical laboratory section. We hope these details help provide potential solutions and approaches for other hospitals facing COVID-19 surges or other future pandemics.

Setting

Brigham and Women's Hospital (BWH) is a 793-bed tertiary care hospital located in Boston, MA. The BWH Department of Pathology has several Divisions including the Center for Advanced Molecular Diagnostics (CAMD) and the Clinical Laboratories. The Clinical Laboratories process approximately 3 million specimens/year and includes the chemistry, hematology and microbiology laboratories, among others. The laboratory information system (LIS) is Sunquest (SQ; Sunquest Information Systems, Inc., Tucson, AZ) and electronic health record (EHR) is Epic (Epic Healthcare Systems, Verona, WI). The CAMD bioinformatics team has developed and deployed customized information systems (IS) to expand capabilities beyond what can be performed with the commercial systems.

BWH is a founding member of Mass General Brigham (MGB) (formerly Partners Healthcare), an integrated healthcare delivery system that includes Cooley-Dickinson Hospital, Brigham and Women's Faulkner Hospital (BWFH), Martha's Vineyard Hospital, Massachusetts General Hospital, Nantucket Hospital, Massachusetts Eye and Ear, Newton-Wellesley Hospital, North Shore Medical Center and Wentworth-Douglas Hospital. BWH and BWFH are collectively named Brigham Health (BH).

Initial Testing, Validation, and Testing Redundancy During the Pandemic

By late February it became clear that the coronavirus disease 2019 (COVID-19) pandemic would spread through North America (1,2). At this time, the U.S. Food and Drug Administration (FDA) sent notices to clinical laboratories mandating that only the U.S. Centers for Disease Control and Prevention (CDC) and state Department of Public Health

(DPH) laboratories were approved to run severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) reverse-transcriptase polymerase chain reaction (RT-PCR) molecular tests, and that no other laboratories or businesses were permitted to run or design their own assays. Within a few days the FDA issued another statement, allowing clinical laboratories to run only the CDC developed SARS-CoV-2 test, but required the test to be run using the specific instrumentation and reagents previously validated by the CDC (3). According to the CDC, clinical laboratories would initially only be permitted to run SARS-CoV-2 testing using the EZ1 (Qiagen, Germantown, MD) platform and reagents for RNA extraction, the 7500 Fast DX (Applied Biosystems, Beverly, MA) real time thermocycler and reagents for RT-PCR, and a specific lot of oligonucleotide primers and probes from Integrated DNA Technologies (IDT) (Coralville, IA). Accordingly, these reagents and supplies instantly became backordered and unavailable for most laboratories.

Despite the challenges imposed by the FDA on clinical laboratories, initiating the Emergency Use Authorization (EUA) process, we assembled a dedicated research and development (R&D) team working under the leadership of the CAMD and the microbiology laboratory directors to implement the CDC SARS-CoV-2 molecular test (4).

Unable to obtain the instruments and/or reagents that had been approved by the FDA for RNA extraction, we made the decision to develop and validate an in-house, laboratory developed test (LDT) using the Maxwell (Promega, Madison, WI) platform, in conjunction with the EUA-cleared 7500 Fast Dx PCR platform. This instrument was already deployed in the CAMD laboratory for other clinical tests and the EUA-cleared lot of IDT primers for the CDC assay had been ordered in January, 2020, when we first became concerned that testing would be needed. We utilized RNA (BEI Resources,

Manassas, VA) spiked into a negative matrix and positive samples from a reference or state laboratory for validation studies. Although validation of a typical molecular test in the CAMD takes roughly nine months and occurs when technologists can spare time away from clinical testing, our dedicated R&D team was able to validate the SARS-CoV-2 LDT in five days, shortly after the FDA allowed commercial manufacturers and hospital laboratories to utilize their own assays. The LDT went live on March 17th and the documentation was submitted to the FDA. The nucleic acid extraction was done in the microbiology laboratory, because of its experience handling infectious samples under biosafety level 2 (and 3) conditions, but the isolated RNA then had to be transported to the molecular laboratory, in another building, for RT-PCR testing, making the workflow logistically challenging, and limiting throughput. This first version of the LDT could accommodate 22 samples per run, at a maximum of six runs per day, resulting approximately 500 tests a week. Early on, specimens from the emergency department were prioritized over inpatient samples and ambulatory volumes were negligible (5-7).

By late March, the FDA had begun issuing EUAs for closed commercial systems that integrated all steps of the procedure into one automated platform. These included assays from Cepheid (Sunnyvale, CA) and Hologic (Marlborough, MA), two relatively fast turnaround, moderate throughput platforms already in use in our microbiology laboratory (8,9). However, anticipating future shortages as foreshadowed by the initial scarcity of reagents (Table 1), our R&D team began evaluation/development of several LDT molecular assays for SARS-CoV-2 in CAMD, including internally developed amplicon and capture-based next generation sequencing assays, two different "strip based" assays using recombinase polymerization amplification/loop mediated amplification and CRISPR,

and a novel cartridge-based rapid system (Fluxergy, Irvine, CA). This was done in parallel with validating and deploying a higher capacity manual batch assay with EUA (TaqPath COVID-19, Thermo Fisher, Waltham, MA) to improve resiliency to future supply chain limitations. Any R&D assay implemented clinically required the development of custom software in order to track specimens along the process, monitor results and quality control, and interface with the LIS.

In addition, over the course of the pandemic, BWH clinical laboratories developed multiple in-house and send-out options, which allowed our laboratory to offer testing with acceptable turn-around-time (TAT), even with reagent delays and nation-wide shortages. Table 2 depicts our platforms as of submitting this report. All in-house platforms have comparable sensitivity and specificity and correlation studies are frequently performed amongst platforms. The in-house testing performed in our microbiology laboratory on the GeneXpert and Panther Fusion is available 24 hours a day, 7 days a week and provides the fastest TAT of 1-6 hours but has limited capacity due to reagent allocation and/or ongoing supply shortages. Supplies have been more stable for the Thermo Fisher TaqPath COVID-19 assay. However, this assay is a manual, batched method that is only operated 12 hours per day, 7 days per week, resulting in an 8 to 24 hour TAT. Our TAT's have remained relatively stable on our testing platforms for both collection to result (Figure 1a) and receipt to result (not shown) despite a steady increase in testing volumes (Figure 1b). We attribute this to the recruitment of additional staff, modifications in workflow and close integration with clinical operation teams. Our algorithms to route testing to different platforms is discussed in the next section.

Nation-wide shortages of other testing components for SARS-CoV-2 assays (e.g. nasopharyngeal swabs, viral transport media, specimen containers, reagent and sampling pipette tips, nucleic acid extraction kits) were problematic at different times throughout the pandemic. This necessitated the validation of backup options (not only for SARS-CoV-2 but other assays) for media, specimen collection supplies, and testing reagents, as well as the outlining of contingency plans should one or more testing platforms become unavailable temporarily or permanently (Table 1). Alternative specimen types (lower respiratory samples, saliva, anterior nares (AN)) were also validated. We adopted AN swabs as the preferred specimen type for all non-pre-procedural ambulatory patients despite their reported lower sensitivity (10) to handle the unprecedented demands for outpatient testing. Given the risk of a false negative in a patient undergoing an aerosol generating procedure, MGB decided to utilize NP swabs for pre-procedural collections.

Our hospital recently experienced an outbreak of SARS-CoV-2 among inpatients who tested positive for SARS-CoV-2 after admission, for which the hospital responded with widespread employee and patient testing and viral genome sequencing for contact tracing. From late September to early November, we collected specimens from approximately 12,980 employees who volunteering participated in employee screening and specimens were sent directly to the Broad for testing (bypassing the laboratory). Inpatients were tested every third day on our in-house platforms for several weeks to identify any individuals who may have turned positive after their initial testing at the time of admission (e.g., had tested negative during the incubation phase), and the decision was made to continue surveillance testing for hospitalized patients.

Internal Clinical Collaborations and Role of Pathology Informatics

Strong collaboration both within and outside of Pathology were critical in helping us face the unique challenges of the COVID-19 pandemic. Early in the pandemic, the BWH Pathology Department created a COVID-19 response team that was subdivided into several focus areas to facilitate coordinated action across the Department. These areas included central operations and communications, clinical expert, supply chain and phlebotomy, in-house COVID PCR testing, clinical pathology and testing response, send-out and Broad testing, blood bank, blood donor and apheresis, anatomic pathology, and translational research and novel testing (Supplemental Table 1). Each team was run by a team lead (e.g. clinical laboratory director, pathologist) and directors participated in no more than two teams to improve their ability to manage, focus, and quickly respond to the demands of the COVID-19 pandemic. During the surge, daily 30-minute huddles were held to update departmental and hospital leadership.

In addition to dedicated pathology teams, laboratory directors were part of a hospital-wide incident command structure, including the hospital-wide daily huddles, and assisted in forming policies to address the pandemic. Close collaboration occurred between pathology, infectious disease, and infection control leaders (Table 1). This allowed the laboratory to respond more rapidly to changing clinical needs, but perhaps more importantly, gave hospital leadership an understanding of the evolving staffing and resource constraints in the laboratory. We continue to work with hospital leadership to ensure the laboratory is engaged early in the decision-making process and is therefore able to support operational and clinical decisions.

The Pathology Informatics team, working closely with the laboratory directors as well as with infectious disease and infection control, was tasked to not only track SARS-CoV-2 testing volumes and positivity rates, but to electronically triage and direct specimens to different SARS-CoV-2 assays to maintain optimal efficiencies (Table 1). An algorithm was developed in our EHR to direct specimens to certain assays based on patient specific criteria and required TAT (Figure 2a), all of which occurred prior to receipt in the laboratory (Table 1). For example, ambulatory testing (Figure 2b) arrived in the laboratory barcoded at the time of collection with either our CAMD or send-out LIS code, while our most urgent specimens arrived with the LIS code for the in-house rapid TAT Cepheid assay. The algorithm was adaptable and could change in real-time as we responded to supply shortages or adjusted to changes in testing volumes. We have also adapted our algorithm for the respiratory season, which requires not only SARS-CoV-2 PCR testing, but also influenza A/B, respiratory syncytial virus and other respiratory virus testing depending on the patients' symptom severity, underlying disease and disposition.

Result routing required custom IS software to meet regulatory guidelines including the ability to report SARS-CoV-2 results to the state DPH laboratory for epidemiologic studies. We modified an existing interface with DPH to accommodate additional fields such as clinical and demographic parameters per state guidelines and developed a report to track positivity rates per federal guidelines. This took considerable IS resources and coincided with developing and implementing new assays. To our advantage, we had an existing interface, dashboards and tools to allow us to meet the state and federal guidelines.

Furthermore, due to the often critical and unpredictable disease course of COVID-19, the clinical laboratories also experienced an increase in phone, email, and paging inquiries about the status and anticipated resulting time of SARS-CoV-2 testing. A call center consisting of laboratory staff, resident and attending physicians in Pathology, and IS volunteers was also implemented to specifically answer questions about SARS-CoV-2 testing. The call center was operated 12 hours per day, 5 days per week and allowed for the processing and laboratory testing staff to focus on their work instead of answering an influx of calls. Many of the staff operating the call center worked remotely and had access to dashboard and tracking software to facilitate their ability to respond to questions. To help offset the increased volume of inquiries, the Pathology Informatics team created a dedicated web application for SARS-CoV-2 specimen tracking which was accessible to providers at BWH. The application was populated with data from the LIS database in order to display where a sample was in the clinical pipeline (e.g., collected, undergoing processing/extraction, on the assay) (Table 1).

Additionally, a similar application allowed infection control and select infectious disease physicians with advanced access to review RT-PCR cycle threshold (Ct) values to give a rough assessment of viral RNA burden for positive patients. The use of cycle threshold values is not FDA approved but can provide valuable insight as to the illness trajectory of a patient. Specifically, RT-PCR assay results are interfaced to the LIS, including Ct values for pertinent targets. These values are not transmitted to the EHR. A LIS database query is then performed to capture Ct values and display them in the application. Staff with advanced access are able to search for all SARS-CoV-2 tests performed for a patient, along with the Ct values for the appropriate targets.

We continue to have discussions with infection control on the advantages and limitations of Ct values and have often found the answers to the following questions are both patient and circumstance dependent: How can clinicians troubleshoot questionable qualitative results? What is the clinical significance of a low positive result (high Ct) that does not repeat or a persistently low positive result in an immunocompromised patient? Can we utilize Ct to help prioritize contact tracing?

External Clinical Collaborations

From the start of the pandemic, it was clear that a bottleneck to care would be availability of testing. In early March, tests could only be sent out to state DPH laboratories as no commercial vendors had been allowed to develop assays. Within the month, multiple reference laboratories (e.g., Viracor (Lee's Summit, MO), Quest (Secaucus, NJ), ARUP (Salt Lake City, UT), Mayo Medical Laboratories (Rochester, MN)) began to offer testing. However, their capacity was limited, and their TAT's were several days long and inconsistent. Despite the disadvantages of their initial offerings, it was apparent that we did not have the capacity to perform all testing in-house and unless we made a significant investment in space and resources, we would need to continue to send out our less time-sensitive testing.

In the spring of 2020, research laboratories in Boston and Cambridge had almost all shut down their activities. The Broad Institute, a research institution affiliated with Harvard University and the Massachusetts Institute of Technology (11), had extensive sequencing capabilities and a CLIA license to perform next generation sequencing assays for somatic and germline DNA analysis, which had primarily been used to support

clinical research trials and projects that required analysis in a CLIA-certified lab. In a joint effort, staff and pathologists across MGB assisted the Broad in expanding their operations to handle infectious samples under biosafety level 2 conditions, and to run and report viral diagnostic RT-PCR tests for clinical care under CLIA (Table 1). Within two weeks, the BWH Pathology Informatics team also developed a custom interface between the BWH and the Broad Institute information systems to facilitate order transmittal, results reporting, and positive patient identification by transmitting alternative patient identifiers that met our security and patient safety standards. The Broad Institute is currently able to run approximately 100,000 samples a day using its automated platform and provides testing for Massachusetts schools and hospitals.

Community Outreach

Heeding the warnings from Wuhan, Italy, and New York City, the city of Boston established the Boston Hope field hospital in the Boston Convention and Exhibition Center in the Seaport area with the help of several local hospitals, including MGB (Table 1). This served as a lower acuity step-down facility for clinically stable SARS-CoV-2 positive patients with no safe place to quarantine post-discharge. Though Boston Hope was a state-run facility, the BWH clinical laboratories were asked to assist Boston Hope with ordering and routing basic laboratory testing to BWH clinical laboratories and establishing on-site waived and moderate complex point of care testing (POCT).

BWH aided in establishing the Boston Hope POCT program within a week of its anticipated opening, including obtaining a CLIA certificate for waived and moderate complexity testing, implementing interfaced POC whole blood glucose,

chemistry/electrolytes and hematology (hematocrit/hemoglobin) testing, , and completing training and competency for hundreds of Boston Hope staff performing POCT. For rapidity, an existing CLIA license was expanded to cover Boston Hope.

A dedicated team comprised of laboratory directors, point of care coordinators, and nursing and administrative leadership established workflow and training for temporary staff who were involved in laboratory testing orders, specimen collection, and POCT. These staff would often work at the field hospital for a week or two at a time, then transition back to their roles at other healthcare facilities, many without prior experience working with the on-site EHR. Point of care training and competency documentation for staff was particularly challenging and required close collaboration with Boston Hope nursing staff. We encountered many challenges setting up testing at the field-hospital, ranging from data connectivity to obtaining refrigerators for reagent storage. For testing sent to the BWH clinical laboratories, a limited panel of tests was created to simplify ordering (Supplemental Table 2) and programmed into an IS site-specific build to minimize test orders and processing errors. We educated the staff that paper test requisitions could be utilized in extenuating circumstances, when orders could not be placed via the EHR. Frequent, almost daily visits were made to the field hospital to stay ahead of supply shortages and to maintain operational workflows.

As the pandemic widened, community outreach became necessary for multiple departments, including clinical pathology. We worked closely with underserved ambulatory care practices to offer community-wide testing for any resident of Massachusetts, including those who were asymptomatic. A tent was set up outside BWH to register patients and perform curbside collections for SARS-CoV-2 testing. Working

closely with our clinical colleagues, we were able to receive and process up to 600 specimens per day for community testing.

Modeling Projections and Supply Chain Issues

In early March the BWH incident command modeled different scenarios for the state of Massachusetts and BWH. In response, non-emergent, elective procedures were reduced (which eventually was mandated at the state level), and each hospital department developed protocols regarding how they would respond to the pandemic; the clinical laboratory was no exception. Although SARS-CoV-2 testing and associated supplies were in the spotlight, it was also necessary for the laboratory to review the prediction models and determine their potential impact on other testing performed in the clinical laboratory (Table 1).

Working with our critical care intensivists, the essential laboratory testing required for managing COVID-19 patients was defined and communicated early on (12). With this information, and based on the proposed patient modeling, we developed dashboards to display daily volumes for critical tests (e.g., blood gas, D-dimer, procalcitonin, ferritin, blood cultures), and as a result, the clinical laboratories were able to anticipate the necessary assay reagents, and the staff, and testing platforms that would be required. There was an expected drop off in routine ambulatory testing (Figure 3a), as evidenced by routine lipid panels and Vitamin D testing volumes, and a rise in inflammatory, critical care and coagulation testing (Figure 3b) that mirrored the increase in SARS-CoV-2 PCR testing (Figure 1b).

Prior to the pandemic, the BWH chemistry laboratory performed approximately 150-200 arterial blood gases (ABG) per day. Based on the hospital modeling, we estimated that we could have received up to 800 ABGs per day at the height of the surge. With an increasing number of COVID-19 admissions, our peak hit 516 ABGs per day in the Spring. The increase in blood gas testing was similar across the country and with supply allocations, led to a critical shortage of blood gas syringes, requiring daily management and working with our clinical colleagues to reduce overutilization. At its worst point, we had only a single-day supply of syringes on-hand and had to work within the MGB network to reallocate our security supply to the hospitals that needed them. We were able to act quickly by assessing our daily inventory and blood gas volumes across the network. In addition, we quickly established contingency plans to implement newly validated POC blood gas methods, evaluated the feasibility of the redeployment of bedside instrumentation from the cardiac surgical suites to use with non-anticoagulated syringes, validated blood gas syringes from alternative manufacturers, and even investigated the ability for our pharmacy to prepare our own heparinized syringes.

Staffing and Management

In early March, BWH incident command projected about a 20% increase in admissions and planned for a maximum occupancy of 280 patients in the ICU and 685 on the general care floors. Like in many other hospitals across the country, ORs and cardiac ICUs were converted to critical care units and set aside for SARS-CoV-2 positive patients. At the same time, incident command also asked each department to only bring in the minimum necessary staff to maintain physical distancing. The clinical laboratories,

like all other departments, were paradoxically trying to simultaneously prepare for a surge in volume while decreasing staff numbers which was only possible due to the decreased workload resulting from the deferral of elective and non-emergent procedures. Based on the information provided by incident command, we established staffing models that were dependent on testing volumes and minimal testing requirements. This allowed us to quickly assess daily staffing levels (reflective of routine callouts, but also COVID-19 exposures and mandatory quarantine) and open/close necessary testing benches/areas (13,14).

Clinical laboratory staff play a unique, important, and highly specialized role in the hospital and their skills and required credentials are not easily interchangeable with other healthcare providers, making it challenging to create staffing models. Where other clinical departments could downsize to roughly 25% of their normal workforce, the clinical laboratories kept the minimum number of staff needed to maintain minimal testing, or approximately 75% of normal staff, particularly on weekend and off-hour shifts. Due to the decrease in ambulatory testing volumes, which were primarily run on the day shift, we were able to create two groups of day shift staff (Group A and B). Unfortunately, this was not possible on the evening or night shift. Group A worked on-site for one week, while Group B was working remotely and vice versa.

It was challenging for staff to set up their remote workspace, so we provided informatics support. Pathology Informatics assisted our staff with logging into virtual computers, setting up microphones, and accessing necessary files and software (Table 1). The staff working from home supported remote efforts like the newly established call center, preparing for upcoming laboratory inspections, reviewing method validations and

quality control reports, and updating Standard Operating Procedures (SOP). Staff were also asked to use their time working remotely to take courses and obtain continuing education credits.

Infection control was extremely helpful by touring the laboratory space and providing guidance on physical distancing, specimen handling, and air quality. Following the CDC guidelines, we worked with infection control to enforce the policy to hand-deliver SARS-CoV-2 swabs to the laboratory as opposed to through the pneumatic tube system. We also equipped our hematology laboratory to be able to handle bronchoalveolar lavage and other highly infectious specimen types and designated space for staff to eat safely.

Patient-Facing Pathology Services and Reopening

As the Boston community began to reopen, BWH and its affiliates were faced with new challenges regarding increasing ambulatory patient volumes, particularly those areas of Pathology that were patient-facing such as phlebotomy. While many departments maintained physical distancing by increasing virtual visits, this was not feasible for blood draws. Infection control provided the standards required so that our phlebotomy locations could safely draw both symptomatic and asymptomatic patients. Ideally, symptomatic patients should be drawn in an isolated room, however, if necessary, floor length curtains and proper personal protective equipment would be sufficient. We continue to struggle to obtain adequate supplies of plexiglass barriers and curtains, which has led to our continued drawing of symptomatic patients in separate exam rooms. This unfortunately limits throughput and is not universally available at all collection sites requiring re-routing of patients.

Maintaining physical distance in the phlebotomy waiting areas is also challenging. Many of our phlebotomy draw stations have a small footprint and/or limited waiting area space, necessitating us to reduce the number of waiting room chairs and determine an overflow area for patients. Patients were anxious about using the overflow area in fear that they would miss their turn in line.

With the help of Informatics team, we reviewed electronic applications to register and manage the flow of patients (Table 1). We are currently piloting a mobile application that allows patients to log in, enter a queue at a specific phlebotomy location, and receive a text message when the phlebotomist is ready to draw their blood. Patients can wait in the overflow area, or at another location depending on the anticipated wait time and position in the queue. Our workflow has undergone several iterations as we prepare to expand to include additional sites and symptomatic patients.

Lessons Learned (Table 1)

Lesson 1: Diversify your SARS-CoV-2 testing methodology

In effect, during the height of the pandemic, the clinical laboratories were running a start-up operation while maintaining all of our routine testing operations (2,15). Situations would change, overnight or often within hours. Upon reflection, each laboratory stated what ultimately contributed to success was the flexibility that was needed to adapt to reagent shortages amid rising volumes. This was identified early on; each laboratory designated dedicated teams that almost continuously validated new specimen types and reagents for SARS-CoV2 and other laboratory testing, anticipating the pending shortages.

Permanent dedicated space, resources and personnel (e.g., informatics, directors, staff) for research and validation will assist with the flexibility and adaptability to respond to another pandemic or crisis requiring laboratory support.

In the absence of a robust testing and reagent supply pipeline, we recommend that laboratories validate various options, when possible, for all testing components, develop contingency plans, and anticipate supplies and resources required for additional validations not limited to just molecular, but also for expanded testing such as antigen testing. Laboratories should also consider associated regulatory impacts such as need for additional proficiency testing and comparison of performance among different SARS-CoV-2 testing platforms. Our clinical laboratories were able to effectively manage the increased SARS-CoV-2 testing demands during the surge by: (1) increasing staffing and shifting personnel and resources so that we could rapidly validate and upscale testing and respond to supply shortage, (2) consolidating specimen processing and testing into a single laboratory to increase efficiency and minimize errors, (3) identifying patient populations and testing that could be sent out to reference laboratories, if needed, to continue to maintain adequate testing TAT for inpatients and respond to reagent allocation/shortages across various testing platforms, and (4) dedicating space for training and development to help us respond to surge testing volumes.

Lesson 2: Have your informatics team at the table

An effective and responsive Pathology Informatics team that is knowledgeable in laboratory operations was also critical to the pandemic response (16). Informatics support was instrumental in every operation: interfacing LDTs to the LIS, creating algorithms to

triage specimens (to up to seven different platforms at one point) based on needed turn-around time, developing dashboards with volumes and metrics and designing new software to facilitate the clinical implementation of LDTs and workflow for Broad Institute send-out testing. The Informatics team was pervasive behind all testing efforts.

Collaborations across hospital departments and divisions, especially with the Pathology Informatics team, were critical components of our and others' responses to the pandemic (16). Beyond Infection Control and Infectious Disease, relationships established with the Emergency Department, Labor and Delivery, Procedural and Peri-Procedural Departments, Nursing, Patient Bed Management, Materials Management and Quality and Safety teams were essential in our multi-disciplinary response to the COVID-19 pandemic. Furthermore, we encourage laboratories to collaborate with clinicians to create an algorithm in their EHR to electronically triage and direct specimens to different SARS-CoV-2 assays based on clinical need, so the burden does not fall on the laboratory at specimen receipt and accessioning to determine which testing platform to utilize.

The ability to operate and/or activate a call center was also extremely beneficial for our laboratory staff and is an activity that can be done remotely. Our call center has now been expanded across the MGB network and includes dedicated staff with access to tracking software developed by the Informatics team.

Lesson 3: Communicate and collaborate

Effective communication between different clinical laboratories, within the pathology department, and between departments was also critical. The microbiology laboratory was key in working with infectious disease clinicians in deciding testing

guidelines for SARS-CoV-2 as well as other respiratory viruses, the utility of tools such as Ct and necessary performance characteristics of testing, media and specimen types. Near constant communication between MGB hospitals was established to triage reagent supplies between sites. And communication at the state and national level will continue to be instrumental in curtaining the pandemic.

Fostering existing external relationships and forming new relationships was necessary for us to successfully increase our testing capacity and serve our community. Laboratories should collaborate with research or other specialized facilities that exist in their surrounding communities, who may offer additional resources, space, and expertise. We should also recognize the role we can play in the local community during a pandemic and be prepared to assist. For those asked to be involved in the creation or reopening of a field hospital, we recommend using an existing CLIA and limiting both the POC and send out testing menu to what is essential for the acuity of patients treated, especially due to the frequency of staff turnover and consequential challenges with training.

Lesson 4: Anticipate - Plan for the worst, hope for the best

Laboratories should work with their local materials management department to ensure they have the resources to track and maintain supplies and to validate alternative supplies, ahead of time, in the event of shortages. For laboratory testing that may increase during a pandemic, laboratories should order additional supplies and forgo the 'just in time' rule in inventory management. An electronic database that tracks reagents, pipette tips, tubes, swabs, collection kits, media and storage and freezer capacity should be available and continuously monitored.

Unfortunately, we have now all experienced how unpredictably and rapidly our environment can change. We learned from the cluster of inpatients and employees who recently tested positive for SARS-CoV-2 that we should plan for periodic spikes in testing volume and new policies on surveillance testing (e.g. repeat testing on patients who test negative upon admission or patients who are at high risk for transmitting disease such as those undergoing aerosol generating procedures). Viral genome sequencing will be increasing relevant to workup additional clusters and understand disease transmission and viral mutation. Our laboratory is considering performing the sequencing in-house so we do not have to rely on the state laboratory. Anticipating any possible scenario and developing contingency plans with appropriate clinical input will be critical as we face the possibility of another surge and future pandemics.

Lesson 5: Reimagine, step outside your comfort zone

As part of our recovery and reimagining efforts following the surge, we used our experience with staff working remotely to create a work from home procedure and have arranged for new staff to work with the Pathology Informatics team during the onboarding process to be equipped to work remotely so that they are prepared for future surges or pandemics. We recommend that clinical laboratories work with their hospital leadership to define staffing and minimal laboratory testing contingency plans based on the information on unit conversations, expansions, and regional and national modeling data. This prepared us for future surges and other catastrophes that are ready to implement with little forewarning. Infection control can help guide and enforce policies as they relate to the clinical laboratory and minimizing staff contact and potential exposures.

Laboratories should consider alternatives locations for patients to have their blood drawn including a mobile unit or home draws. As our world has become exponentially more digital, the laboratory must follow suit and implement novel technologies to not only help us respond to the pandemic but also to improve efficiency and patient care.

Conclusions: While still ongoing, we believe that this pandemic has highlighted key areas of importance and enabled us to strengthen intra- and inter-departmental communication, reactionary contingency planning, and rapid assay development, validation, and implementation. Many of these experiences have also allowed us to be better prepared for the next pandemic, by establishing clear mechanisms for remote work, deploying specific response teams and customizing our specimen tracking applications and informatics dashboards. As shown in Figure 4, these have been categorized into four general phases of initial response, pathogen testing, recovery and reopening, and planning for future pandemics.

The initial response phase was and will understandably be somewhat reactionary and highly dependent upon the outbreak itself and the mode of transmission. This phase includes establishing structured hospital and departmental response teams with robust interdepartmental communication, clear infection control guidelines for handling potentially infectious material and physical distancing, staffing adjustments and establishing clear routes for remote work, preparing for changes in testing using modelling projections and established clinical order sets, and finally outlining contingency plans for alternative testing options.

Irrespective of the causative pathogen, laboratories will likely have to develop, modify, and/or validate new testing methods. This should be accompanied by testing algorithms and customized informatics dashboards to monitor specimen volumes, specimen routing, testing turnaround time and specimen tracking.

Recovery may be particularly challenging, as physical distancing and patient safety will need to be balanced against surges in patient visit volumes secondary to reopening. We have already seen an impact on phlebotomy workflows and challenges with quality and regulatory compliance (e.g. POCT) in practices that had to shut down or have onboarded a high number of new staff to meet patient demands. It's essential that sites are engaged early on and the requirements for reopening or expanded are clearly outlined.

Finally, many of the lessons learned through this COVID-19 pandemic have equipped us with a roadmap for future pandemics. Importantly, laboratories should develop standard operating procedures, discuss dedicated staff and space for new assay development, and create dashboards to assist with inventory management and test utilization. We hope that this document will serve as a guide when dealing with future pandemics and allow laboratories to become more proactive when possible during future challenges. These new set of challenges will likely be super-imposed on those of the ongoing pandemic, though with a silver lining that we will hopefully be better prepared as we have learned from our recent past.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 4 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; (c) final approval of the published article; and (d) agreement to be accountable for all aspects of the article thus ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.*

N.I. Lindeman, administrative support, provision of study material or patients.

Authors' Disclosures or Potential Conflicts of Interest: *Upon manuscript submission, all authors completed the author disclosure form. Disclosures and/or potential conflicts of interest:*

Employment or Leadership: N.V. Tolan, *The Journal of Applied Laboratory Medicine*, AACC; M. Brigl, Brigham and Women's Hospital Boston.

Consultant or Advisory Role: None declared.

Stock Ownership: None declared.

Honoraria: None declared.

Research Funding: None declared.

Expert Testimony: None declared.

Patents: None declared.

Role of Sponsor: No sponsor was declared.

References

1. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First case of 2019 novel coronavirus in the United States. *N Engl J Med* 2020;382:929–936.
2. Greninger AL, Jerome KR. The first quarter of sars-cov-2 testing: The university of Washington medicine experience. *J Clin Microbiol* 2020;58:1416-1420.
3. Coronavirus (COVID-19) Update: FDA Issues New Policy to Help Expedite Availability of Diagnostics | FDA. Available at: <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-new-policy-help-expedite-availability-diagnostics>. (Accessed October 2020).
4. Mitchell SL, St. George K, Rhoads DD, Butler-Wu SM, Dharmarha V, McNult P, Miller MB. Understanding, verifying, and implementing emergency use authorization molecular diagnostics for the detection of sars-cov-2 RNA. *J Clin Microbiol* 2020;58:796-820.
5. Miller GA, Buck CR, Kang CS, Aviles JM, Younggren BN, Osborn S, Keay CR. COVID-19 in Seattle-Early lessons learned. *J Amer Coll Emerg Phys Open* 2020;1:85-91.
6. Kim J-H, An JA, Min P-K, Bitton A, Gawande AA. How South Korea responded to the COVID-19 outbreak in Daegu. *NEJM Catalyst* 2020;1:1-14.
7. Brody BD, Parish SJ, Kanellopoulos D, Russ, MJ. A COVID-19 testing and triage algorithm for psychiatric units: One hospital's response to the New York region's pandemic. *Psych Res* 2020;291:113244
8. Loeffelholz MJ, Alland D, Butler-Wu SM, Pandey U, Perno CF, Nava A, et al. Multicenter evaluation of the cepheid xpert xpress sars-cov-2 test. *J Clin Microbiol*

2020;58:926-920.

9. Hogan CA, Sahoo MK, Huang C, Garamani N, Stevens B, Zehnder J, Pinsky BA. Comparison of the Panther Fusion and a laboratory-developed test targeting the envelope gene for detection of SARS-CoV-2. *J Clin Virol* 2020;127:104843.
10. Hanson KE, Barker AP, Hillyard DR, Gilmore N, Barrett JW, Orlandi RR, Shakir SM. Self-collected anterior nasal and saliva specimens versus health care worker-collected nasopharyngeal swabs for the molecular detection of SARS-CoV-2. *J Clin Microbiol* 2020;58:824-820.
11. The Broad Institute. <https://www.broadinstitute.org> (Accessed October 2020).
12. Brigham and Women's Hospital COVID-19 Clinical Guidelines. <https://www.covidprotocols.org> (Accessed October 2020).
13. Chambliss AB, Tolan NV. Contingency planning in the clinical laboratory: Lessons learned amidst COVID-19. *J Appl Lab Med* 2020;5:832-836.
14. Lippi G, Plebani M. The critical role of laboratory medicine during coronavirus disease 2019 (COVID-19) and other viral outbreaks. *Clin Chem Lab Med* 2020;58:1063-1069.
15. Liew MF, Siow WT, MacLaren G, See KC. Preparing for Covid-19: Early experience from an intensive care unit in Singapore. *Critical Care* 2020;24:83.
16. Grange ES, Neil EJ, Stoffel M, Singh AP, Tseng E, Rasco-Summers K, et al. Responding to COVID-19: The UW medicine information technology services experience. *Appl Clin Inform* 2020;11:265-275.

Table 1. Lessons Learned During the COVID-19 Pandemic

Lesson 1: Diversify your SARS-CoV-2 PCR testing methodology.

- Offer multiple testing platforms (including send out options) with designated backups
- Consolidate specimen processing and testing into a single laboratory
- Validate different media and specimen types for critical laboratory testing
- Monitor testing volumes, prepare for COVID-19 surges and anticipate supply shortages
- Designate space and identify personnel for ongoing validations and troubleshooting

Lesson 2: Have your informatics team at the table.

- Develop algorithms to route testing, from collection, with instrumentation-specific barcoding
- Create dashboards, metrics and applications to manage laboratory testing
- Establish a virtual call center to reduce the burden on the accessioning personnel
- Work collaboratively to ensure new informatics tools optimize operations

Lesson 3: Communicate and collaborate.

- Ensure the laboratory is engaged and included early in hospital decision-making
- Standardize test interpretation and troubleshooting across platforms
- Establish relationship with researchers that may offer additional testing capacity
- Advocate for the laboratory at the state and national level

Lesson 4: Anticipate - Plan for the worst, hope for the best.

- Expect COVID-19 clusters and associated increases in employee and patient testing
- Implement electronic inventory management systems
- Routinely evaluate testing to send out to alleviate stress on staff and/or testing capacities
- Develop response teams, SOPs, and contingency plans with identified activation triggers
- Provide community assistance and outreach through training and/or existing resources

Lesson 5: Reimagine, step outside your comfort zone.

- Set up virtual workstations and define tasks for staff to work remotely
- Employ electronic scheduling or wait-time applications that can be utilized on mobile devices
- Consider alternative solutions for blood draws particularly for high-risk patients
- Understand that your staff may be asked to adapt to new workflows and informatics tools

Table 2. BWH SARS-CoV-2 PCR Platforms and Their Characteristics (as of 11/10/20)

Platform (Performing Lab)	Hours Testing Offered	Turnaround Time (from Receipt)	Daily Capacity	Specimen Type	Acceptable Media	Additional Respiratory Testing
Cepheid GeneXpert (Microbiology)	24/7	1-2 hours	50/day*	NP	VTM, Saline	Flu A/B RSV
Hologic Panther Fusion (Microbiology)	24/7	4-6 hours	250-750/day	NP, AN	VTM, Saline	Flu A/B RSV Extended respiratory panel
Thermo Fisher TaqPath (CAMD)	12/7	8-24 hours	450-800/day	NP, AN	VTM, MTM, Saline	Flu A/B
Broad (Sent Out)	24/7	18-48 hours	1200/day	NP, AN	VTM, MTM, Saline	None

*Limited reagent supplies

NP = nasopharyngeal, AN = anterior nares, VTM = viral transport media, MTM = molecular transport media, CAMD = Center for Advanced Molecular Diagnostics

Figure 1. Turnaround Time and Volumes for In-House and Send Out SARS-CoV-2 Testing

a) The average daily turnaround time in hours from collection to result is shown for Broad (green), Thermo Fisher (yellow), Panther Fusion (gray) and Cepheid (orange) from mid-April to December 2020 and b) The weekly testing volumes for SARS-CoV-2 PCR (total (blue), Cepheid (orange), Panther Fusion (gray), Thermo Fisher (yellow), Broad (green)) are shown from mid-April to December 2020

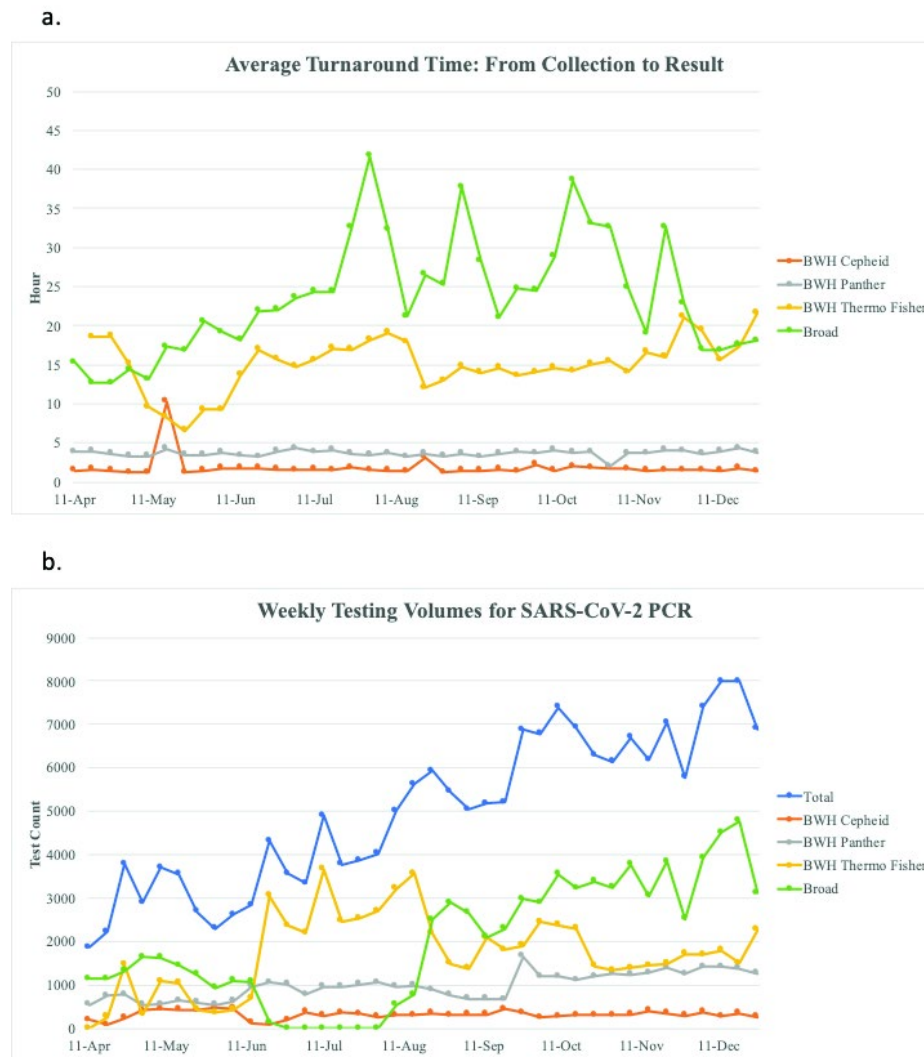
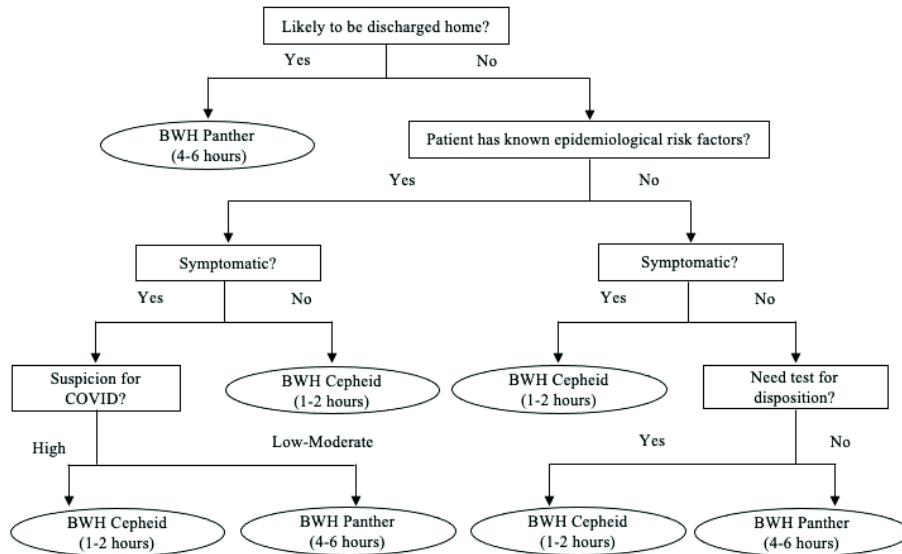


Figure 1

Figure 2. EHR Algorithm for SARS-CoV-2 Routing

The algorithm developed by informatics for triaging of SARS-CoV-2 laboratory testing for patients seen in the a) emergency department or b) ambulatory setting. Indications to route to one of four tests with different turnaround times included likelihood of discharge, known risk factors and patient symptoms.

a. Emergency Department Triage



b. Ambulatory Triage

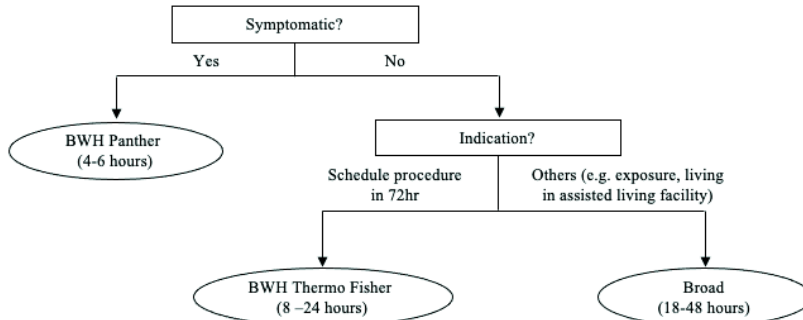
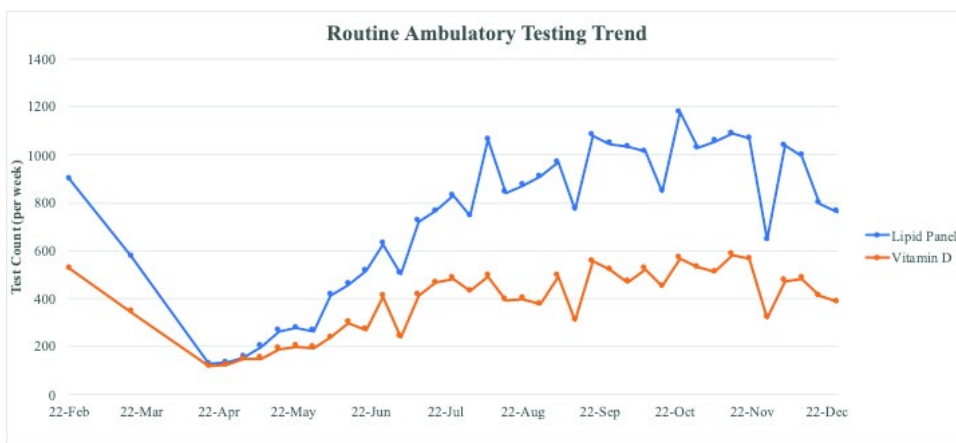


Figure 2

Figure 3. SARS-CoV-2 and Related Testing Volumes

Weekly testing volumes for a) routine ambulatory (lipid panel (blue), vitamin D (orange)) and b) inflammatory, critical care and coagulation (procalcitonin (medium blue), creatine kinase (orange), troponin T (gray), NT-proBNP (yellow), ferritin (light blue), blood gas (green), C-reactive protein (dark blue), D-dimer (brown), blood cultures (black)) from February to December of 2020 are shown.

a.



b.

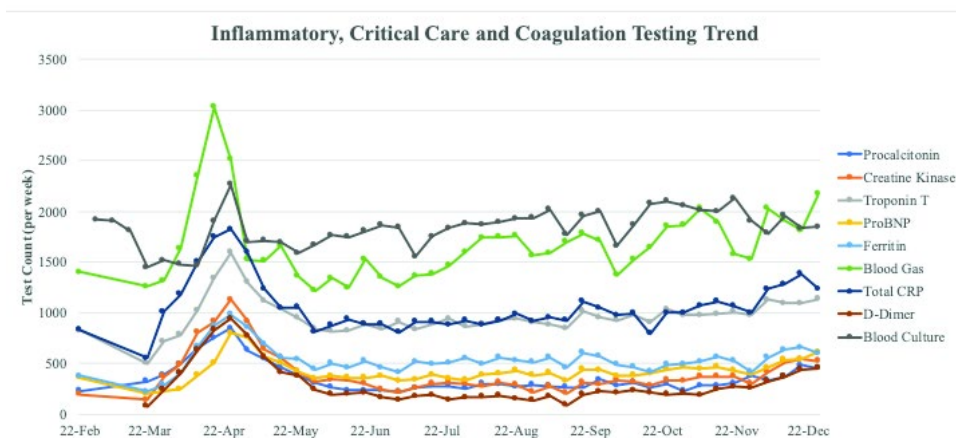


Figure 3

Figure 4. Pandemic Checklist

A flowchart and checklist of priority issues that are recommended during the current and or future pandemics, categorized into “Initial Response,” “Pathogen Testing,” Recovery and Reopening,” and “Planning for Future Pandemics.”

