Special Collection: COVID-19–Regular Article

Academic Pathology: Volume 8
DOI: 10.1177/23742895211010247
journals.sagepub.com/home/apc

SAGE

Experience With Pretravel Testing for SARS-CoV-2 at an Academic Medical Center

Katherine L. Imborek, MD[1], Matthew D. Krasowski, MD, PhD[2], Paul Natvig, MD[3], Anna E. Merrill, PhD[2], Daniel J. Diekema, MD[2,4], and Bradley A. Ford, MD, PhD[2]

Abstract

International travel has been a significant factor in the coronavirus disease 2019 pandemic. Many countries and airlines have implemented travel restrictions to limit the spread of the causative agent, severe acute respiratory syndrome coronavirus-2. A common requirement has been a negative reverse-transcriptase polymerase chain reaction performed by a clinical laboratory within 48 to 72 hours of departure. A more recent travel mandate for severe acute respiratory syndrome coronavirus-2 immunoglobulin M serology testing was instituted by the Chinese government on October 29, 2020. Pretravel testing for severe acute respiratory syndrome coronavirus-2 raises complications in terms of cost, turnaround time, and follow-up of positive results. In this report, we describe the experience of a multidisciplinary collaboration to develop a workflow for pretravel severe acute respiratory syndrome coronavirus-2 reverse-transcriptase polymerase chain reaction and immunoglobulin M serology testing at an academic medical center. The workflow primarily involved self-payment by patients and preferred retrieval of results by the patient through the electronic health record patient portal (Epic MyChart). A total of 556 unique patients underwent pretravel reverse-transcriptase polymerase chain reaction testing, with 13 (2.4%) having one or more positive results, a rate similar to that for reverse-transcriptase polymerase chain reaction testing performed for other protocol-driven asymptomatic screening (eg, inpatient admissions, preprocedural) at our medical center. For 5 of 13 reverse-transcriptase polymerase chain reaction positive samples, the traveler had clinical history, prior reverse-transcriptase polymerase chain reaction positive, and high cycle thresholds values on pretravel testing consistent with remote infection and minimal transmission risk. Severe acute respiratory syndrome coronavirus-2 immunoglobulin M was performed on only 24 patients but resulted in 2 likely false positives. Overall, our experience at an academic medical center shows the challenge with pretravel severe acute respiratory syndrome coronavirus-2 testing.

Keywords

antibodies, coronavirus disease 2019 nucleic acid testing, immunoglobulin M, polymerase chain reaction, severe acute respiratory syndrome coronavirus-2, serology

Received February 21, 2021. Received revised March 16, 2021. Accepted for publication March 21, 2021.

[1] Department of Family Medicine, University of Iowa Hospitals and Clinics, IA, USA
[2] Department of Pathology, University of Iowa Hospitals and Clinics, IA, USA
[3] Division of Student Life, Student Health, University of Iowa, IA, USA
[4] Division of Infectious Diseases, Department of Internal Medicine, University of Iowa Hospitals and Clinics, IA, USA

Corresponding Author:
Matthew D. Krasowski, MD, PhD, Department of Pathology, University of Iowa Hospitals and Clinics, 200 Hawkins Drive, C671 GH, Iowa City, IA 52242, USA.
Email: matthew-krasowski@uiowa.edu

Introduction

Coronavirus disease 2019 (COVID-19) pandemic has caused major impacts on travel within and between countries, as international travel has been a significant driver of the pandemic.[1-4] In order to limit the spread of the causative agent, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2),[5] many countries and local regions have instituted travel bans and restrictions.[3,6,7] The emergence of variant strains of SARS-CoV-2, some associated with increased risk of transmission, have added new urgency to efforts to limit global spread of the virus.[8,9] To date, an estimated 106 000 000 cases and 2 130 000 deaths throughout the world have been attributed to SARS-CoV-2 infection.[10,11] International travel presents a particular challenge during the COVID-19 pandemic, due to variability in restrictions between countries that may change over time.[3,4,12,13] Travelers run the risk of not being able to reach their final destination and may additionally end up temporarily stranded in another country.

Diagnostic testing for SARS-CoV-2 mainly utilizes reverse-transcriptase polymerase chain reaction (RT-PCR) on a variety of specimen types from the respiratory tract.[14] Reverse-transcriptase polymerase chain reaction testing generally has the highest sensitivity and specificity of available diagnostic methods for detecting active infection. More recently, antigen tests have emerged as an option for acute diagnosis, including some point of care and at-home tests.[14,15] However, compared to RT-PCR, antigen tests have lower sensitivity, particularly for asymptomatic disease, and most also have lower specificity. Serologic assays for antibodies against SARS-CoV-2 represent an alternative resource, although they are far more useful for defining epidemiology with seroprevalence studies than they are for clinical diagnosis.[16-18]

In an effort to increase safety of international travel, destination countries and/or airlines may mandate SARS-CoV-2 testing in addition to other measures.[3,7,12,13,19] Common requirements include a negative SARS-CoV-2 RT-PCR performed by a clinical laboratory within 48 to 72 hours of departure, with official documentation of the results. This requirement can be difficult to satisfy whether there are limitations on test availability and/or slow turnaround time for results. In the United States, SARS-CoV-2 testing capacity varies considerably by state, with an amalgam of testing performed by entities such as hospital laboratories, commercial reference laboratories, public health facilities, and public–private partnerships. Supply chain and turnaround time issues with SARS-CoV-2 testing have been a recurring problem in the United States.[18,20,21] To our knowledge, antigen tests have not been an acceptable alternative to RT-PCR testing for international travel, although this testing may be useful for travel within countries.[2,22,23]

In addition to SARS-CoV-2 RT-PCR testing, China issued a requirement on October 29, 2020, that international travelers needed to have both negative RT-PCR and immunoglobulin M (IgM) serology tests, which are used as part of the "green health code" biological passport needed within 48 hours of boarding a direct flight to China.[24] The rationale for this strategy is presumably to increase the detection window for acute SARS-CoV-2 infection using IgM as an early serology marker, as there are people who may be negative by SARS-CoV-2 RT-PCR several weeks or more after initial infection but still positive for SARS-CoV-2 IgM serology.[25] However, by the time RT-PCR is negative, IgM serology may be positive even though transmission risk of SARS-CoV-2 is minimal. In the original mandate, SARS-CoV-2 RT-PCR and IgM testing could be performed at any location (including the original departure city).[24] This requirement was modified on December 23, 2020, so that the testing needed to be performed in the city of the direct flight to China.[26] To meet this demand, clinical laboratories within or near major United States departure cities (eg, Los Angeles, New York City, San Francisco, Seattle) and international airports now offer this testing with short turnaround time. The testing may be performed by private laboratories, public–private partnerships, or regional public health entities.[2,3,7,13,23,27,28] A survey of sites offering this type of testing show typical prices of US$150 to US$350 for RT-PCR or IgM serology performed with short turnaround time (sometimes cheaper prices for slower turnaround time), with services such as custom travel certificates and documentation available at additional cost.[29-31] Some localities such as Alaska offer free testing for residents upon arrival but charge for nonresidents.[31,32] Hawaii currently (February 2021) requires pretravel RT-PCR testing at the expense of travelers and, uniquely, will not accept test results generated by laboratories outside their own "preferred provider" list.[33]

In this report, we describe the workflow adopted for pretravel SARS-CoV-2 testing at an academic medical center. We analyze pretravel SARS-CoV-2 RT-PCR and IgM testing and issues encountered with this testing. Lastly, we discuss findings in the broader context of the possible downstream consequences of SARS-CoV-2 testing in asymptomatic individuals.

Methods

Institutional Setting

The University of Iowa Hospitals and Clinics (UIHC) is an 845-bed tertiary/quaternary care medical center located in Iowa City, Iowa. UIHC is currently the only academic medical center in Iowa, a predominantly rural state with few urban areas. UIHC is a regional center for management of COVID-19 patients, including those who require critical care.

Patients

The present study had approval from the Institutional Review Board of University of Iowa as a retrospective study with waiver of informed consent (protocol #202012362). UIHC uses Epic Hyperspace (Epic, Inc) as the electronic health record (EHR) for both inpatient and outpatient clinical care. UIHC uses Epic MyChart as the electronic portal for patients or

designated proxies to access individual patient medical information including results of diagnostic tests.[34] The laboratory information system is Epic Beaker Clinical Pathology.[35] Data for this study were extracted with Epic Reporting Workbench (RWB), a tool for querying the Epic database for patient data (including laboratory tests) meeting specified parameters.[36] In the time frame of October 27, 2020, through January 26, 2021, patient demographics and test results for SARS-CoV-2 RT-PCR and IgM were obtained. A specialized RWB report identified the subset of RT-PCR testing that was documented as "pre-travel" in the order entry workflow. The first documented orders for pretravel SARS-CoV-2 RT-PCR and IgM serology were on October 27, 2020, and November 18, 2020, respectively.

Assays

In the retrospective time frame of this study, the vast majority of RT-PCR testing was performed on the TaqPath COVID-19 Combo Kit, using KingFisher Flex nucleic acid extraction and QuantStudio 5 thermocyclers (all ThermoFisher Scientific) according to the manufacturer's instructions.[37] Samples were collected using nasopharyngeal swabs and non-inactivating viral transport media from several manufacturers, all of which were internally validated for equivalent performance. In rare instances (primarily for preadmission testing of asymptomatic psychiatric patients, and never for exposures or outpatients) the Cepheid Xpert Xpress SARS-CoV-2 was used to generate a more rapid result (Cepheid).[38]

The SARS-CoV-2 IgM assay used was the DiaSorin Liaison SARS-CoV-2 IgM assay (DiaSorin Inc) run on the DiaSorin Liaison XL analyzer. This assay received an Emergency Use Authorization (EUA) from the United States Food and Drug Administration (FDA) on September 29, 2020.[39] At the time of decision-making, this represented the only option for a SARS-CoV-2 IgM assay (other than point of care) that would run on existing instrumentation in the UIHC clinical laboratories. The assay is a chemiluminescent immunoassay that detects IgM targeting the spike (S) receptor-binding domain antigen. Positivity is defined as an assay signal of 1.1 or greater. Other SARS-CoV-2 serology testing performed at UIHC included the Roche Diagnostics Elecsys Anti-SARS-CoV-2 assay and the DiaSorin SARS-CoV-2 S1/S2 immunoglobulin G (IgG) assays using validations previously published.[40] The Roche serology assay was run on a cobas e602 analyzer and detects total antibodies (IgG, IgM, immunoglobulin A [IgA]) targeting the nucleocapsid (N) antigen. The Roche serology assay obtained EUA from the FDA on May 4, 2020. The DiaSorin IgG assay targets the S1 and S2 antigens and received EUA from the FDA on April 26, 2020. Similar to the DiaSorin IgM assay, the DiaSorin IgG runs on the DiaSorin Liaison XL analyzer. The State Hygienic Laboratory of the University of Iowa performed the Beckman-Coulter Access SARS-CoV-2 IgM assay, which targets the spike receptor-binding domain antigen. The Hygienic Laboratory brought their SARS-CoV-2 IgM assay to production later than UIHC; however, once available, the Beckman assay represented a different platform option for SARS-CoV-2 IgM testing. This became an alternative testing methodology, especially in working up suspected SARS-CoV-2 IgM false positives on the DiaSorin assay. The Beckman-Coulter IgM assay received EUA from the FDA on October 8, 2020.

Results

Developing Workflow for Pretravel Severe Acute Respiratory Syndrome Coronavirus-2 Reverse-Transcriptase Polymerase Chain Reaction and Immunoglobulin M Testing at University of Iowa Hospitals and Clinics

In the early phases of the COVID-19 pandemic at UIHC (April through August 2020), there were difficulties in accommodating requests for pretravel SARS-CoV-2 testing given uncertain RT-PCR supply chain and steadily increasing test volumes for clinical indications that expanded to include protocol-driven testing for inpatient admissions and prior to aerosol-generating surgeries or procedures. Some pretravel testing occurred through outpatient clinics or other mechanisms; however, we do not have a reliable way of capturing that volume. As the supply chain stabilized at UIHC in autumn 2020, attention turned toward developing a workflow that allowed for pretravel testing by a standardized process, with patient self-pay and encouragement to retrieve the results in the patient electronic portal (MyChart). By this time, SARS-CoV-2 RT-PCR tests results were being released to MyChart within one hour of the final result appearing in the EHR, a contrast to the typical one full business delay for most laboratory tests at UIHC during this time frame.[34]

Figure 1 shows the basic workflow for pretravel testing developed, with an emphasis on directing patients to their primary care provider (PCP), if they had one within UIHC, or to the UIHC Travel Clinic. Optimization of the workflow was a multidisciplinary process that involved leadership for primary care clinics, travel clinics, patient financial services, and hospital information technologies. Positive RT-PCR results for pretravel testing were followed up by a pool of staff from the influenza-like illness (ILI) clinics, similar to other outpatient SARS-CoV-2 RT-PCR ordering.

The rationale for the workflow choices were as follows. The travel clinic did not have the resources to handle the volume of patients projected to need pretravel testing. Therefore, the decision was made to reserve the specific expertise of the travel clinic for only those patients without a PCP in our health system. For those patients with a PCP, the system had adequate resources to absorb the number of patients requesting pretravel testing. Thus, the decision was made to branch the workflow at the presence or absence of a PCP in our system. All RT-PCR results across our ambulatory environment (excluding emergency department, Labor and Delivery, and inpatients) have been viewed by and managed by the central ILI triage team. In this manner, there was a standardized process of follow-up for a positive RT-PCR test. This included the following as

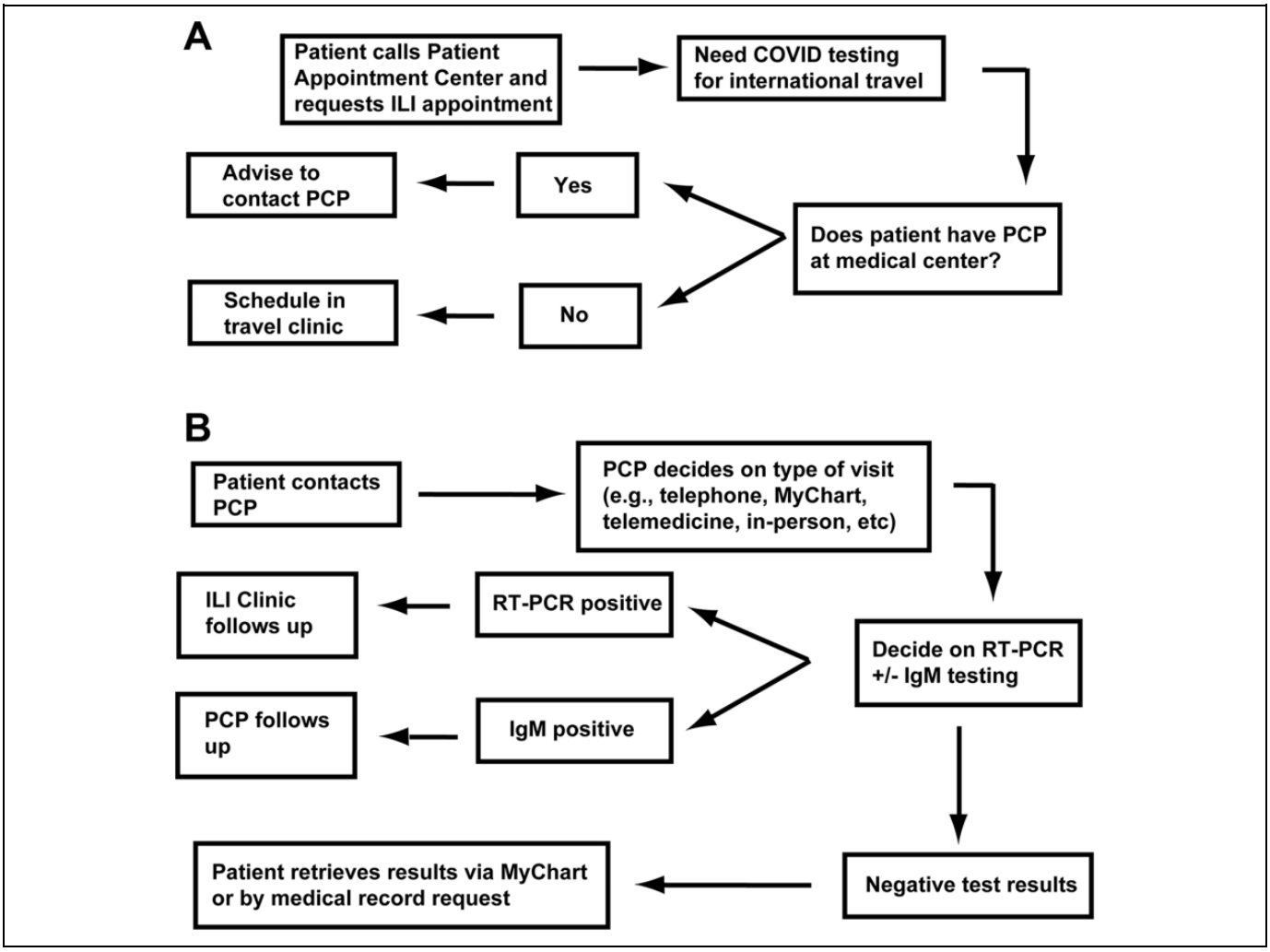

Figure 1. Workflow for pretravel testing. (A) Process for patient to request testing through the patient appointment center. (B) Workflow for testing ordered through primary care physician. ILI indicates influenza-like illness; PCP, primary care physician; RT-PCR, reverse-transcriptase polymerase chain reaction.

appropriate to the specific patient: assessment of symptoms, determination of the need to escalate care, enrollment into the appropriate home monitoring pathway, and instruction regarding isolation and quarantine of the patient and close contacts.

Because the SARS-CoV-2 IgM testing was newer and considered less straightforward for interpretation, the decision was made to have the PCPs or travel clinic follow-up and manage these results. The general guidance for a positive SARS-CoV-2 IgM results was the following: RT-PCR testing, monitor for symptoms, and, if appropriate, retest RT-PCR. For patients who remain without symptoms, follow-up testing with a SARS-CoV-2 total antibodies or IgG test 1 to 2 weeks later was to be considered. PCPs or travel clinic providers would discuss with the patient the meaning of the result, for example, need for isolation, further testing. If the SARS-CoV-2 IgM and RT-PCR was both positive, then it was easy to interpret as a likely recent positive. In the more challenging scenario of a negative RT-PCR but positive SARS-CoV-2 IgM, the guidance was to manage on a case-by-case basis including more detailed exposure history (including close contacts with suspected or proven infection), thorough history for any signs and symptoms of COVID-19, and review of other diagnostic testing. In some cases, a decision to repeat IgM by another methodology was an option to ensure reliability, especially with concerns over false positives.

The Diasorin SARS-CoV-2 IgM assay was validated and brought in-house at UIHC solely for pretravel-related testing. The UIHC clinical laboratories also perform the Roche SARS-CoV-2 total antibodies assay. Although this assay is designed to bind IgM antibodies in addition to IgG and IgA, the assay manufacturer makes no specific claims about detection of IgM in the package insert. Given that the China travel requirements clearly specify IgM-specific assays,[24,26] we did not feel the Roche total antibodies assay would satisfy the IgM requirement. Multidisciplinary discussions did not identify any indications for IgM testing other than to meet the new international travel requirements from China. Clinical benefit for IgM-specific assays has also not been identified in practice

Table 1. Demographics and Characteristics of Patients Who Underwent RT-PCR Testing.*

Variable	RT-PCR asymptomatic screening*	RT-PCR exposure and/or symptomatic*	Overall RT-PCR testing*
Number of unique patients (female/male/total)	8379/8039/16 418	20 089/16 633/36 722	27 699/24 106/51 805
Age in years (mean/median/range)	44.7/47.3 (0.0->89)	32.4/29.3 (0.0->89)	36.1/32.8 (0.0->89 years)
Total number of tests	32 125	48 553	80 678
Unique patients with at least 1 positive result	629 (3.8%)	8755 (23.8%)	9385 (18.1%)
Overall number of positive tests	724 (2.3%)	8,791 (18.1%)	9515 (11.8%)
Overall number of indeterminate test results	60 (0.2%)	91 (0.2%)	151 (0.2%)
Number of results viewed in MyChart	15 002 (46.7%)	39 225 (80.8%)	54 463 (67.5%)

Abbreviation: RT-PCR, reverse transcriptase polymerase.
* The overall data covered October 26, 2020, through January 29, 2021. "Asymptomatic Screening" encompasses orders in asymptomatic patients without known exposure as part of screening protocols such as inpatient admissions, preprocedural, or pretravel. "Exposure and/or Symptomatic" include all other orders based on possible COVID-19 symptoms and/or exposure to individuals with COVID-19 infection. There were 1335 patients who had testing in both categories.

guidelines for SARS-CoV-2 serology testing.[16,41] Iowa does not have an airport with direct flights to China, with the nearest large international airports located in Chicago, IL (217 miles away), St. Louis, MO (246 miles), and Minneapolis, MN (270 miles). Direct flights to the major West Coast international airports (eg, Los Angeles, San Francisco, Seattle) are also limited from the smaller Eastern Iowa Airport (Cedar Rapids, IA) and Quad City International Airport (Moline, IL). Thus, travelers from Iowa had to consider time factors involved in getting the testing locally or obtain that testing in the city where the direct flight to China departed.

The requirement for SARS-CoV-2 IgM testing caught travelers off-guard. As of the date in which the requirement took effect (October 29, 2020),[24] none of the local or major commercial reference laboratories that UIHC utilized for send-out studies offered this testing. Early requests for testing included visiting Chinese scholars who were attempting to return to China at the end of their visa. University of Iowa Student Health was an important collaborator throughout this process, as international students returning to China were predicted to constitute a high proportion of those needing testing.

The process for ordering pretravel SARS-CoV-2 IgM testing built on the workflow established for pretravel SARS-CoV-2 RT-PCR testing. The expectation was that the ordering provider (Student Health, PCP, or Travel Clinic) would do follow-up of positive results. Infectious Disease and Epidemiology assisted with provider education on the IgM testing, with information distributed via institutional Marketing and Communication. This educational information built on material developed for the earlier rollout of SARS-CoV-2 total antibodies testing in May 2020.[42]

Pretravel Severe Acute Respiratory Syndrome Coronavirus-2 Reverse-Transcriptase Polymerase Chain Reaction Testing Results

In the retrospective analysis time frame, a total of 80 678 SARS-CoV-2 RT-PCR tests were run on 51 805 unique patients (Table 1). The overall positive rate per test was 11.8% (0.2% indeterminate), with 18.1% of unique patients tested in this time frame having at least one positive result. Ordering of RT-PCR testing was restricted, with multiple test codes subdividing type and priority of testing depending on clinical indication or protocol. Severe acute respiratory syndrome coronavirus-2 RT-PCR testing could be broadly separated into asymptomatic screening (encompassing testing performed for protocol indications such as inpatient admission or preprocedural testing) and exposure/symptomatic indications (active symptoms consistent with COVID-19 and/or exposure to known cases). Not surprisingly, exposure/symptomatic RT-PCR testing had an overall positivity rate roughly 8-fold higher than asymptomatic screening, with 18.1% overall test positivity (0.2% indeterminate) and 23.8% of unique patients tested having at least one positive. Asymptomatic testing yielded overall 2.3% positive tests (0.2% indeterminate) and 3.8% of unique patients tested having at least one positive. Pretravel RT-PCR was performed 582 times (0.7% of all RT-PCR testing) on 556 unique patients (Table 2), with overall test positivity of 2.2% (0.2% indeterminate) and 2.4% of unique patients tested for pretravel had at least one positive. These positive rates are similar to the overall asymptomatic testing cohort described above.

Patients accessed pretravel RT-PCR results in Epic MyChart at a high rate, with 555 (95.4%) of 582 results viewed in MyChart (Table 2). The average time to view was 9.4 ± 6.8 hours (mean $\pm$ SD) after result released to MyChart, with 482 (86.8%) of the 555 transmitted results viewed within 12 hours and 529 (95.3%) of 555 results viewed within 24 hours. In contrast, 15 002 (46.7%) of 32 125 asymptomatic SARS-CoV-2 RT-PCR tests and 39 225 (80.8%) of 48 553 exposure/symptomatic RT-PCR tests were viewed in MyChart (Table 1). For comparison, we also calculated MyChart view rates to 3 other tests (basic metabolic panel, complete blood count, and D-dimer) commonly ordered in patients with a differential diagnosis that includes COVID-19. The aggregate MyChart view rates for these 3 tests were as follows: inpatient, 1595 (22.6%) of 7066 results viewed in MyChart; outpatient, 5770 (32.2%) of 17 940 results; and total, 7365 (29.5%) of 25 006 results.

Table 2. Demographics and Characteristics of Patients Who Underwent Pretravel SARS-CoV-2 Testing Compared to Overall RT-PCR Testing.

Variable	Pretravel RT-PCR*	Pretravel SARS-CoV-2 IgM*	SARS-CoV-2 total antibodies (not for travel)*
Number of unique patients (female/male/total)	271/285/556	15/9/24	413/350/763
Age in years (mean/median/range)	38.9/37.3 (0.9-86 years)	28.2/23.0 (2.5-59.9 years)	44.2/43.6 (0.3->89 years)
Total number of tests	582	27	787
Unique patients with positive results	13 (2.3%)†	3 (12.5%)	191 (25.0%)†
Number with previous positive RT-PCR result	6	0	156
Average days (SD) since previous positive	43.7 (22.2)	NA	4.4 (10.1)
Number with previous negative RT-PCR result	3	3	249
Overall number of positive tests	13 (2.2%)	6 (22.2%)	194 (24.7%)§
Overall number of indeterminate test results	0 (0.0%)	NA	41 (5.2%)§
Number of results viewed in MyChart	555 (95.4%)	24 (88.9%)	491 (62.4%)

Abbreviations: IgM, immunoglobulin M; RT-PCR, reverse transcriptase polymerase; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SD, standard deviation; UIHC, University of Iowa Hospitals and Clinic; NA, not applicable.

*Pretravel RT-PCR are orders where "pre-travel" was documented reason in order entry for the RT-PCR testing. SARS-CoV-2 IgM testing was restricted to travel protocols. The overall data covered October 26, 2020, through January 29, 2021.

†There were no indeterminate RT-PCR results in the pretravel group. For the overall RT-PCR testing, a total of 9530 (21.7%) patients had either an indeterminate or positive RT-PCR result or both. Indeterminate results at UIHC were always repeated from the beginning to rule out false positives and were reported as "indeterminate" but flagged as positive.

§For the overall RT-PCR testing, 32 070 (39.8%) of 80 678 tests were ordered in asymptomatic patients without known exposure as part of screening protocols such as inpatient admissions, preprocedural, or pretravel. Within this group, 717 (2.2%) of 32 070 were positive and 60 (0.19%) were indeterminate. The remaining 48 608 (60.2%) of 80 678 tests were ordered for patients with symptoms and/or suspected exposure to someone else with infection. Within this group, 8798 (18.1%) of 48 608 were positive and 91 (0.19%) were indeterminate.

Table 3. Patients Who Tested Positive in Pretravel SARS-CoV-2 Testing.

		RT-PCR target cycles			
Age/Sex	Previous testing results	Nucleocapsid	ORF1ab	Spike	Repeat testing results
20 Female	NA	33.6	34.6	38.9	NA
23 Male	Positive, 94 days prior*	28.0	28.5	29.1	NA
24 Male	NA	>40	33.2	>40	NA
27 Female	Positive, 45 days prior*	34.3	35.9	>40	NA
30 Male	Negative, 35 days prior	33.2	31.4	31.9	Negative, 1 day after
36 Male	NA	33.5	32.9	36.5	NA
37 Male	NA	32.5	31.9	34.3	NA
40 Male	Positive, 45 days prior*	32.1	32.4	33.2	NA
44 Female	Positive, 24 days prior*	32.2	31.4	39.3	NA
44 Male	NA	34.5	33.9	>40	NA
54 Male	NA	27.9	26.3	27.0	NA
68 Male	Positive, 76 days prior*	32.1	32.5	32.2	NA
71 Male	NA	31.1	30.2	35.1	Negative, 1 day after

Abbreviations: NA, not available; RT-PCR, reverse-transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.
* Pretravel RT-PCR showed higher cycle threshold than the prior positive.

Table 3 summarizes RT-PCR testing for the 13 patients who tested positive by RT-PCR for pretravel testing. Five of the patients had a prior RT-PCR positive (range: 24-94 days); each of these showed higher PCR cycle thresholds, suggesting a lower residual RNA burden, for the pretravel testing compared to the initial positive but were all still positive for the 3 viral regions targeted by the assay [nucleocapsid (N), ORF1ab, spike (S)]. Interestingly, 2 patients were retested a day after their pretravel testing was positive and were each negative on retest. Both were cases where the pretravel testing was positive but with high cycle thresholds for all 3 RT-PCR targets. For those testing negative for pretravel RT-PCR, 12 (2.1%) of 569 results were associated with patients who had at least one prior positive for RT-PCR testing performed for clinical reasons.

Pretravel Severe Acute Respiratory Syndrome Coronavirus-2 Immunoglobulin M Serology Testing

Severe acute respiratory syndrome coronavirus-2 IgM was performed for only 27 tests on 24 unique patients, with 3 (12.5%) patients testing positive. Testing was discontinued after China amended the requirements so that testing had to be performed in the city of the departing flight to China. All 3 who tested positive were students.

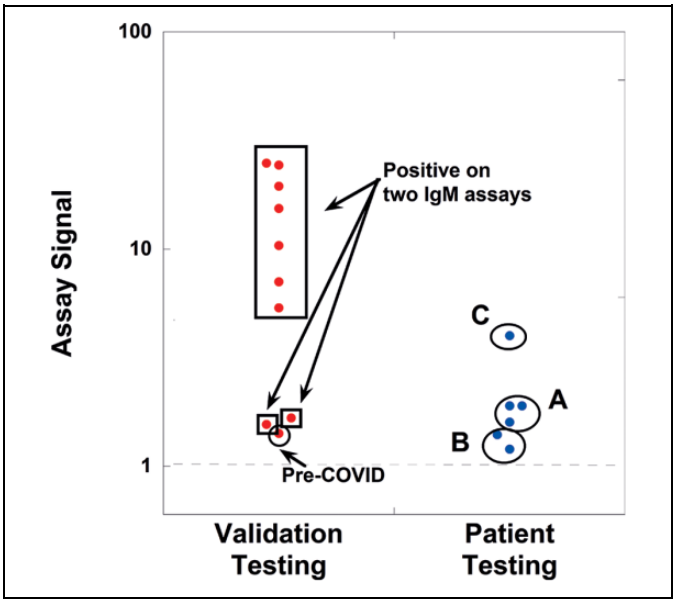

Figure 2. Assay cutoff values for immunoglobulin M (IgM) positive samples. The samples on the left side of the figure are samples that tested positive in assay validation studies. The validation samples are annotated by those that were positive on 2 different IgM assays versus one sample that was collected prior to the pandemic ("pre-COVID"). The samples on the right side of the figure are patient samples from pretravel testing. Patients A, B, and C are discussed in more detail in the article. The criteria for assay positivity are a signal of 1.10 or greater (dashed line).

Two of the students positive by IgM serology were asymptomatic and reported no known exposures. These 2 students were tested for IgM serology more than once (one student twice and the other thrice) and repeatedly IgM reactive, thus disrupting travel plans multiple times. Interestingly, the raw signal for the IgM testing in these 2 individuals were all weakly positive (cutoff indices of 1.2, 1.4, 1.6, 1.9, and 1.9), only slightly above the positive cutoff index of 1.10 (Figure 2). Both students were negative by SARS-CoV-2 RT-PCR twice (tested concurrently with IgM testing). One of the students was additionally tested by the Roche SARS-CoV-2 total antibodies assay and DiaSorin SARS-CoV-2 IgG and was negative for both of these tests. One specimen from this same student was also tested later at the state public health laboratory (State Hygienic Laboratory) and was negative by the Beckman-Coulter Access SARS-CoV-2 IgM assay. The third student was a stronger positive on the IgM assay (cutoff index of 4.0) and was RT-PCR negative but reported a possible exposure to someone with COVID-19 2 to 3 weeks prior to testing. This student did not seek repeat testing at our institution.

Figure 2 shows the cutoff indices for the positive IgM samples relative to the subset of validation study samples that we were able to test by a second SARS-CoV-2 IgM method along with a single pre-COVID validation sample that tested positive by the DiaSorin IgM method but was negative by DiaSorin IgG and Roche total antibodies assays. In Figure 2, the results labeled A and B represent the 2 students who showed repetitive IgM positives while RT-PCR negative. The result labeled C is the specimen from the student who had a possible COVID-19 exposure 2 to 3 weeks prior to testing.

Similar to the pre-travel RT-PCR testing, a high percentage of SARS-CoV-2 IgM results (24 of 27, 88.9%) were viewed in MyChart. Of the 24 results viewed in MyChart, all were viewed within 4 hours of result availability in MyChart. For comparison, viewing in MyChart of SARS-CoV-2 total antibodies (not used for pretravel) was 491 (62.4%) of 787 results.

Discussion

Pretravel SARS-CoV-2 testing raises practical and medical challenges. First, the logistics of getting the assays performed in an acceptable time frame can be difficult, especially with supply chain issues. Second, the test results may be misleading, since the tested population is asymptomatic and has low baseline pretest likelihood of active SARS-CoV-2 infection.[23,43-47] Third, in those with known past SARS-CoV-2 infection, testing may continue to be positive even in those with resolving infection and very low risk of disease spread.[46,48,49] Fourth, there is less experience with IgM serology testing compared to other SARS-CoV-2 testing and thus more limited data on how long positive results may persist in a variety of patient populations.[25,50-52] Lastly, testing can result in substantial out-of-pocket expense for travelers, with additional costs and disruptions to travel associated if results are positive.

Multiple ethical issues also arise with pretravel testing. In a setting where SARS-CoV-2 testing resources are scarce, pretravel testing may divert from clinical testing. This may be heightened by repeated testing of travelers who initially test positive. At our institution, we elected to delay a workflow for pretravel testing until the RT-PCR supply chain and resources stabilized to allow for this additional testing without risk of compromising other testing. There is also the possibility that travelers may seek testing via the routine clinical pathway by falsely endorsing infection signs/symptoms and/or exposure history to obtain testing without the need for self-payment or visit to PCP or travel clinic. This strategy would be hard to detect by telehealth or, in some cases, even in-person screening.

For RT-PCR testing, our pretravel positivity rate was similar to the overall cohort of asymptomatic testing at our institution. Of those testing positive for pretravel RT-PCR, results with high cycle thresholds (lower residual RNA burden) were common. Of these, 38% had a prior history of positive RT-PCR testing for SARS-CoV-2 within a time frame that defined these travelers as immune and not at risk of transmission. This situation raises the issue of the growing pool of patients who seek travel before becoming RT-PCR negative from a primary infection. Two main scenarios will be encountered. Some presenting for pretravel RT-PCR testing have been tested previously. However, many will have not been testing previously as they were asymptomatic at time of primary infection or unable to get tested for various reasons. Detection of residual RNA in either scenario may not reflect current infection. From

August 2020, The Centers for Disease Control and Prevention (CDC) has recommended not retesting patients within 90 days for clinical purposes,[53] but for travel purposes this boundary is not necessarily respected. In 2 cases in our study, repeat testing a day after a positive resulted in a negative result, indicating RT-PCR positivity near limit of detection, and further illustrating the arbitrariness of RT-PCR positivity in cases of resolved infection.

A main concern with SARS-CoV-2 IgM testing is the risk of false positives and the difficulty of adjudicating a positive result.[25] Immunoglobulin M serology assays in general are often prone to higher rates of false positives relative to other serology assays.[54] The requirement for international travel to China specifically dictates IgM testing and not alternatives such as total antibodies.[24,26] Our medical center is part of a state university with many international students and staff, and the testing requirement impacted travelers who had already set flight reservations to China. The requirement for IgM testing is also controversial in its benefit.[25] For example, SARS-CoV-2 IgM assays are positive on average only several days prior to other SARS-CoV-2 assays.[52,55,56] In addition, the performance characteristics of SARS-CoV-2 IgM assays have been inferior to IgG or total antibodies assays.[52,56]

Two positives in our experience were that multidisciplinary collaboration formulated a successful workflow for pretravel testing and that a very high rate of patients accessed results by the electronic patient portal (Epic MyChart). Our institution moved SARS-CoV-2 RT-PCR and serology testing to a faster release schedule to MyChart than other laboratory testing, a change well received by patients and providers.

In summary, the combination of issues outlined above (persistent RT-PCR positivity long after acute infection has resolved and false positive IgM tests) resulted in almost half of our positive pretravel test results being potentially misleading. For 5 of 13 RT-PCR positives, the traveler had prior positive tests and high cycle thresholds values indicating remote infection and absent transmission risk, and 2 of the 3 IgM positives were almost certainly false positives. This raises the question as to whether pretravel testing is a wise resource investment when other prevention strategies are available.

Limitations of our study include data from a single academic center. The test volume and patient population were influenced by the employee and student population within the medical center and broader university community. Lastly, the choice of assays was influenced by existing testing platforms within our clinical laboratories.

Acknowledgments

The processes described in this report were a multidisciplinary effort. The authors especially thank Patient Financial Services, Health Care Information Systems, and Patricia Wong in Student Health for all their work with pretravel testing workflow and the State Hygienic Laboratory for collaborations related to SARS-CoV-2 test validation and comparisons.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Katherine L. Imborek https://orcid.org/0000-0002-8560-8992
Matthew D. Krasowski https://orcid.org/0000-0003-0856-8402

References

1. Al-Tawfiq JA, Sattar A, Al-Khadra H, et al. Incidence of COVID-19 among returning travelers in quarantine facilities: a longitudinal study and lessons learned. *Travel Med Infect Dis*. 2020;38. doi:10.1016/j.tmaid.2020.101901
2. Bielecki M, Patel D, Hinkelbein J, et al. Air travel and COVID-19 prevention in the pandemic and peri-pandemic period: a narrative review. *Travel Med Infect Dis*. 2020;39. doi:10.1016/j.tmaid.2020.101915.
3. Dickens BL, Koo JR, Lim JT, et al. Strategies at points of entry to reduce importation risk of COVID-19 cases and reopen travel. *J Travel Med*. 2020;27. doi:10.1093/jtm/taaa141
4. Ribeiro SP, W DA, Barbosa DS, et al. Worldwide COVID-19 spreading explained: traveling numbers as a primary driver for the pandemic. *An Acad Bras Cienc*. 2020;92:e20201139. doi:10.1590/0001-3765202020201139
5. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. 2020;382:727-733. doi:10.1056/NEJMoa2001017
6. Arino J, Bajeux N, Portet S, Watmough J. Quarantine and the risk of COVID-19 importation. *Epidemiol Infect*. 2020;148:e298. doi:10.1017/S0950268820002988
7. Harries AD, Martinez L, Chakaya JM. SARS-CoV-2: how safe is it to fly and what can be done to enhance protection? *Trans R Soc Trop Med Hyg*. 2021;115:117-119. doi:10.1093/trstmh/traa106
8. Eurosurveillance editorial team. Updated rapid risk assessment from ECDC on the risk related to the spread of new SARS-CoV-2 variants of concern in the EU/EEA—first update. *Euro Surveill*. 2021;26. doi:10.2807/1560-7917.ES.2021.26.3.2101211
9. Tegally H, Wilkinson E, Lessells RJ, et al. Sixteen novel lineages of SARS-CoV-2 in South Africa. *Nat Med*. 2021;27:440-446. doi:10.1038/s41591-021-01255-3
10. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis*. 2020;20:533-534. doi:10.1016/S1473-3099(20)30120 -1
11. Johns Hopkins University of Medicine Coronavirus Resource Center. COVID-19 dashboard by the center for systems science and engineering (CSSE) at Johns Hopkins university (JHU). 2021. Accessed February 21, 2021. https://coronavirus.jhu.edu/map.html.
12. Dollard P, Griffin I, Berro A, et al. Risk assessment and management of COVID-19 among travelers arriving at designated U.S. airports, January 17-September 13, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:1681-1685. doi:10.15585/mmwr.mm6945a4
13. Shaimoldina A, Xie YQ. Challenges of SARS-CoV-2 prevention in flights, suggested solutions with potential on-site diagnosis resembling cancer biomarkers and urgency of travel medicine. *Eur Rev*

Med Pharmacol Sci. 2020;24:12589-12592. doi:10.26355/eurrev_202012_24056
14. Lai CKC, Lam W. Laboratory testing for the diagnosis of COVID-19. *Biochem Biophys Res Commun*. 2020;538:226-230. doi:10.1016/j.bbrc.2020.10.069
15. La Marca A, Capuzzo M, Paglia T, Roli L, Trenti T, Nelson SM. Testing for SARS-CoV-2 (COVID-19): a systematic review and clinical guide to molecular and serological in-vitro diagnostic assays. *Reprod Biomed Online*. 2020;41:483-499. doi:10.1016/j.rbmo.2020.06.001
16. Hanson KE, Caliendo AM, Arias CA, et al. Infectious diseases society of America guidelines on the diagnosis of COVID-19: serologic testing. *Clin Infect Dis*. 2020. doi:10.1093/cid/ciaa1343
17. Loeffelholz MJ, Tang YW. Laboratory diagnosis of emerging human coronavirus infections—the state of the art. *Emerg Microbes Infect*. 2020;9:747-756. doi:10.1080/22221751.2020.1745095
18. Ward S, Lindsley A, Courter J, Assa'ad A. Clinical testing for COVID-19. *J Allergy Clin Immunol*. 2020;146:23-34. doi:10.1016/j.jaci.2020.05.012
19. Centers for Disease Control and Prevention. Testing and international air travel. 2021. Accessed February 21, 2021. https://www.cdc.gov/coronavirus/2019-ncov/travelers/testing-air-travel.html.
20. Esbin MN, Whitney ON, Chong S, Maurer A, Darzacq X, Tjian R. Overcoming the bottleneck to widespread testing: a rapid review of nucleic acid testing approaches for COVID-19 detection. *RNA*. 2020;26:771-783. doi:10.1261/rna.076232.120
21. Pettengill MA, McAdam AJ. Can we test our way out of the COVID-19 pandemic? *J Clin Microbiol*. 2020;58. doi:10.1128/JCM.02225-20
22. Bielecki M, Patel D, Hinkelbein J, et al. Reprint of: air travel and COVID-19 prevention in the pandemic and peri-pandemic period: a narrative review. *Travel Med Infect Dis*. 2020;39. doi:10.1016/j.tmaid.2020.101915
23. Kiang MV, Chin ET, Huynh BQ, et al. Routine asymptomatic testing strategies for airline travel during the COVID-19 pandemic: a simulation analysis [published online ahead of print]. *MedRxiv*. 2020. doi:10.1101/2020.12.08.20246132
24. Embassy of the People's Republic of China in the United States of America. Notice on airline boarding requirements for certificates of negative nucleic acid and anti-body blood tests results. 2020. Accessed February 21, 2021. http://www.china-embassy.org/eng/notices/t1828184.htm.
25. Yi X, Chan CW, Yeo KJ. Is adding IgM antibody to polymerase chain reaction testing useful for COVID-19 travel screening? *Am J Clin Pathol*. 2021;155:321-323. doi:10.1093/ajcp/aqaa270
26. Embassy of the People's Republic of China in the United States of America. Notice on the requirement adjustment of the nucleic acid rt-PCR and IgM serum antibody tests. 2020. Accessed February 21, 2020. http://www.china-embassy.org/eng/notices/t1841416.htm.
27. Chen LH, Steffen R. SARS-CoV-2 testing to assure safety in air travel. *J Travel Med*. 2021;28. doi:10.1093/jtm/taaa241
28. Khatib AN, Carvalho AM, Primavesi R, To K, Poirier V. Navigating the risks of flying during COVID-19: a review for safe air travel. *J Travel Med*. 2020;27. doi:10.1093/jtm/taaa212
29. Next-Day COVID-19 RT-PCR Test for Travel to the People's Republic of China. 2021. My doctor medical group. Accessed February 21, 2021. https://mydoctorsf.com/covid-19-testing-for-travel-to-china.
30. Coronavirus Testing at the Airport. Frankfurt airport, Germany. 2021. Accessed February 21, 2021. https://www.frankfurt-airport.com/en/transfer-at-frankfurt-airport/covid-19/coronavirus-testing-at-the-airport.html.
31. These U.S. and international airports have COVID-19 testing facilities. 2020. Accessed Feburary 21, 2021. https://www.afar.com/magazine/these-us-airports-to-have-covid-19-testing.
32. State of Alaska. COVID-19 (coronavirus) information. 2021. Accessed February 21, 2021. https://covid19.alaska.gov/travelers/.
33. Hawai'i COVID-19 Daily News Digest.Hawai'i's Pre-travel testing program. 2021. Accessed February 21, 2021. https://hawaiicovid19.com/travel-partners/.
34. Oest SER, Hightower M, Krasowski MD. Activation and utilization of an electronic health record patient portal at an academic medical center-impact of patient demographics and geographic location. *Acad Pathol*. 2018;5. doi:10.1177/2374289518797573
35. Krasowski MD, Wilford JD, Howard W, et al. Implementation of epic beaker clinical pathology at an academic medical center. *J Pathol Inform*. 2016;7:7. doi:10.4103/2153-3539.175798
36. Krasowski MD, Ford BA, Klutts JS, et al. Using focused laboratory management and quality improvement projects to enhance resident training and foster scholarship. *Acad Pathol*. 2017;4. doi:10.1177/2374289517722152
37. TaqPath™ COVID-19 Combo Kit and TaqPath™ COVID-19 Combo Kit Advanced* Instructions For Use. Publication number MAN0019181. 2020. Accessed February 21, 2021. https://www.fda.gov/media/136112/download.
38. GeneXpert. Xpert Xpress SARS-CoV-2 instructions for use under an emergency use authorization (EUA) only. 2021. Accessed February 21, 2021. https://www.fda.gov/media/136314/download.
39. DiaSorin LIAISON SARS-CoV-2 IgM (REF 311480).For emergency use authorization only. 2020. Accessed February 21, 2021. https://www.fda.gov/media/142552/download.
40. Merrill AE, Jackson JB, Ehlers A, Voss D, Krasowski MD. Head-to-head comparison of two SARS-CoV-2 serology assays. *J Appl Lab Med*. 2020;5:1351-1357. doi:10.1093/jalm/jfaa125
41. Interim guidelines for COVID-19 antibody testing. 2020. Accessed February 21, 2021. https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html.
42. Humble RM, Merrill AE, Ford BA, Diekema DJ, Krasowski MD. Practical considerations for implementation of SARS-CoV-2 serological testing in the clinical laboratory: experience at an academic medical center. *Acad Pathol*. 2021;8 doi:10.1177/23742895211002802
43. Chau NVV, Thanh Lam V, Thanh Dung N, et al. The natural history and transmission potential of asymptomatic SARS-CoV-2 infection. *Clin Infect Dis*. 2020;71:3679-3687. doi:10.1093/cid/ciaa711
44. Long QX, Tang XJ, Shi QL, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Nat Med*. 2020;26:1200-1204. doi:10.1038/s41591-020-0965-6
45. Meyers KJ, Dillman B, Williams C, et al. Follow-up of SARS-CoV-2 positive subgroup from the asymptomatic novel

CORonavirus iNFection study [published online ahead of print]. *J Med Virol*. 2021. doi:10.1002/jmv.26810

46. Ra SH, Lim JS, Kim GU, Kim MJ, Jung J, Kim SH. Upper respiratory viral load in asymptomatic individuals and mildly symptomatic patients with SARS-CoV-2 infection. *Thorax*. 2021;76:61-63. doi:10.1136/thoraxjnl-2020-215042
47. Uhm JS, Ahn JY, Hyun J, et al. Patterns of viral clearance in the natural course of asymptomatic COVID-19: comparison with symptomatic non-severe COVID-19. *Int J Infect Dis*. 2020;99: 279-285. doi:10.1016/j.ijid.2020.07.070
48. Kandetu TB, Dziuban EJ, Sikuvi K, et al. Persistence of positive RT-PCR results for over 70 days in two travelers with COVID-19. *Disaster Med Public Health Prep*. 2020:1-7. doi:10.1017/dmp. 2020.450
49. Rhee C, Kanjilal S, Baker M, Klompas M. Duration of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infectivity: when is it safe to discontinue isolation? [published online ahead of print]. *Clin Infect Dis*. 2020. doi:10.1093/cid/ ciaa1249
50. Iyer AS, Jones FK, Nodoushani A, et al. Persistence and decay of human antibody responses to the receptor binding domain of SARS-CoV-2 spike protein in COVID-19 patients. *Sci Immunol*. 2020;5:eabe0367. doi:10.1126/sciimmunol.abe0367
51. Long QX, Liu BZ, Deng HJ, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. *Nat Med*. 2020;26:845-848. doi:10.1038/s41591-020-0897 -1
52. Miller TE, Garcia Beltran WF, Bard AZ, et al. Clinical sensitivity and interpretation of PCR and serological COVID-19 diagnostics for patients presenting to the hospital. *FASEB J*. 2020;34: 13877-13884. doi:10.1096/fj.202001700RR
53. Centers for Disease Control and Prevention. Investigative criteria for suspected cases of SARS-CoV-2 reinfection (ICR). 2020. Accessed February 21, 2021. https://www.cdc.gov/coronavirus/ 2019-ncov/php/invest-criteria.html#:∼:text=Since%20August %202020%2C%20CDC%20has,Isolation%20and%20Precautions %20for%20Adults.
54. Landry ML. Immunoglobulin M for acute infection: true or false? *Clin Vaccine Immunol*. 2016;23:540-545. doi:10.1128/ CVI.00211-16
55. Phipps WS, SoRelle JA, Li QZ, et al. SARS-CoV-2 antibody responses do not predict COVID-19 disease severity. *Am J Clin Pathol*. 2020;154:459-465. doi:10.1093/ajcp/aqaa123
56. Risch M, Weber M, Thiel S, et al. Temporal course of SARS-CoV-2 antibody positivity in patients with COVID-19 following the first clinical presentation. *Biomed Res Int*. 2020;2020. doi:10. 1155/2020/9878453