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# Diagnostic yield of repeat testing for SARS-CoV-2: Experience from a large health system in Los Angeles

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ABSTRACT

*Objective:* To determine the diagnostic yield of repeat testing for SARS-CoV-2.
*Methods:* A retrospective analysis was performed of all SARS-CoV-2 test results within the UCLA Health System between March 9th and April 29th, 2020. All patients with repeat test results were identified, and those with discordant results were reviewed.
*Results:* Between March 9th and April 29th, there were 10,165 SARS-CoV-2 test results, of which 630 (6.2%) were positive. Among the 904 patients with repeat test results, 808 (89.4%) were initially negative, and 96 (10.6%) were initially positive. Among the 808 patients with an initial negative test, 15 (1.9%) subsequently tested positive. Eleven cases with an initial negative SARS-CoV-2 test and without a known prior positive SARS-CoV-2 test were reviewed; 6 were employed as healthcare workers, and 10 were positive on the second test.
*Conclusions:* We found a low diagnostic yield of repeat testing for SARS-CoV-2 in our health system. Repeat testing might prove useful in certain clinical scenarios, such as in healthcare workers, when symptoms develop after a negative test, and in hospitalized patients with a high clinical suspicion of COVID-19.


## Background

In the United States, diagnostic testing capacity for SARS-CoV-2, the virus causing coronavirus disease 2019 (COVID-19), has increased (Adalja et al., 2020). A key public health intervention to mitigate the spread of COVID-19 is timely testing for early diagnosis of infections (Pan et al., 2020). Early in the epidemic, SARS-CoV-2 PCR testing was prioritized in clinical settings for symptomatic people who were: hospitalized, healthcare workers, or at high risk for complications (Centers for Disease Control and Prevention, 2020c). Many diagnostic tests for SARS-CoV-2 have been developed and received Emergency Use Authorizations (EUA) by the U.S. Food and Drug Administration (FDA). Yet, concerns exist about the clinical sensitivity and specificity of those tests, particularly with regard to the frequency of false negative test results, which might lead to missed infections and ongoing transmission (Woloshin et al., 2020).

Although repeat testing has been suggested as an approach to increase diagnostic yield, there are sparse data on the yield of repeat testing (Lee et al., 2020; Omer et al., 2020). Moreover, repeat testing further limits supply and, among hospitalized patients, necessitates continued isolation and use of personal protective equipment, which is a limited commodity in the US (Livingston et al., 2020). Therefore, it is of high importance for clinicians to understand the diagnostic yield of repeat testing for SARS-CoV-2. We aimed to provide insight into the diagnostic yield of repeat testing for SARS-CoV-2 within a large health system in Los Angeles, and to highlight the clinical scenarios of discordant results in individuals with an initial negative test.

## Methods

We reviewed all SARS-CoV-2 tests within the UCLA Health System collected between March 9th and April 29th, 2020. Nasopharyngeal specimens were the preferred specimen collection method at our institution. During the time period of the study, nasal and oropharyngeal swabs were not used. For inpatients with concern for lower respiratory tract disease, clinicians could order

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**Table 1**
SARS-CoV-2 tests performed among 904 patients with repeat tests from March 9th to April 29th, 2020, at UCLA Health System in Los Angeles, CA, USA. Total tests and SARS-CoV-2 positivity are reported by diagnostic assay and specimen type.

| | | SARS-Cov-2 Test Positivity n (%) | Total Tests |
|---|---|---|---|
| **All Tests** | | 209 (9.9) | 2108 |
| **Diagnostic Assay** | | | |
| | Diasorin Simplexa COVID-19 Direct RT-PCR | 118 (8.6) | 1370 |
| | CDC 2019-nCoV RT-PCR Diagnostic Panel | 56 (15.6) | 358 |
| | TaqPath COVID-19 Combo Kit | 35 (9.2) | 380 |
| **Specimen Type** | | | |
| | Nasopharyngeal | 195 (9.9) | 1977 |
| | Bronchoalveolar lavage | 9 (9.3) | 97 |
| | Sputum | 2 (10.5) | 19 |
| | Tracheal specimen | 3 (30.0) | 10 |
| | Other | 0 (0) | 5 |

lower respiratory tract specimens (e.g. – expectorated sputum, bronchoalveolar lavage (BAL), tracheal aspirate).

Testing was either performed at the UCLA clinical microbiology laboratory or was conducted at a commercial laboratory (Quest Diagnostics). Testing at UCLA was done using three tests: 1) the U. S. Centers for Disease Control and Prevention's (CDC's) 2019-nCoV Real-Time Reverse Transcriptase (RT-) PCR Diagnostic Panel protocol (Atlanta, GA), which uses probes targeting the nucleocapsid gene (N1 & N2) of SARS-CoV-2 (Centers for Disease Control and Prevention, 2020a) the Diasorin Simplexa COVID-19 Direct RT-PCR (Diasorin Molecular LLC, Cypress, CA), which has two different targets: the S gene encoding for the spike glycoprotein of SARS-CoV-2 and the ORF1ab region encoding well-conserved non-structural proteins (DiaSorin Molecular, 2020); or 3) the TaqPath COVID-19 Combo Kit (Thermo Fisher Scientific Inc., Waltham, MA), which uses probes targeting ORF1ab, N, and S genes (ThermoFisher Scientific, 2020). Quest Diagnostics utilized the Quest SARS-CoV-2 rRT-PCR test (Quest Diagnostics, San Juan Capistrano, CA), which targets two regions of the N gene (N1 & N3) (Quest Diagnostics, 2020). All assays received EUA by the FDA for the qualitative detection of SARS-CoV-2 RNA in upper and lower respiratory specimens. Each specimen submitted for testing was tested using only one of the aforementioned diagnostic assays.

We defined multiple tests performed for the same patient as repeat tests. We excluded cases where the initial test was inconclusive. We report total number of tests, overall test positivity, and the number of patients with repeat tests and discordant results.

## Results

In total, there were 10,165 SARS-CoV-2 tests performed, and 6.2% (630/10,165) were positive. There were 906 patients with repeat test results, and 2 were excluded due to inconclusive initial results. Among the 904 total cases, 808 (89.4%) were initially negative, and 96 (10.6%) were initially positive. Those 904 patients accounted for 2108 tests with an overall positivity of 9.9% (n = 209). The vast majority (93.7%) of those tests were performed on nasopharyngeal specimens, and 65% were performed on the Diasorin platform. The number of tests and SARS-CoV-2 positivity by diagnostic assay and specimen type are shown in Table 1.

Among the 96 patients with initial positive tests, 56 (58.3%) were repeat tested once, 24 (25.0%) were repeat tested twice, eight

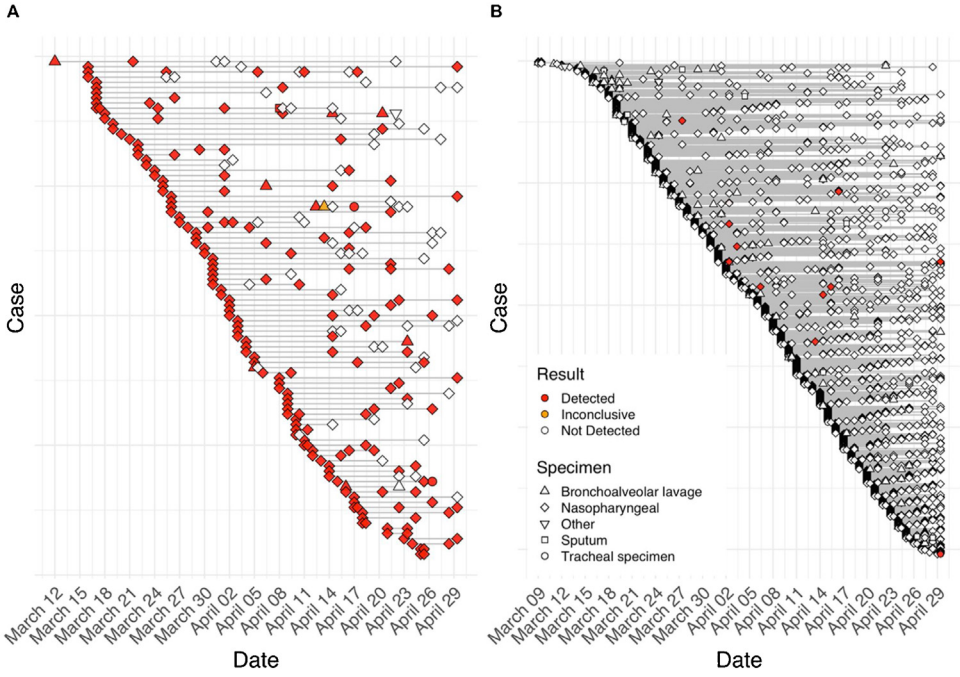


**Fig. 1. Panel A)** Repeat SARS-CoV-2 testing results among patients with an initial positive test result for SARS-CoV-2. **Panel B).** Repeat SARS-CoV-2 testing results among patients with an initial negative test result for SARS-CoV-2.

**Table 2**
Review of clinical and testing data for patients within a large health system in Los Angeles, CA, who underwent repeat testing for SARS-CoV-2, had an initial negative test and a subsequent positive test, and were without a known prior positive SARS-CoV-2 test result.

| Initial Negative Test | | | Subsequent Positive Test | | | | |
|---|---|---|---|---|---|---|---|
| Clinical Scenario | Setting/ Specimen Type | Assay* | Scenario for repeat testing | Days after initial test | Setting / Specimen Type | Assay* | Possible reason for negative test |
| Presented to the hospital with 10–14 days of fever, fatigue, dyspnea, and cough, and imaging showed bilateral infiltrates | Emergency Department / NP | A | Worsening hypoxemia and high clinical suspicion of infection | 2 | Inpatient / NP + Sputum | A + B | Poor sampling or Inconsistent viral shedding |
| Patient with history of liver transplantation and end-stage renal disease who presented with 1 day of fever, myalgias, cough, and diarrhea | Outpatient / NP | A | Worsening fever and dyspnea | 2 | Inpatient / NP | A | Poor sampling or Inconsistent viral shedding |
| HCW with history of asthma, presented with 2 days of chest tightness and dyspnea, both relieved by inhalers; reported having a roommate with COVID-19 | Emergency Department / NP | B | New symptoms - 3 days of fever and progressive cough with dyspnea | 7 | Emergency Department / NP | A | Pre-symptomatic |
| HCW who presented with 6 days of dry cough, post-nasal drip, and headache | Outpatient / NP | A | Developed one day of fevers and chills | 21 | Outpatient / NP | A | Prior to infection |
| HCW reporting 1-day of rhinorrhea, cough, and chest tightness | Outpatient / NP | A | Developed symptoms of fatigue, arthralgias, fever, cough, and nausea for 4 days | 6 | Outpatient / NP | A | Pre-symptomatic |
| HCW, reporting 4-days of sinus congestion and sore throat | Outpatient / NP | B | Developed 1 day of fever, chills, diarrhea, and cough; domestic partner diagnosed with COVID19 after initial testing | 4 | Outpatient / NP | A | Pre-symptomatic |
| HCW reporting 2 days of sore throat and work exposure 3 days prior | Outpatient / NP | A | Developed 2 days of fever, myalgias, and arthralgias | 3 | Outpatient / NP | A | Poor sampling or Inconsistent viral shedding |
| HCW reporting 1-day of fever, chills, and myalgias | Outpatient / NP | C | Ongoing fevers, cough, and fatigue | 8 | Outpatient / NP | C | Poor sampling or Inconsistent viral shedding |
| Patient was admitted to the hospital with fever and was found to have septic arthritis of the knee. Initial testing done on admission. | Inpatient / NP | A | Testing performed prior to surgery for epidural abscess | 4 | Inpatient / NP | A | Poor sampling or Inconsistent viral shedding |
| Patient admitted to the hospital after being found unconscious at home. Cardiac arrest in Emergency Room. Chest imaging showed bilateral infiltrates. | Inpatient / NP | A | Repeat testing done per infection control policy | 0 | Inpatient / Sputum | B | Poor sampling or Inconsistent viral shedding |
| Patient residing in a skilled nursing facility who presented with 1-day history of fever | Inpatient / NP | A | Persistent fevers; repeat tests done on hospital days 1, 5, and 9 | 9** | Inpatient / NP | A | Poor sampling or Inconsistent viral shedding |

HCW – healthcare worker; NP – nasopharyngeal.
* Assay A – Diasorin Simplexa COVID-19 Direct RT-PCR (Diasorin Molecular LLC, Cypress, CA), Assay B – CDC 2019-nCoV Real-Time Reverse Transcriptase (RT-) PCR Diagnostic Panel (CDC, Atlanta, GA), Assay C - TaqPath COVID-19 Combo Kit (Thermo Fisher Scientific Inc., Waltham, MA).
** Positive result occurred on the fourth test; the second and third test results were negative.

(8.3%) were repeat tested thrice, and eight (8.3%) were repeat tested four or more times. Repeat testing among positive cases was often done for infection control practices and for discharge planning. Among those with an initial positive test, 50% had a subsequent negative result (48/96); the median time between positive and negative tests was 16 days (interquartile range: 9–27 days). (Fig. 1, Panel A)

Among the 808 patients with an initial negative test, 646 (80.0%) were repeat tested once, 110 (13.6%) were repeat tested twice, 39 (4.8%) were repeat tested thrice, and 13 (1.6%) were repeat tested four times; fifteen tests (1.9%) were subsequently positive. (Fig. 1, Panel B) Clinical information was not available for one case. In three instances, patients were transferred from an outside facility where they had a positive SARS–COV-2 test. All transferred patients had a negative test on arrival, but a subsequent positive test within 24 h.

There were 11 cases with an initial negative SARS-CoV-2 test, without a known prior positive SARS-CoV-2 test, and with reasons for repeat testing available for review. All of the initial tests were done on nasopharyngeal specimens, and ten of the cases tested positive the second time. Six individuals with an initial negative test and a subsequent positive test had been employed as healthcare workers (HCWs). The clinical scenarios for testing, as well as the specimen type, setting, diagnostic assay, and possible reasons for the initial negative result are presented in Table 2. Testing prior to infection was likely in one case, as there were 20 days between the negative test and the development of symptoms. In three cases, pre-symptomatic testing was the likely explanation, as symptoms of acute illness developed after the initial test. In the remaining cases, possible reasons for the initial negative test result were inadequate specimen collection or inconsistent viral shedding.

## Discussion

We found that repeat testing for SARS-CoV-2 had low diagnostic yield. Discordant results occurred in only 1.3% of patients with an initial negative test and without a prior diagnosis of SARS-CoV-2 infection. Consideration of the pretest probability alongside the estimated test performance can be used to guide repeat testing (Woloshin et al., 2020). For example, our report highlighted that repeat testing might prove useful in HCWs with ongoing exposures, as over half of those with initial negative tests and a subsequent positive test were employed as HCWs.

Other scenarios where repeat testing after a negative test might be useful include when symptoms of COVID-19 develop after a negative test, when inadequate specimen collection is suspected, and in hospitalized patients with high clinical suspicion for COVID-

19 (Lee et al., 2020). Moreover, public health interventions to mitigate the spread of COVID-19 rely on timely testing and early diagnosis of infections in order to inform isolation, contact tracing, and quarantine efforts, and repeat testing will be needed in these situations (Pan et al., 2020).

SARS-CoV-2 viral shedding can be variable, and the timing related to exposure and symptom onset is important for test result interpretation (Wölfel et al., 2020; Zou et al., 2020). Available data suggest that SARS-CoV-2 is typically detectable by RT-PCR in the nasopharynx by symptom onset, and that viral loads are highest in the nasopharynx in the first week of the infectious course (Sethuraman et al., 2020; Wölfel et al., 2020; Zou et al., 2020). In our report, testing prior to infection was the likely explanation in one case, and testing prior to symptom onset appeared to be the reason for three cases. In most cases, it was not possible to differentiate between variability in viral shedding and poor specimen collection. While the timing and quality of specimen collection are key, a false negative test result is still possible. Data regarding the clinical sensitivity remain quite limited. Preliminary reports suggest that nasopharyngeal specimens might have up to 27% false negativity, and a systematic review estimated false negatives in 2%–29% of specimens, although the quality of evidence was low (Arevalo-Rodriguez et al., 2020; Yang et al., 2020).

Retesting positive cases was recommended an an approach to document viral clearance and remove isolation precautions (Centers for Disease Control and Prevention, 2020b). In our report, approximately half of those with an initial positive test had a subsequent negative test. Prior reports have documented prolonged duration of SARS-CoV-2 positivity by RT-PCR, up to 6 weeks in some cases (Lan et al., 2020; Qi et al., 2020; Zhou et al., 2020). RT-PCR tests are characteristically sensitive, but are unable to discriminate between the presence of replicating virus and non-infectious remnants that contain nucleic acid targets. However, emerging evidence now suggests that there is very low likelihood of infectivity, as measured by culturing viable SARS-CoV-2, if more than 8 days have elapsed since time of symptom onset (Bullard et al., 2020; Wölfel et al., 2020).

Our results should be considered in light of the following limitations. First, our study was performed within one health system and might not be generalizable to other settings. The report highlighted instances where repeat testing yielded discordant results in a clinical setting and might not be generalizable to repeat testing as part of a broader public health response. Second, we could not assess differences in tests by anatomic site, as we did not have paired specimens. Nevertheless, we provided data on repeat testing for SARS-CoV-2 within a large health system and highlighted cases where repeat testing improved diagnostic yield. In a clinical setting, repeat testing can be considered based on changes to clinical status and the pre-test probability of infection.

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## Ethical approval

The retrospective analysis was undertaken as a quality assurance project and did not meet research criteria for review by our institutional review board.

## Declaration of Competing Interest

The authors report no declarations of interest.

## References

Adalja AA, Toner E, Inglesby TV. Priorities for the US Health Community Responding to COVID-19. JAMA 2020;.

Arevalo-Rodriguez I, Buitrago-Garcia D, Simancas-Racines D, Zambrano-Achig P, del Campo R, Ciapponi A, et al. FALSE-NEGATIVE RESULTS OF INITIAL RT-PCR ASSAYS FOR COVID-19: A SYSTEMATIC REVIEW. medRxiv 2020;2020: 04.16.20066787.

Bullard J, Dust K, Funk D, Strong JE, Alexander D, Garnett L, et al. Predicting infectious SARS-CoV-2 from diagnostic samples. Clin Infect Dis 2020;.

Centers for Disease Control and Prevention. CDC 2019-Novel Coronavirus (2019-nCoV) Real-Time RT-PCR Diagnostic Panel. [package insert]. Atlanta, GA. 2020. https://www.fda.gov/media/134922/download.

Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19) - Discharging Hospitalized Patients. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized-patients.html. [Accessed June 18. 2020.

Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19) - Evaluation and Testing Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-criteria.html. [Accessed April 8. 2020.

DiaSorin Molecular. Simplex COVID-19 Direct real-time RT-PCR assay [package insert]. Cypress, CA. 2020. https://www.fda.gov/media/136286/download.

Lan L, Xu D, Ye G, Xia C, Wang S, Li Y, et al. Positive RT-PCR Test Results in Patients Recovered From COVID-19. JAMA 2020;323(15):1502.

Lee TH, Lin RJ, Lin RTP, Barkham T, Rao P, Leo Y-S, et al. Testing for SARS-CoV-2: Can We Stop at Two?. Clin Infect Dis 2020;.

Livingston E, Desai A, Berkwits M. Sourcing Personal Protective Equipment During the COVID-19 Pandemic. JAMA 2020;.

Omer SB, Malani P, Del Rio C. The COVID-19 Pandemic in the US. JAMA 2020;.

Pan A, Liu L, Wang C, Guo H, Hao X, Wang Q, et al. Association of Public Health Interventions With the Epidemiology of the COVID-19 Outbreak in Wuhan, China. JAMA 2020;323(19):1915.

Qi L, Yang Y, Jiang D, Tu C, Wan L, Chen X, et al. Factors associated with the duration of viral shedding in adults with COVID-19 outside of Wuhan, China: a retrospective cohort study. Int J Infect Dis 2020;96:531–7.

Quest Diagnostics. SARS-CoV-2 RNA Qualitative Real-Time RT-PCR [package insert]. San Juan Capistrano, CA. 2020. https://www.fda.gov/media/136231/download.

Sethuraman N, Jeremiah SS, Ryo A. Interpreting Diagnostic Tests for SARS-CoV-2. JAMA 2020;323(22):2249.

ThermoFisher Scientific. TaqPath COVID-19 Combo Kit [package insert]. Pleasanton, CA. 2020. https://www.fda.gov/media/136112/download.

Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature 2020;.

Woloshin S, Patel N, Kesselheim AS. False Negative Tests for SARS-CoV-2 Infection — Challenges and Implications. N Engl J Med 2020;.

Yang Y, Yang M, Shen C, Wang F, Yuan J, Li J, et al. Evaluating the accuracy of different respiratory specimens in the laboratory diagnosis and monitoring the viral shedding of 2019-nCoV infections. medRxiv 2020;2020: 02.11.20021493.

Zhou B, She J, Wang Y, Ma X. Duration of Viral Shedding of Discharged Patients With Severe COVID-19. Clin Infect Dis 2020;.

Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. N Engl J Med 2020;382 (12):1177–9.