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CoV-2 cause harm to guide research and work toward a better understanding of both conditions.

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<https://doi.org/10.1016/j.mayocp.2020.08.008>

Repeated Testing in SARS-CoV-2 Infection



To the Editor: In a recently published article in the journal, Challener et al¹ showed that 2.0% of participants (ie, 22 of 1113) tested positive within 1 week of the first negative nasopharyngeal swab for identification of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. This evidence persuaded the authors to conclude that repeating an identical test in a low-prevalence environment is unlikely to generate added clinical value. However, some important considerations would lead us to disagree with this conclusion.

The fact that the SARS-CoV-2 identification is directly related to the number of subsequent nasopharyngeal swabs collected is now widely acknowledged. Zhang et al² found that 99% diagnostic sensitivity could be achieved after the fourth consecutive specimen collection. This suboptimal accuracy is attributable to a vast number of preanalytical and analytical issues, which have been comprehensively reviewed elsewhere.³ Besides these technical aspects, our perception is that a 2% rate of false-negative results on initial testing is not a negligible value and is not reassuring even (or especially) in a low-prevalence environment.

The underdiagnosis or delayed diagnosis of SARS-CoV-2 infection has been highlighted as an important reason for rapid spread of infection in the community. It has now been clearly established that the viral load of asymptomatic patients, which

represent most SARS-CoV-2 infections in low-prevalence areas, is almost identical to that of symptomatic patients.⁴ This would imply that underdiagnosing these asymptomatic individuals would lead to a substantial risk of contagion and generation of new local outbreaks, especially in a low-prevalence scenario, where a perception of scarce virus circulation may have attenuated the degree of vigilance (ie, social distancing, use of face masks, quarantine, and so forth). From this perspective, a recent analysis by Li et al⁵ highlighted that asymptomatic cases may have been responsible for nearly 80% of SARS-CoV-2 contagions to date, thus further emphasizing the need for timely identification and immediate isolation of positive cases to prevent further spread of the virus. Notably, with an estimated basic reproduction number (ie, R₀) of 3.3 for SARS-CoV-2, even a single presymptomatic infected individual may rapidly contribute to infect nearly 270 people within 5 days, which is the typical incubation time of SARS-CoV-2 infection.⁶ Moreover, although we agree that collection of alternative specimens (eg, bronchoalveolar fluid or sputum) may potentially yield higher diagnostic accuracy, it must also be acknowledged that this approach is impractical, or even unfeasible, as a screening strategy for outpatients, especially when these are asymptomatic, presymptomatic, or mildly to moderately symptomatic.

Unlike what has been concluded by Challener and colleagues, we believe that short-interval repeated collection and testing of nasopharyngeal swabs in individuals with high baseline clinical and environmental risk of being infected by SARS-CoV-2 (eg, those with a high likelihood

calculated using the so-called Corona Score)⁷ should be regarded as an essential containment measure.

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<https://doi.org/10.1016/j.mayocp.2020.08.007>

In Reply—Repeated
Testing in SARS-CoV-2
Infection



To The Editor: We appreciate the points raised by Lippi et al regarding our article describing repeated testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.¹ In summary, the authors emphasize that repeated testing may be helpful in improving the negative predictive value of testing and ensuring that cases of COVID-19 are identified. The authors include evidence supporting the conclusion that identification of the SARS-CoV-2 virus is directly related to the number of nasopharyngeal swabs that are collected and also emphasize the importance of case-finding in control of the pandemic. In general, we agree that repeated testing may be helpful in certain situations of ongoing high suspicion for active infection where alternative approaches are not feasible; however, we believe that testing should not be applied indiscriminately in a resource-constrained situation.

The results of several studies have suggested that the number of unique patient specimens tested for SARS-CoV-2 is directly related to the positive identification of the virus and that there may be a high false-negative rate of molecular testing.^{2,3} The study by Zhang et al² reported 41 hospitalized patients with an initial negative polymerase chain reaction test who had at least 1 positive result on subsequent testing. However, the timing between tests was not reported in this article, which raises the possibility that some of the patients could have become

infected after their first test. No laboratory test has 100% sensitivity, and we agree that the likelihood of detecting infected individuals will increase if they are tested more frequently. This characteristic of laboratory testing is not unique to SARS-CoV-2 but could be applied to molecular testing for many other infectious diseases. However, widespread indiscriminate repeated testing is not currently possible.

Unfortunately, supply chain challenges continue to limit the widespread availability of SARS-CoV-2 polymerase chain reaction testing in the United States. Tests should be used in an efficient manner and guided by principles of diagnostic stewardship.⁴ We agree that there may be a role for repeated testing in patients with high clinical suspicion of coronavirus 19, and where a positive result would change clinical management. However, in situations with low pre-test probability and limited resources, repeated testing of a sample collected from the same anatomical site demonstrated a low yield (2%) in our study. The clinical stage of illness can be used to determine whether an upper or lower respiratory specimen may provide more useful information, with detection of SARS-CoV-2 in lower respiratory sources becoming more likely as the disease progresses. The data on test characteristics in asymptomatic patients remain limited. Further studies are needed to identify the utility of repeated testing in this population.

Even in the absence of widespread test availability, there are a variety of strategies that have been proposed to mitigate the risk of false-negative testing, including strict infection control measures,