for personally being spared infection by the virus. For them, gratitude rather than guilt is a more prominent emotion.

Most of the retired physicians reading JAMA Internal Medicine are no more than 2 decades older than me. They were peers of my teachers and personified the physician I aspired to be. For the most part, they loved their work and understood what being a physician was all about. They lived careers of service caring for patients, which, in turn, fostered their values about the sanctity of the human condition. As is true of physicians practicing today during the COVID-19 pandemic, for much of their careers, these physicians had limited therapeutic options for some of the most devastating diseases and were placed in roles of caring and comforting, often while watching illnesses run their destructive courses. There is much to be learned from them about turning empathy into action to improve the lives of many during the pandemic and beyond.

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Negative Conversion Rate of SARS-CoV-2 Infection

To the Editor By September 11, 2020, there were more than 28 million people infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) worldwide (https://coronavirus.jhu.edu/). In a recent issue of JAMA Internal Medicine, an Original Investigation by Lee et al1 found that the negative conversion rate in asymptomatic cases was higher than that in symptomatic cases, although to a statistically insignificant degree (Figure 1). However, the negative conversion rate and its comparison between symptomatic and asymptomatic cases may be biased for the following reasons.

First, use of a single negative test result of reverse transcription-polymerase chain reaction as negative conversion may overestimate negative conversion rate, as a negative result may occur purely owing to failure in sampling of specimens.2,3 Previous studies suggest that at least 2 consecutive reverse transcription-polymerase chain reaction tests are needed for confirming negative conversion,4 and the China National Health Commission guideline also requires that the 2 consecutive tests be at least 24 hours apart.5

Second, 26 of 89 asymptomatic case patients received negative SARS-CoV-2 test results within 9 days (from March 6 to March 15) of quarantine and were released from isolation and counted as asymptomatic cases.1 However, research shows that it requires an average of some 15 days for asymptomatic patients to eventually develop symptoms.1 Thus, some of these 26 “asymptomatic cases” may later develop symptoms and should be counted as symptomatic cases. Misclassification of these cases will overestimate the conversion rate in asymptomatic cases and may thus partly explain the observation of the study that the conversion rate was higher in asymptomatic cases than in symptomatic cases (Figure 1).

Third, as there was no testing performed before day 8 and between days 10 and 14 of quarantine,1 the conversion time will be overestimated in those who turned negative before day 8 and between days 9 and 15. As a result, the median time from diagnosis to the first negative conversion may also have been overestimated in the study.

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In Reply We wish to thank Zhang et al for their comments on our Original Investigation.1 They considered the overestimation of the negative conversion rate to the use of a single negative result to define negative conversion. During the study, the Korean Center for Disease Control and Prevention also recommended that quarantined individuals should be released after 2 consecutive negative polymerase chain reaction results from the upper respiratory tract in a 24-hour interval,2 similar to the guidelines from the China National Health Commission.3 We defined the first negative conversion as the first negative result for both upper and lower respiratory tract specimens. In Kaplan-Meier curves of 2 consecutive negative conversion proportions of specimens from the upper and lower respiratory tract, we confirmed that negative conversion rates are not statistically different between symptomatic and asymptomatic patients in either upper respiratory or lower respiratory specimens.1
Zhang et al also considered whether the overestimation of asymptomatic proportion was owing to an insufficient observation period. Actually, the observation period was not insufficient compared with the known incubation period of coronavirus disease 2019. The median observation period from diagnosis to release was 16 days (interquartile range, 14-17 days) for 26 asymptomatic patients. In addition, upon daily evaluation of the new symptoms of all quarantined individuals, we tried to find symptomatic patients.

Finally, Zhang et al assert the possibility of overestimation of conversion time owing to skipped tests before day 8 and between days 9 and 15. In practice, daily testing to check negative conversion is impossible because of inconvenience to the patient, risk of exposure to infection, and additional labor for health care personnel. Despite the limitation of the test schedule, intervals between the diagnosis and follow-up tests were variable because quarantined individuals had different diagnosis dates. Thus, the first negative conversion proportion and the rate of change of cyclic threshold values could be analyzed statistically by time variability, and there were no significant differences between asymptomatic and symptomatic cases in an analysis that incorporated missing test results.

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**Substitution of Generic Drugs and Biosimilars**

**To the Editor** In a recent issue of *JAMA Internal Medicine*, Sacks and colleagues examined the variation in state regulations regarding how pharmacists can substitute prescriptions for brand-name drugs with generic drugs and biosimilars. The authors found substantial variation in state regulations, suggesting a need to optimize state drug product selection laws to promote bioequivalent generic drug and biosimilar substitution.

While this variation highlights an opportunity to reduce health system spending and improve population health, the study lacks a discussion of 2 crucial factors in substituting generic drugs and biosimilars. First, most expensive and popular biologics are dispensed and administered by physicians in an outpatient setting, often bypassing the pharmacy. Second, the ability of new state regulations to mandate generic drug and biosimilar substitution is likely negligible because pharmacists have a profit motive to substitute generic drugs regardless of state policy.

Sacks and colleagues discussed the state laws and regulations allowing generic drug and biosimilar substitution by pharmacists. However, except for adalimumab and etanercept, most top-selling, expensive biologics and their biosimilars, when they become available, need to be administered intravenously at an outpatient setting or clinic under the physician’s supervision. Pharmacists may not be involved in this process, especially for clinics that operate independently from large hospital systems with pharmacy departments. The Invited Commentary by Crosson also recognizes this point when addressing the recommendations from the Medical Payment Advisory Commission on Medicare Part B & D payment for specialty drugs. While Sacks and colleagues primarily focus on how pharmacists can substitute prescription drugs, it should be recognized that physicians also play an important role in substituting generic drugs and biosimilars.

The authors referenced a study by Shrank et al from 2010 that assessed the comparative effects of different state laws on generic drug use. However, the study used Medicaid data to examine only 1 class of drugs (statins), and it is unclear whether such comparisons can be interpreted as a causal effect of state laws and regulations. This limitation motivated a recent study by Song and Barthold. Using difference-in-differences and a discrete choice model, the study demonstrated that mandatory substitution laws would have an insignificant effect on the uptake of generic drugs because pharmacists are already motivated to dispense generic drugs to increase profits. In fact, the gross margin of generic drugs is much higher than that of branded drugs (42.7% vs 3.5%). This difference is often large enough to make up for the lower price of generic drugs, especially for a generic drug that first enters the market following the patent expiration of a brand-name drug.

Insurance management tools also play a critical role in the substitution of generic drugs or biosimilars. As noted by Sacks et al in the study’s limitation section, pharmacy benefit managers often require generic substitution using tiering and prior authorization requirements. From the pharmacists’ perspective, a profit motive and pharmacy benefit managers’ policies are the primary factors in driving generic substitution, and current state-level policy merely regulates the pharmacists’ dispensing process.

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