Effects of Patient Characteristics on Diagnostic Performance of Self-Collected Samples for SARS-CoV-2 Testing

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We evaluated the performance of self-collected anterior nasal swab (ANS) and saliva samples compared with healthcare worker–collected nasopharyngeal swab specimens used to test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We used the same PCR diagnostic panel to test all self-collected and healthcare worker–collected samples from participants at a public hospital in Atlanta, Georgia, USA. Among 1,076 participants, 51.9% were men, 57.1% were ≥50 years of age, 81.2% were Black (non-Hispanic), and 74.9% reported ≥1 chronic medical condition. In total, 8.0% tested positive for SARS-CoV-2. Compared with nasopharyngeal swab samples, ANS samples had a sensitivity of 59% and saliva samples a sensitivity of 68%. Among participants tested 3–7 days after symptom onset, ANS samples had a sensitivity of 80% and saliva samples a sensitivity of 85%. Sensitivity varied by specimen type and patient characteristics. These findings can help physicians interpret PCR results for SARS-CoV-2.

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Detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease (COVID-19), originally relied mainly on nasopharyngeal swab (NPS) samples collected by healthcare workers (HCWs). However, NPS sample collection requires substantial amounts of time and personal protective equipment (PPE) that could be preferentially used for patient care. In light of >98 million confirmed COVID-19 cases globally as of January 27, 2021, relying solely on HCW-collected specimens for testing is not feasible (*1*). During the COVID-19 pandemic, many healthcare sites have experienced shortages of PPE and testing supplies. In addition, NPS sample collection often causes coughing or sneezing, which can generate infectious aerosols and thereby put the HCW at increased risk for exposure (*2*). Furthermore, NPS collection can cause discomfort and occasional nosebleeds, possibly affecting a patient's willingness to be retested. The use of self-collected saliva and anterior nasal swab (ANS) samples reduces HCW contact, limits need for PPE, and preserves transport media and other collection supplies needed for NPS samples.

Various upper respiratory specimen types, including saliva and oral swab samples, have demonstrated similar sensitivity to NPS samples in nucleic acid amplification tests for SARS-CoV-2 (*3*–*6*). However, most patients in these studies reported the recent onset of respiratory symptoms. Other investigations have shown that many infected persons, especially those who are young and otherwise healthy, are

[1]Members are listed at the end of this article.

asymptomatic or have mild symptoms (*7*–*9*). SARS-CoV-2 RNA has been detected in NPS samples nearly 2 months after initial detection; however, the performance of self-collected ANS and saliva samples of patients with prolonged viral shedding remains unclear (*10*,*11*). Understanding how these less invasive, self-collected specimens perform in a variety of contexts can inform testing strategies. We compared the diagnostic performance of self-collected ANS and saliva samples and HCW-collected NPS samples used in SARS-CoV-2–specific PCR by patient characteristics and symptom status.

Methods

We recruited patients from several inpatient and outpatient departments of Grady Memorial Hospital (Atlanta, GA, USA), where a high proportion of patients are uninsured (24%) or have Medicare/Medicaid insurance (57%) (*12*). Patients were eligible if their treating physician ordered collection of an NPS sample for SARS-CoV-2–specific reverse transcription PCR (RT-PCR) for any reason, including diagnostic (e.g., patients were symptomatic or exposed) or screening (e.g., preoperative requirement or before admission for non–COVID-19 reasons) purposes. Patients were excluded if they were unable to provide consent, declined consent, were <18 years of age, had a contraindicated NPS specimen (e.g., had a condition that prevented NPS sample collection), were unable to self-collect specimens, or had previously participated in this investigation. Trained interviewers used a standardized questionnaire to collect data on patient demographics, reason for visit, current and previous symptoms, and medical history (including previous SARS-CoV-2 testing). Each participant received a US $25 gift card.

During interviews, patients were given an infographic outlining steps for self-collection of saliva and ANS samples (Appendix Figure, https://wwwnc.cdc.gov/EID/article/27/8/21-0667-App1.pdf) (*13*). Patients self-collected raw (unenhanced) saliva in a 50-mL tube. Patients then inserted a miniature flocked-tip swab into 1 anterior naris, twirled the swab for 10 seconds, removed the swab and placed it directly into the other naris, and twirled it again for 10 seconds. Patients inserted the swab into 3 mL of viral transport media. After the interview and self-collection of specimens, a HCW collected an NPS sample from the participant and inserted the swab into 3 mL of viral transport media. Hospital laboratory staff conducted RT-PCR on the NPS sample on the same day; these results were used to inform clinical care and were not included in the performance analysis. NPS samples then were aliquoted and transferred to the Centers for Disease Control and Prevention (CDC) for RT-PCR. CDC staff extracted nucleic acid and tested samples using the CDC 2019-nCoV Real-Time Reverse Transcription PCR (rRT-PCR) Diagnostic Panel, which is selective for the SARS-CoV-2 nucleocapsid 1 (N1) and 2 (N2) genes, as per the Emergency Use Authorization Instructions for Use (*14*,*15*) (Appendix).

We entered and stored completed questionnaires and laboratory results in a REDCap version 10.0.8 (https://www.project-redcap.org) database hosted at CDC. We grouped patients according to COVID-19 symptom status: always asymptomatic participants reported no COVID-19 symptoms at specimen collection or in the previous 14 days; currently asymptomatic participants reported no COVID-19 symptoms at specimen collection but had symptoms in the previous 14 days; and currently symptomatic participants reported COVID-19 symptoms at specimen collection. We categorized symptoms according to previously defined case definitions (*16*–*18*) (Appendix). We calculated sample size using a 1-sided, 1-sample proportions test with a continuity correction to determine whether sensitivity of self-collected samples was ≥90% compared with HCW-collected NPS samples, assuming that NPS samples had a true sensitivity of 98% (*3*). Using $\alpha = 0.05$, 80% power, and 5% NPS percent positivity, we calculated the minimum sample size to be 920 and the required number of positive self-collected specimens to be 46.

We compiled demographic and clinical characteristics for patients according to the results of their NPS samples. To analyze the benefit of using both self-collected ANS and saliva specimens for diagnosis, we merged each patient's ANS and swab sample results to create a self-collected combination result. If ≥1 self-collected specimen was positive, we marked that patient's self-collected combination result as positive. If neither was positive and ≥1 was negative, then we marked that patient's self-collected combination result as negative. We calculated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of ANS, saliva, and self-collected combination samples compared with NPS samples for all patients who had a definitive (i.e., positive or negative) NPS result and ≥1 self-collected specimen. Because NPS samples do not show all SARS-CoV-2 infections, we reran the sensitivity analysis with a combined variable for any positive result from ANS, saliva, or NPS samples as the comparator. We compiled proportions of concordant and discordant results for each self-collected and HCW-collected sample and calculated Cohen's κ

coefficient to compare result agreement by specimen type. We calculated the sensitivity of self-collected specimens by patient characteristics and determined significant differences using a 1-sample, 2-sided test of proportions ($p<0.05$). We used the Pearson correlation coefficient to compare the cycle threshold (C_t) values of positive self-collected and HCW-collected specimens; we used the Mann-Whitney U test to compare the C_t values of NPS samples by patient characteristic. We analyzed the data in R version 4.0.2 (The R Project for Statistical Computing, https://www.r-project.org).

This investigation was reviewed by CDC and conducted in accordance with applicable federal law and CDC policy (e.g., 45 C.F.R. part 46, 21 C.F.R. part 56, 42 U.S.C.; 241(d); 5 U.S.C. 552a; 44 U.S.C. 3501 et seq.). This investigation was determined to be an exempt public health activity by the Emory University Institutional Review Board and Grady Memorial Hospital Research Oversight Committee.

Results

During August 31–November 23, 2020, a total of 1,096 patients consented to and enrolled in the study; 20 were excluded because they did not meet inclusion criteria (Figure 1). Among 1,076 participants, overall positivity of any specimen was 8.0%; NPS samples had 7.4% positivity, ANS samples had 4.4% positivity, and saliva samples had 4.8% positivity. Among the 1,076 participants, 51.9% (559) were men, 57.1% (614) were ≥50 years of age, 81.2% (874) were Black (non-Hispanic), and 74.9% (806) had ≥1 chronic medical condition (Table 1). Most (80.0%; 861) participants were enrolled in the emergency department: nearly half sought care for a COVID-19–related concern (18.2%; 196) or had a chief complaint including COVID-19–like symptoms (30.6%; 329). Over half (56.7%; 610) of participants had ≥1 current COVID-19 symptom; among currently symptomatic participants, 68.9% (420) reported symptom onset ≤1 week previously.

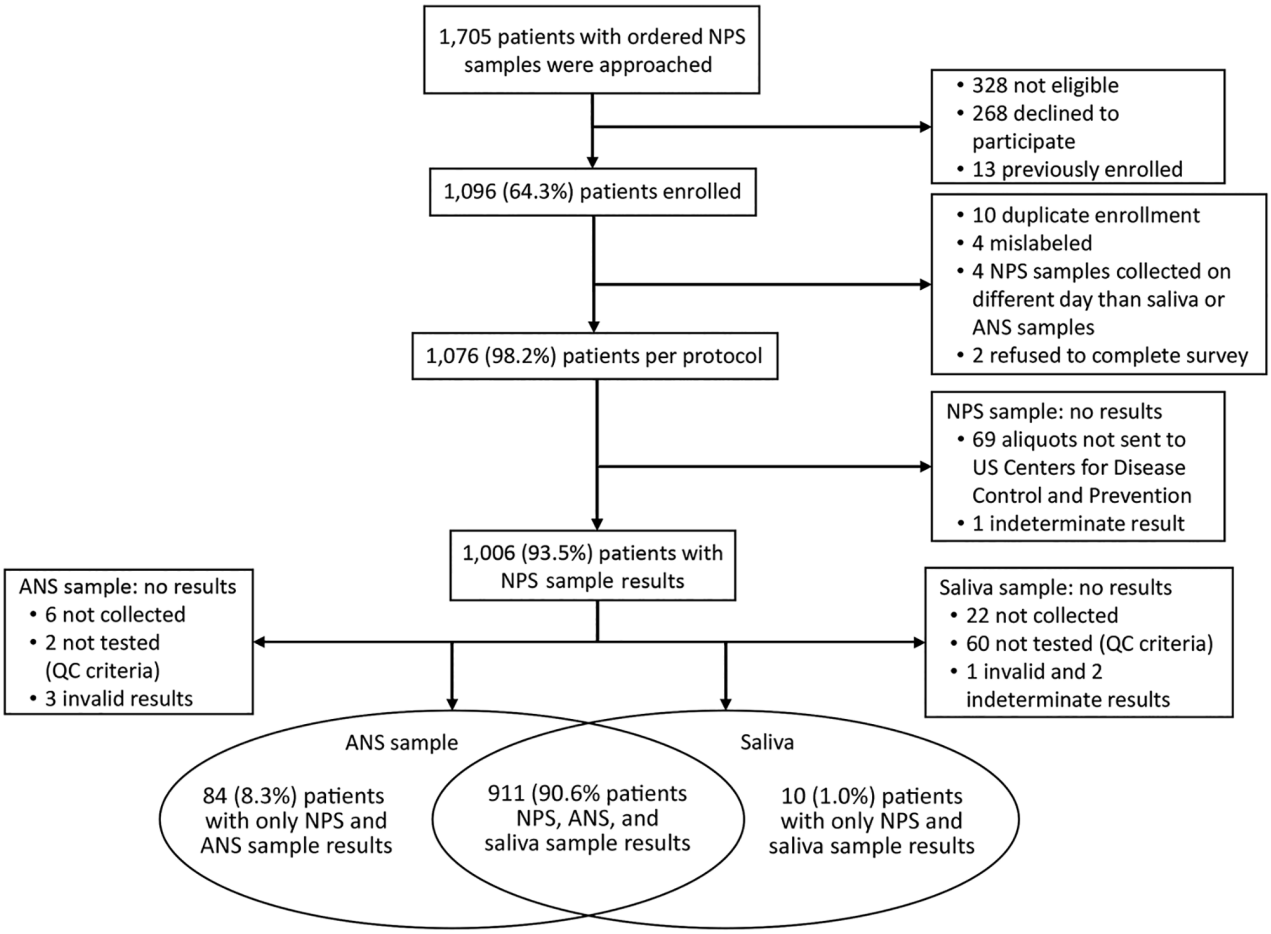

Figure 1. Flowchart of patient enrollment and sample results for investigation of the effects of patient characteristics on self-collected and healthcare worker–collected samples for severe acute respiratory syndrome coronavirus 2 testing, Atlanta, Georgia, USA. ANS, anterior nasal swab; NPS, nasopharyngeal swab; QC, quality control.

Most (93.5%; 1,006) participants provided an NPS sample, of which 8.0% (80/1,006) tested positive for SARS-CoV-2. A total of 911 participants had an RT-PCR result for all 3 specimens (i.e., saliva, ANS, and NPS samples), 10 participants had results for only saliva and NPS samples, and 84 participants had results for only ANS and NPS samples (Figure 1).

Performance of Self-Collected Sample Types

Among 995 participants who provided ANS and NPS samples that produced definitive results, 963 (96.8%) had concordant results (κ = 0.73, 95% CI 0.64–0.82). Compared with NPS samples, ANS samples had 59% sensitivity (95% CI 47%–70%), 100% specificity (95% CI 100%–100%), 100% PPV (95% CI 92%–100%), and 97% NPV (95% CI 95%–98%). Among 921 participants who provided saliva and NPS samples that produced definitive results, 894 (97.1%) had concordant results (κ = 0.76, 95% CI 0.67–0.85). Compared with NPS samples, saliva had 68% sensitivity (95% CI 55%–78%), 99% specificity (95% CI 99%–100%), 90% PPV (95% CI 79%–97%), and 97% NPV (95% CI 96%–98%).

To understand the benefit of using both self-collected specimens for diagnosis, we analyzed data from 1,005 participants who had definitive results for >1 self-collected specimen. We found that 977 (97.2%) had concordant results between the self-collected combination and NPS samples (κ = 0.79, 95% CI 0.71–0.86). Using NPS as the comparator, we found self-collected combination samples had 71% sensitivity (95% CI 60%–81%), 99% specificity (95% CI 99%–100%), 92% PPV (95% CI 82%–97%), and 98% NPV (95% CI 96%–98%). When any positive was used as the comparator, we observed little change in the overall findings: the overall sensitivity of the ANS swab sample decreased slightly, the sensitivity of saliva samples increased slightly, and sensitivity of self-collected combination samples increased slightly (Appendix Table 1).

Sensitivity by Patient Characteristics and Symptoms

Saliva and self-collected combination samples had higher overall sensitivities than ANS samples; this pattern was reflected among men, participants 18–29 years of age and 50–59 years of age, and Black (non-Hispanic) participants (Table 2). Among Hispanic/Latinx participants, sensitivity was significantly lower for saliva and self-collected combination samples. Sensitivity was higher among those not reporting any chronic medical conditions, whose reason for hospital visit was a COVID-19–related concern or whose chief complaint included COVID-19–like symptoms, who reported close contact to a COVID-19 patient during the previous ≤14 days, and who did not report a previous positive COVID-19 test. Sensitivity was lower among participants who reported a previous positive COVID-19 test (Table 2).

Sensitivity was higher among samples from currently symptomatic participants (62% for ANS, 72% for saliva, and 76% for self-collected combination) and was highest among samples from participants who provided samples 3–7 days after symptom onset (80% for ANS, 85% for saliva, and 88% for self-collected combination); these differences were statistically significant for ANS and self-collected combination samples ($p<0.05$). Sensitivity was higher for most individual symptoms, but highest among participants reporting measured fever, congestion or runny nose, new loss of smell, new loss of taste, cough, or subjective fever. Similarly, sensitivity was higher among participants who met most symptom case definitions, but highest among patients who had influenza-like illness, COVID-19–like symptoms, or upper respiratory symptoms accompanied by loss of smell or taste. Sensitivity was lower among patients with nonconstitutional symptoms (Table 2).

C_t Values

Among 46 participants with positive ANS and NPS samples, 85% (for PCR target N1) and 78% (for PCR target N2) had an ANS sample with a higher C_t value than that of its paired NPS sample (Figure 2, panels A, B). We observed a moderate positive correlation between the C_t values of ANS and NPS samples (r = 0.75 for N1, r = 0.71 for N2); both targets had median NPS C_t values of 22.8 (range 14.6–34.1 for N1, 14.7–35.0 for N2). Among 46 participants with positive saliva and NPS samples, 57% (N1) and 59% (N2) had a saliva sample with a higher C_t value than that of its paired NPS sample (Figure 2, panels C, D). We observed a low positive correlation between the C_t values of saliva and NPS samples (r = 0.53 for both N1 and N2); targets had median NPS C_t values of 23.1 (range 14.6–38.3) for N1 and 23.8 (range 14.7–37.7) for N2. When limiting the analysis to the 72 participants who had 3 definitive and ≥1 positive result, C_t values were lowest when all paired specimens were SARS-CoV-2–positive; for N1, the median C_t values were 27.2 for ANS, 24.9 for saliva, and 22.6 for NPS samples (Figure 3). When ≤2 specimens were positive, all specimens had median C_t values >30. Participants who did not have COVID-19 symptoms had higher median NPS C_t values (33.5 for N1, 34.4 for N2) than did those who reported ≥1 COVID-19 symptom (25.6 for N1, p = 0.03; 26.9 for N2, p = 0.03). Among those

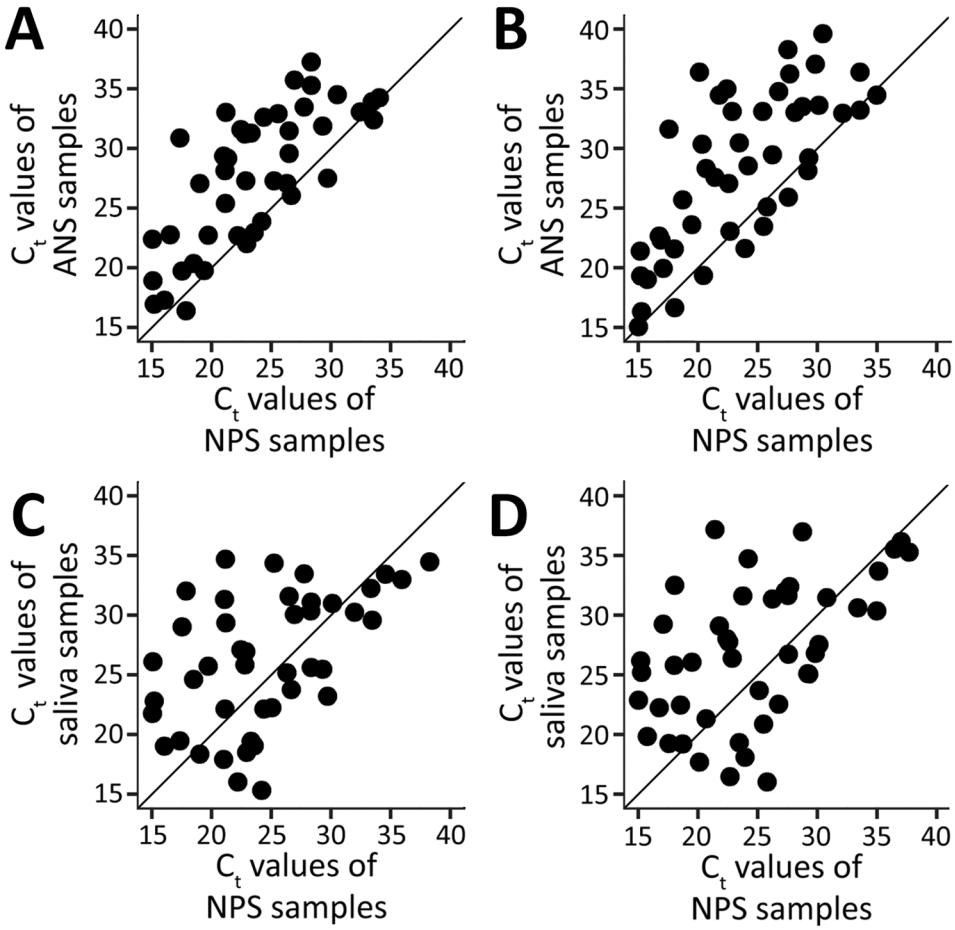

Figure 2. C_t values of self-collected and healthcare worker–collected samples for severe acute respiratory syndrome coronavirus 2 testing, Atlanta, Georgia, USA. PCR completed using CDC 2019-nCoV Real-Time Reverse Transcriptase PCR Diagnostic Panel (*15*). A) ANS and NPS samples at PCR target N1. B) ANS and NPS samples at PCR target N2. C) NPS and saliva samples at PCR target N1. D) NPS and saliva samples at PCR target N2. ANS, anterior nasal swab; C_t, cycle threshold; NPS, nasopharyngeal swab.

reporting COVID-19 symptoms, participants who had symptom onset ≤1 week before testing had the lowest median NPS C_t values (23.5 vs. 30.8 for N1, p<0.01; 24.2 vs. 33.3 for N2, p<0.01).

Discussion

In this investigation, we found that self-collected saliva samples had a higher sensitivity than self-collected ANS samples (68% vs. 59%) compared with HCW-collected NPS samples. However, each sample type had lower sensitivity than suggested by most previously published data (*3*,*6*,*19*–*21*). The self-collected combination had a higher sensitivity (71%) than NPS samples. We found that the sensitivity of self-collected samples (separately and in combination) differed according to patient characteristics. The presence of COVID-19 symptoms at time of specimen collection and the time since symptom onset affected sensitivity. We also noted differences in sensitivity across demographic groups, possibly reflecting differences in access to care or care-seeking behavior rather than differences in viral shedding. Our results illustrate that certain patient characteristics are associated with the sensitivity of self-collected specimens used for RT-PCR.

We found lower sensitivities for saliva and ANS samples than those for most other published studies, including 2 recent meta-analyses that found saliva samples to have sensitivities of 83.2% and 86.9% (*21*,*22*). Many studies showing high sensitivity of self-collected specimens enrolled symptomatic patients who were recently hospitalized for confirmed COVID-19 or whose symptom onset was ≤1 week before sample collection (*3*,*4*). A strength of our investigation was that we included symptomatic and asymptomatic patients being tested for SARS-CoV-2 for screening and diagnostic purposes. Because a substantial proportion of patients infected with SARS-CoV-2 have asymptomatic or mild illness, physicians must be able to analyze results in the context of test sensitivity in patients with few or no symptoms. Sample sensitivity was highest among participants reporting symptom onset 3–7 days before sample collection. Similarly, another study found that the sensitivity of saliva samples was highest (95%) among symptomatic patients tested ≤1 week after symptom onset and lowest

(50%) among patients tested >1 week after symptom onset (*23*). The sample sensitivity differences among patients with different demographic characteristics might reflect differences in access to care or healthcare-seeking behavior. Delayed access to care might postpone specimen collection, decreasing the sensitivity of the samples. For example, Hispanic/Latinx participants who had a positive NPS sample had longer symptom duration compared with participants of other race/ethnicity categories (data not shown).

Using 2 self-collected specimens could increase overall test sensitivity, which reached 88% among participants whose symptoms began 3–7 days before sample collection. Similarly, Tan et al. (*24*) found that combining self-collected oropharynx and midturbinate swab and saliva results increased test sensitivity. Using multiple noninvasive specimens might improve SARS-CoV-2 detection in persons tested ≤1 week after symptom onset and reduce demand for PPE and HCW exposure. However, testing multiple specimens might put additional strain on laboratory systems that are already overburdened. Pooling self-collected specimens before testing might alleviate some of this additional strain on laboratories, but this practice should be investigated further for accuracy.

Similar to other studies, we found that most NPS samples had lower C_t values than did their paired saliva and ANS samples (*4*,*25*,*26*). We also found that median C_t values were lowest when all 3 specimens were SARS-CoV-2–positive; the median C_t value increased to >30 when ≤2 specimens were positive (Figure 3). The lower sensitivity in this investigation might be due to high C_t value discordant specimens, which can occur as infection subsides. We also found slightly higher overall median C_t values for NPS samples than reported in similar studies (*5*,*27*). However, many of these previous studies were implemented earlier in the pandemic when previous infection or exposure was less common. Our investigation began after the first 2 peaks in Atlanta; by the end of enrollment, Atlanta was entering its third peak. When the C_t value of the NPS sample is high, discordance with the self-collected specimens also could increase. Salvatore et al. (*28*) found that C_t values for NPS samples were lowest ≤1 week after symptom onset. Furthermore, Wolfel et al. (*29*) found viral subgenomic mRNA in throat swab specimens collected <5 days after symptom onset and in sputum samples taken 4–11 days after symptom onset, indicating active infection. Although C_t values are not directly correlated with viral load, they provide a semiquantitative assessment of viral RNA concentration.

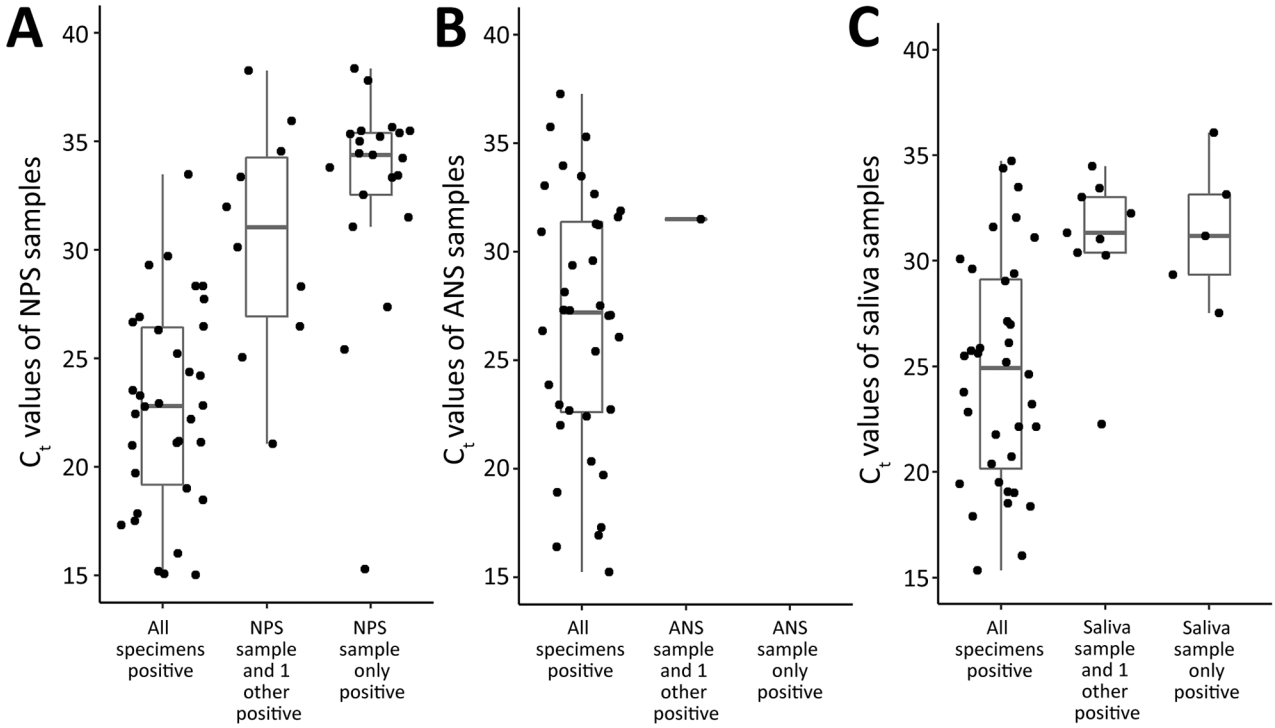

Figure 3. C_t values of self-collected and healthcare worker–collected samples for N1 target of severe acute respiratory syndrome coronavirus 2 PCR, Atlanta, Georgia, USA. PCR completed using CDC 2019-nCoV Real-Time Reverse Transcriptase PCR Diagnostic Panel (*15*). Horizontal lines within boxes indicate medians; box tops and bottoms indicate 25th and 75th percentiles; whiskers indicate the range. ANS, anterior nasal swab; C_t, cycle threshold; NPS, nasopharyngeal swab.

Specimen collection method might also affect sensitivity. Procop et al. (*5*) compared NPS and enhanced saliva samples (i.e., self-collected nasal secretions or mucus, phlegm, and saliva stored in a single tube) and found 100% positive agreement and 99.4% negative agreement. This method of saliva collection provides a mixture of upper and lower respiratory secretions, thereby enabling detection for a longer time after symptom onset. We used general spitting for saliva collection, which has the lowest sensitivity estimate in comparison with other saliva collection methods (*22*). General spitting does not require special devices or transport media, enabling our methods and results to be broadly applicable. The duration and pressure applied while swabbing the anterior nares also might affect ANS sample quality. The sequence of specimen collection, which was not always clear from published studies, could also affect sensitivity (*19*). In our investigation, saliva and ANS samples were collected before NPS samples. Collecting ANS samples after NPS samples could displace virus from nasopharyngeal tissue or midturbinate before the swab leaves the nares, thereby biasing self-collected ANS toward higher sensitivity.

The first limitation of our study is that because we used a cross-sectional design, we did not have information on whether patients were asymptomatic or presymptomatic at specimen collection; we also did not have data on disease severity. In presymptomatic patients, samples might have been collected too early to detect viral RNA in some or all specimen types. Second, we lacked the statistical power to detect significant differences in sensitivity by most variables because the initial sample size calculation assumed self-collected specimens to have ≥90% sensitivity. Third, all responses were self-reported and could have been affected by recall bias. Fourth, the CDC 2019-nCoV rRT-PCR Diagnostic Panel has a higher limit of detection than many commercially available, high-throughput assays (*30*), limiting our ability to detect lower concentrations of viral RNA. However, the clinical and public health utility of detecting these lower concentrations is unknown. Fifth, the CDC 2019-nCoV rRT-PCR Diagnostic Panel does not currently include saliva; instead, the assay was designed for qualitative detection of nucleic acid from SARS-CoV-2. Of 1,006 NPS samples, 64 aliquots did not meet storage requirements approved under the assay's instructions for use (samples should be stored at 4°C for ≤72 hours after collection) (*15*). Because some samples were stored for longer than recommended, viral RNA degradation might have affected the assay's performance. Because the CDC RT-PCR results were not used for clinical care, excluding these specimens did not change sensitivity; furthermore, CDC RT-PCR results were in concordance with the hospital's RT-PCR results (data not shown). As a result, we decided to include these specimens in the analysis (Appendix). Our findings might not be generalizable to other assays or techniques. Sixth, heterogenous self-collection coaching techniques might have introduced differences in the quality of samples collected under the guidance of different interviewers. Finally, PCR does not indicate whether active replication is occurring. Therefore, we are unable to determine whether patients with positive NPS samples but negative saliva or ANS samples have older infections or if the self-collected specimens are less sensitive than NPS samples. Additional laboratory testing is required to clarify the viability of different specimen types and how viability affects clinical presentation and transmissibility. Our study highlights that the sensitivities of saliva and ANS samples are different than that of NPS samples. These findings show that physicians should consider the patient's clinical history, exposures, and time of symptom onset when interpreting PCR results.

Overall, the sensitivities of ANS and saliva samples were lower than that of NPS samples from patients being tested for SARS-CoV-2 for diagnostic and screening purposes. The sample sensitivity was highest among participants with symptom onset within 3–7 days of specimen collection, especially when the reason for the patient visit was COVID-19–related, and those not reporting a previous positive test. Encouraging persons to seek testing within a week of symptom onset could increase the accuracy and usefulness of self-collected specimens used for diagnosing SARS-CoV-2 infections. It is important that clinicians are aware of how differences in patient characteristics and specimen type can affect test sensitivity. Testing programs and clinical settings might consider patient characteristics, previous test results, and timing of symptom onset when determining which specimen types to use.

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Effects of Patient Characteristics on Performance of Self-Collected Samples for SARS-CoV-2 Testing

Appendix

Appendix Methods

Specimen Collection

Patients collected ≈2 mL raw saliva into a sterile 50 mL conical centrifuge tube. Patients were then advised to collect anterior nasal swab (ANS) samples by inserting a mini flocked tip swab into 1 anterior naris, twirling the swab for 10 s, removing the swab and placing it directly into the other naris, and twirling again for 10 s. Upon collection, ANS samples were stored in 3 mL universal viral transport media (Becton, Dickinson and Company, https://www.bd.com). All self-collected specimens were stored at 4°C or frozen (ANS samples only) before extraction. After interview and self-collection of specimens were completed, a nasopharyngeal swab (NPS) sample was collected by healthcare workers at Grady Memorial Hospital (Atlanta, Georgia, USA) using flocked foam swabs and placed into a vial of 3 mL Smart Transport Medium (MedSchenker, https://medschenker.com). Reverse transcription PCR (RT-PCR) on the NPS samples was performed the same day by the hospital laboratory and these results were used for clinical care per hospital protocol and not included in the diagnostic performance analysis. NPS samples were stored at 4°C and remnant Smart Transport Medium was aliquoted and transferred to the US Centers for Disease Control and Prevention (CDC; Atlanta) laboratory for RT-PCR.

Extraction and Testing Methods

Nucleic acid was extracted from 120 μL of viral transport media (ANS and NPS samples) or 120 μL whole saliva at CDC by using the Maxwell RSC 48 automated extraction platform and Maxwell RSC Viral Total Nucleic Acid Purification Kit (Promega, https://www.promega.com). Preprocessing was performed to liquify high-viscosity saliva specimens before extraction by using equal volumes of whole saliva and dithiothreitol and incubated for 30 min at room

temperature. RNA was eluted into 75 μL of nuclease-free water and a 5 μL sample was tested by using the CDC 2019-nCoV Real-Time Reverse transcriptase PCR Diagnostic Panel according to the emergency use authorization instructions for use (IFU) (*1*,*2*). Samples with amplification (cycle threshold <40) of both N1 and N2 gene targets were considered positive, amplification of only 1 N gene target was inconclusive, and amplification of neither N gene target was negative. Lower cycle threshold values represent higher viral RNA concentration. Some NPS aliquots from the hospital were stored outside of the IFU requirements (samples were stored at 4°C for >72 h after collection). Although stability of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA has been demonstrated at 4°C in universal viral transport media for up to 14 days for other RT-PCR assays (*3*,*4*), an analysis excluding NPS aliquots stored outside of IFU requirements was performed to ensure storage conditions did not influence the findings.

Symptom Group and Clinical Case Definitions

Respiratory symptoms were defined as any of the following: runny nose/congestion, sore throat (upper respiratory); or cough, shortness of breath/difficulty breathing, wheezing, and chest pain (lower respiratory). Nonrespiratory symptoms were defined as any of the following: fever (measured or subjective), muscle/body aches, headache, chills, fatigue, loss of smell, loss of taste, nausea, vomiting, and diarrhea. COVID-19–like symptoms were defined as fever (measured or subjective) and cough or shortness of breath/difficulty breathing (*5*). Council of State and Territorial Epidemiologists clinical criteria for COVID-19 reporting was defined as any of the following: cough, shortness of breath/difficulty breathing, new smell disorder, or new taste disorder or ≥2 of the following: fever (measured or subjective), chills, myalgia, headache, sore throat, nausea or vomiting, diarrhea, fatigue, or congestion/runny nose (*6*). Influenza-like illness was defined as measured fever and cough or sore throat (*5*). The World Health Organization defines acute respiratory infection as any shortness of breath/difficulty breathing, cough, sore throat, or congestion/runny nose (*7*).

Appendix Results

Storage Requirement Analysis

Among 1,006 patients with NPS RT-PCR results, 64 NPS samples did not meet the IFU storage requirement of 4°C for ≤72 h from collection. These 64 specimens were received and

tested a median of 4 d after collection (range 4–5 d). The overall sensitivity of ANS samples compared with NPS samples was 59% (95% CI 47%–70%); excluding the specimens that did not meet storage requirements slightly changed the sensitivity (58%; 95% CI 46%–69%). The overall sensitivity of saliva samples compared with NPS samples was 68% (95% CI 55%–78%); excluding the specimens that did not meet storage requirements slightly changed the sensitivity point estimate (67%; 95% CI 54–78). There was no change in specificity. Among those with an RT-PCR result from Grady Memorial Hospital (n = 983), there was no difference in NPS result concordance of CDC RT-PCR results with Grady RT-PCR results among those that did not meet the storage requirement and those that did meet the storage requirement (61/62, 98.4% vs. 907/921, 98.5%; p = 1.0 by Fisher exact test).

Sensitivities of Various Sample Types Compared with Any Positive Result

Because NPS samples do not detect all SARS-CoV-2 infections, we reran the sensitivity analysis with a combined variable for any positive result from ANS, saliva, or NPS samples as the comparator. We calculated sensitivity and 95% CI of self-collected specimens within patient characteristic subgroups to evaluate how patient differences might affect specimen performance. We determined statistically significant sensitivity differences between overall and subgroups using a 1-sample, 2-way test of proportions ($p<0.05$). Among 1,076 per-protocol patients, 85 (7.9%) had $\geq$1 ANS, saliva, or NPS sample test positive for SARS-CoV-2. Among 1,063 participants with a definitive ANS sample result, ANS sample sensitivity compared with any positive was 56% (95% CI 45–67) (Appendix Table). Compared with the ANS versus NPS sample analysis, the only change in statistical significance was the sensitivity among those reporting symptom onset 3–7 d before enrollment was not significantly different than the overall sensitivity. Among 989 participants with a definitive saliva sample result, sensitivity of saliva compared to any positive result was 70% (95% CI 59–80). Compared with the saliva versus NPS sample analysis, the only change in statistical significance was the sensitivity among those with a previous positive result was not significantly different than the overall sensitivity. Among 1,075 participants with a definitive ANS or saliva sample result, sensitivity of self-collected combination compared to any positive was 73% (95% CI 62–82). Compared with the self-collected combination versus NPS sample analysis, the only change in statistical significance was the sensitivity among those reporting symptom onset 3–7 d before enrollment was not significantly different than the overall sensitivity.

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Appendix Table. Sensitivity of self-collected samples for severe acute respiratory syndrome coronavirus 2 testing*

Characteristic	Sensitivity, % (95% CI)†		
	Anterior nasal swab sample	Saliva sample	Self-collected combination‡
Total	56 (45–67)	70 (59–80)	73 (62–82)
Sex			
F	50 (34–66)	68 (49–83)	70 (53–83)
M	61 (45–76)	72 (56–85)	76 (60–87)
Age, y			
18–29	67 (30–93)	86 (42–100)	89 (52–100)
30–39	43 (18–71)	58 (28–85)	57 (29–82)
40–49	44 (22–69)	67 (41–87)	68 (43–87)
50–59	67 (43–85)	89 (67–99)	86 (64–97)
>60	59 (36–79)	56 (31–78)	68 (45–86)
Race/ethnicity			
Black, non-Hispanic	60 (48–72)	75 (62–85)	77 (66–87)
Hispanic/Latino	25 (3–65)	**25 (3–65)**	**25 (3–65)**
White, non-Hispanic	67 (9–99)	100 (16–100)	100 (29–100)
Chronic medical conditions			
0	73 (50–89)	85 (62–97)	83 (61–95)
≥1	51 (37–64)	65 (50–78)	69 (56–81)
Body mass index§			
Underweight	33 (1–91)	0 (0–84)	33 (1–91)
Normal weight	67 (41–87)	69 (41–89)	74 (49–91)
Overweight	56 (31–78)	69 (41–89)	72 (47–99)
Obese	55 (39–70)	77 (61–89)	77 (62–89)
Reason for visit			
COVID-19 concern	59 (41–75)	77 (58–90)	79 (62–91)
No COVID-19 concern, but chief complaint included COVID-19–like symptoms	68 (46–85)	82 (60–95)	81 (61–93)
Preoperative requirements or admission to labor and delivery unit	25 (1–81)	25 (1–81)	25 (1–81)
Other reasons	43 (22–66)	56 (31–78)	62 (38–82)
Known close contact			
Yes	53 (29–76)	73 (45–92)	74 (49–91)
Yes, ≤14 d since most recent exposure	70 (35–93)	83 (36–100)	80 (44–97)
No	58 (44–71)	69 (54–81)	72 (58–83)
Unknown	50 (16–84)	75 (35–97)	78 (40–97)
Reported a previous positive COVID-19 test			
Yes	**7 (0–34)**	50 (21–79)	**43 (18–71)**
No	66 (53–77)	74 (62–84)	79 (68–88)
COVID-19 symptom status			
Always asymptomatic	36 (11–69)	50 (19–81)	55 (23–83)
Currently asymptomatic	50 (16–84)	71 (29–96)	62 (24–91)
Currently symptomatic	60 (47–72)	74 (60–84)	77 (65–87)
Days since symptom onset¶			
0–2	74 (49–91)	72 (47–90)	79 (54–94)
3–7	74 (54–89)	86 (65–97)	89 (72–98)
8–14	33 (10–65)	73 (39–94)	67 (35–90)
>15	0 (0–60)	50 (7–93)	50 (7–93)
Current individual symptoms¶			
Fever, measured	**93 (68–100)**	83 (52–98)	93 (68–100)
Fever, subjective	69 (48–86)	77 (55–92)	81 (61–93)
Cough	62 (47–76)	82 (67–93)	85 (71–94)
Shortness of breath or difficulty breathing	56 (38–72)	76 (58–89)	78 (62–90)
Fatigue	60 (44–74)	78 (62–89)	78 (64–89)
Muscle or body aches	64 (46–79)	79 (61–91)	81 (65–92)
Headaches	60 (41–77)	72 (53–87)	74 (55–88)
New loss of taste	73 (50–89)	74 (49–91)	77 (55–92)
New loss of smell	70 (46–88)	83 (59–96)	85 (62–97)
Sore throat	50 (25–75)	67 (38–88)	69 (41–89)
Congestion or runny nose	72 (51–88)	83 (61–95)	84 (64–95)
Nausea	57 (34–78)	76 (53–92)	77 (55–92)
Vomiting	60 (15–95)	67 (22–96)	67 (22–96)
Diarrhea	46 (19–75)	83 (52–98)	85 (55–98)
Current symptom groups¶			
Respiratory symptoms	61 (47–74)	77 (62–88)	80 (67–90)

Characteristic	Sensitivity, % (95% CI)†		
	Anterior nasal swab sample	Saliva sample	Self-collected combination‡
Upper respiratory symptoms	61 (42–78)	75 (56–90)	77 (59–90)
Lower respiratory symptoms	61 (46–75)	79 (63–90)	82 (69–91)
Nonrespiratory symptoms	61 (47–73)	75 (61–86)	78 (66–88)
Upper respiratory and loss of taste or smell	69 (39–91)	75 (43–95)	77 (46–95)
Gastrointestinal symptoms	54 (33–74)	79 (58–93)	80 (59–93)
Nonrespiratory symptoms excluding loss of taste or smell	62 (49–75)	76 (61–87)	79 (66, 89)
Nonconstitutional symptoms	44 (14–79)	62 (24–91)	67 (30–93)
Common case definitions¶			
COVID-19–like symptoms	71 (49–87)	80 (56–94)	83 (63–95)
COVID-19#	60 (47–72)	75 (62–86)	79 (66–88)
Influenza-like illness	**91 (59–100)**	89 (52–100)	91 (59–100)
Acute respiratory infection**	60 (46–74)	77 (62–88)	80 (66–89)

*COVID-19, coronavirus disease. Boldface type indicates values that are significantly different (p<0.05) than overall sensitivity values, according to a 1-sample test of proportions.
†Using CDC 2019-nCoV Real-Time Reverse Transcriptase PCR Diagnostic Panel (*2*). Results in comparison with all positive samples. Anterior nasal swab and saliva samples were self-collected; nasopharyngeal samples were collected by healthcare workers.
‡Self-collected combination reflects ≥1 positive result in a patient's paired anterior nasal swab and saliva samples.
§Calculated using self-reported height and weight.
¶Among currently symptomatic participants.
#According to definition established by the Council of State and Territorial Epidemiologists (*6*).
**According to definition established by the World Health Organization (*7*).

Appendix Figure. Infographic outlining steps for self-collection of saliva samples. Graphic provided to participants in study on sensitivity of self-collected samples for severe acute respiratory syndrome coronavirus 2 testing. COVID-19, coronavirus disease.