Perspectives on Meeting the COVID-19 Testing Challenge: A Dental School Collaborative

Author: The Testing for Tomorrow (T4T) Collaborative

Wiley: The list of members in this Collaborative appears after the narrative in the main manuscript.

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Introduction and Background

From the earliest days of the COVID-19 pandemic, dental practitioners, organizations, educators, insurers, and manufacturers were concerned about the impact of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on a panoply of issues, including transmission modes; personal protective equipment (PPE) supplies; aerosolization; office disinfection; patient confidence; and screening and testing protocols to determine the viral status of patients, clinicians, and staff members. The shared goals of dental clinicians were to treat patients as safely as possible through optimal use of PPE with disinfection and aerosol mitigation protocols to minimize the risk of viral transmission in the dental office or school clinic. Since initial state and federal pandemic efforts focused on treating the sickest patients, hospital capacity, mass testing, and the global PPE supply, a group of dental schools recognized that dental practices would benefit greatly from the ability to

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evaluate the viral status of their patients using office-based, point-of-care (POC) tests, ideally using sputum, saliva, and/or finger stick blood samples. Since private dental offices and most dental schools lack the analytic instrumentation and the Clinical Laboratory Improvement Amendment (CLIA) certifications to conduct the types of polymerase chain reaction (PCR) viral tests prevalent in the early days of the outbreak, the group of schools focused on POC tests, which did not require CLIA certified labs or expensive equipment.

The Collaborative consisted of the dental schools from the University of California, San Francisco; the University of Michigan; Temple University; the University of Pennsylvania; Rutgers University; and New York University. In addition, the respected health care company Henry Schein Inc., provided market insights and a gateway to the many manufacturers developing tests, and the Santa Fe Group helped coordinate the efforts of the Collaborative and promulgate the findings. Importantly, all tests considered by the Collaborative were "platform neutral," meaning that any manufacturer that could provide an accurate POC test would be considered for use. A small group of physicians and dentists served in an advisory capacity, and the group operated as the Testing for Tomorrow (T4T) Collaborative.

With knowledge about the virus expanding continuously, new tests arriving almost daily, the FDA recall of scores of flawed tests, and schools under constraints from clinic closures and PPE shortages, it was a struggle to evaluate the tests and to establish supporting protocols. The initial goal of identifying the best POC test—be it antigen, antibody, or viral—was elusive, although each school did identify alternative approaches to evaluate their students, faculty, staff, and patients, and developed careful approaches to re-opening their clinics. Thus, while the initial primary goal has not been met, each participating institution in T4T benefited substantially from the shared experience of working through patient assessment protocols, validation testing, and access to content experts and new tests that would not have been readily available to a single institution. Thus, perhaps the most important perspective to consider is that educational institutions should seek the benefits of

collaborating in small groups, especially in the fast-paced environment where completely novel challenges are forced upon them.

Goals of the T4T Collaborative

The T4T Collaborative set the following goals:

1. Recruit intra- and interinstitutional partners, including community-based entities, to develop COVID-19 evaluation protocols for first-responders, frontline healthcare professionals, essential workers, and ultimately patients and private practice staff.
2. Evaluate SARS-CoV-2 tests that are appropriate for use in clinical practice with primary emphasis on those POC tests that would be most useful in private practice settings.
3. Provide guidance on lessons learned, and recommend best practices to both healthcare institutions and the practitioner community.

Factors Antecedent to Actual Testing

An institution desiring to conduct COVID-19 testing should first identify the individuals to be tested (e.g., patients, students, staff, faculty), and then appoint a leader and key personnel from IT, patient services, and the clinical faculty. If state law does not allow dentists to perform COVID-19 tests, the dental school will need to collaborate with other authorized health providers. Finally, it should select an FDA Emergency Use Authorization (EUA) approved COVID-19 test, and a convenient testing location separated from patient clinics or waiting areas.

IT staff can create online recruitment, pre-screening and scheduling tools. Also, they can add systems in the electronic health record (EHR) to allow medical insurance billing, record essential

COVID-19 related patient information, report test results to state and federal health authorities, and track patients for re-testing as necessary.

Informed consent and test results (including post-test recommendations based on federal, state, and local guidance) forms must be created. The Centers for Disease Control and Prevention (CDC) recommends that asymptomatic individuals with a positive COVID-19 viral test must quarantine for seven to ten days after the first laboratory confirmed positive test. If symptomatic, individuals must quarantine for seven to ten days since symptoms first appeared, *and* 24 hours with no fever without the use of fever-reducing medications, *and* symptoms have improved (e.g., cough, shortness of breath). Some organizations also require a negative COVID-19 test to return to work or school. Positive test results should be referred to local health authorities for contact tracing.

Training is crucial for testing accuracy, data integrity, and safety. Training should include how to perform entry screening, collect specimens, load test devices, read test results, enter data, and communicate results to patients. Creating checklists to avoid errors, and videos of the testing procedures, have proven helpful. An infection control officer should be consulted regarding necessary PPE and proper donning and doffing of PPE by staff in the testing location.

When all of this preparation is done, testing can commence.

SARS-CoV-2 Test Considerations

Molecular Testing

Molecular testing is considered the most sensitive and specific of the SARS-CoV-2 tests. It detects the presence of the genetic material (RNA) associated with the virus, and is used to determine the presence of an active infection.

Initial efforts to detect SARS-CoV-2 used standard PCR methods that were accurate, but time consuming, and required equipment and trained personnel. Thus, these methods had limited utility due to the high demand, slow response time, expense, and required laboratory expertise. Although this method remains the gold standard, it is impractical for high volume, rapid testing.

Since SARS-CoV-2 is an RNA virus, the first step is to use reverse transcriptase to convert the RNA to DNA. Briefly, after initial isolation from an infected patient, the SARS-CoV-2 RNA virus is separated from human DNA, reversed transcribed into cDNA for PCR amplification. In the process, PCR primers for the spike protein (S) for viral attachment and penetration of human cells, the envelope protein (E), the matrix protein (M), and the nucleocapsid protein (N) were identified. Once converted to DNA, any of the proteins (S, E, M, or N) can be amplified via PCR primer amplification. This process was simplified by combining step 1 (reverse transcription) and step 2 (cDNA) prior to amplification. In this one-step procedure, PCR amplification was accomplished via cycles of thermal changes (high temps to low temps). The number of cycles and times for each cycle can be used to determine the amount of DNA amplification. Newer methods, using isothermal amplification, use one temperature, less equipment, and show promise for POC testing. Loop mediated isothermal amplification (LAMP) is shown below as one example (see Table 1).

(Insert Table 1)

Other methods using CRISPR technology and terahertz time-domain spectroscopy are also being evaluated for POC rapid testing, but none of these methodologies are approved for use currently.

Antigen Testing

Antigen testing, like molecular testing, is designed to identify active infection, but it detects the presence of viral proteins, not viral RNA. Antigen tests are typically somewhat less sensitive than are molecular tests, but can often be less expensive and faster to run.

POC testing for antigens requires that samples are taken from the patient on site. Commonly, a plate or slide is pre-coated with an antibody designed to capture a variety of SARS-CoV-2 antigens (S, N, M, or E). The antibody-coated plate is then reacted with the chosen antigen to capture the antigen on the plate. The captured antigen is then reacted with a secondary antibody linked to an enzyme that will also react with the antigen. Ultimately, a colorimetric agent is applied to the enzyme containing secondary antibody, which will indicate the presence of the SARS-CoV-2 antigen in the patient sample. This is done either as a lateral flow method, where the process proceeds on a matrix that allows for antigen capture from a patient sample to migrate on the plate, or in an Enzyme Linked Immunoassay (ELISA), which requires a 96 well plate and a reader, in addition to several washing steps. The lateral flow method is usually qualitative (dichotomous – negative or positive – or ordinal – negative, weakly positive, or strongly positive) or semi-quantitative (e.g., subjectively rated 0 = negative, 1, 2, 3, 4, 5, 6 = strongly positive), while the ELISA test can be quantitative.

Antibody Testing

Whereas viral (antigen or molecular) testing detects current infection, antibody testing detects evidence of past infection by finding antibodies specific to SARS-CoV-2 after a suitable latent period.

Antibody testing usually requires a blood or salivary sample from the patient. This can be obtained from a finger stick or from a peripheral blood draw. In this case, the antigen (S, E, N, M) is bound to the plate or lateral flow device as the first step. The serum derived from the blood draw is placed on the plate or matrix, allowed to react, and then the secondary antibody to human antisera derived from the blood draw is reacted with either rabbit or mouse anti-human immunoglobulin (Ig)

M or IgG. The bound secondary antibody is linked to an enzyme that reacts with a colorimetric signal that produces a response and indicates whether the subject has antibody to SARS-CoV-2 or not.

The antibody response has several drawbacks. It does not necessarily measure neutralizing antibody, so it may indicate that the patient reacted by producing antibodies, and therefore was exposed to the virus, but it does not determine whether the virus is neutralized. The likely value of antibody testing is (1) to determine if patients do have neutralizing antibody (depending on the antigen used) and thus can be used as convalescent serum to treat infected patients; and (2) for seroprevalence studies—determining objectively the presence of antibodies, and therefore past infection, in populations. Neutralizing antibody presence can only be definitively determined in viral neutralization/functional assays done in a biosafety level 3 (BSL3) facility with highly trained personnel.

Table 2 provides a comparison of FDA EUA-approved tests that are currently available as well as some additional tests in development, seeking EUA approval.

(Insert Table 2)

Opening Schools and Dental Clinics in the Absence of Ideal Tests

Before the COVID-19 pandemic, donning readily available PPE had been the standard protection of dental providers and patients. The new SARS-CoV-2 (COVID-19) pandemic presented new challenges. Without the ability to perform quick, highly accurate SARS-CoV-2 viral/antibody testing, which can identify who is potentially infectious, schools have to exclude patients with COVID-19 symptoms, or diagnosed active cases, from routine clinical care, and adopt universal precautions, assuming that all others (students, faculty, staff, and patients) may be carrying the virus without symptoms.

Guidance for re-opening dental schools is limited. There is little scientific evidence verifying the effectiveness of strategies to reduce the spread of COVID-19, and it is not feasible for schools

and dental clinics to implement all possible strategies. Research is critically needed to determine which strategies are the most effective and necessary to create the safest environment.

Schools have selected actions based on prevalence of disease in their locales, the design and engineering capabilities of their facilities, the availability of supplies, and the recommendations and policies of their parent universities, cities, counties, and states. Thus, each school has implemented a unique combination of a variety of the following approaches:

- **Good COVID-19 personnel hygiene:** Donning masks, social distancing, and hand sanitation.
- **Social Distancing:** Online education and administration of tests, restriction on patients in waiting rooms and cafeterias, small-group meetings with social distancing, sneeze guards to separate workstations, signage to guide people, and teledentistry to reduce the need for in-person visits.
- **Symptom Checking:** On the day before appointments, and at entrances to the building or clinics, including temperature measurements, on the day of the appointment.
- **Enhanced PPE**: Depending on the dental procedure, donning of surgical masks, fitted N95 masks, face shields, ASTM level 2/3 gowns, gloves, bouffant, and shoe covers are all recommended or required.
- **Facility and environmental system alterations**: Temporary negative pressure or AIIR (Airborne Infection Isolation Rooms) rooms, HEPA or Minimum Efficiency Report Value of 13 (MERV-13) or higher filters and increased air exchanges.
- **Disinfection:** Using Environmental Protection Agency (EPA)-registered disinfectants that have qualified under EPA's emerging viral pathogens program for use against SARS-CoV-2 to disinfect treatment areas before and after dental treatment, as well as high-touch surfaces after each patient visit or several times during a day.
- **SARS-CoV-2 Molecular/Antibody/Antigen Testing**: Testing students as a requirement to return to campus, and testing patients, should be considered.

- **Contact tracing**: Effective risk assessment and swift contact tracing as needed.
- **No Travel Policy/Mandatory "Quarantine":** for students/faculty/staff coming from regions with high positivity rates.
- **Minimizing Aerosol**: Four-handed dentistry, high-speed evacuation units, minimally invasive techniques, restricted use of ultrasonic scalers, and clinics created with aerosol mitigation or protocols.
- **Drive-thru Care Delivery:** Some practices and clinics have adopted drive-thru care, similar to drive-thru COVID-19 testing, for screening and preventive care (e.g., fluoride varnish application, silver diamine fluoride application).

T4T Collaborative Outreach

The T4T Collaborative partners have learned much in the process and have begun to share this learning and argue for improvements in the system. For example:

- T4T submitted a request to the Office of the Surgeon General for dentists to get access to SARS-CoV-2 tests and reimbursement for such tests similar to other health professionals.
- Some members of T4T presented testing protocols in a webinar sponsored by AON, which was attended by representatives of 700 major corporations.
- Several members of T4T will share their experiences in a webinar sponsored by the Organization for Safety, Asepsis and Prevention (OSAP) shortly after this paper is submitted.

It is expected that the T4T Collaborative will produce at least one more publication after it has identified and evaluated appropriate tests. This paper will be oriented to private practitioners and will be available in a suitable publication.

Summary

Although only two of the three T4T Collaborative goals have been met to date, the participants in the effort consider that the collaboration has been very successful and well worth their time. As enormous amounts of information about COVID-19 were generated worldwide, participants from each of the six dental schools, plus the corporate and not-for-profit partners, were able to evaluate rapidly developing information using a shared group skill set that would not have been available to a single institution. These skills were shared with a remarkable esprit de corps. Moreover, the partnership with a large, respected health company created access to new tests, in some cases before they were available for sale, so that validation exercises could begin early. In addition, the schools shared information about how to approach clinic re-opening as safely as possible in the absence of an appropriate POC test. In sum, the use of a multi-school collaborative is a powerful mechanism that should be used when unique challenges to dental education arise in the future. Finally, while the perspectives contained herein are current as of the publication submission date, all institutions are encouraged to check the websites of relevant organizations regularly for important policy updates (e.g. CDC, FDA, WHO, OSHA, etc.).

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Table 1

Comparison of PCR and LAMP		
Procedures:	PCR	LAMP
Amplification	Cycles: Denature: 95^{0}C Annealing : -60^{0}C Polymer Formation: 72^{0}C	One cycle temperature: 60-65^{0}C
Denaturation	High temp needed for separation of strands	Polymerase used for strand separation
Equipment and Time	Thermocycler: 90 minutes	Water bath for 30 minutes or less
Sensitivity and Specificity	Needs nanograms of material Needs careful primer design	Needs fentograms of material
DNA detection	Requires gel electrophoresis	Uses colorimetry
DNA Template Requirements	Purification required	Tolerates impurities

Table 2

COVID-19 TESTS

Test Name	CLIA	EUA / Available	Test Type	Sampling Method	Time to Test (Minutes)	Performance		Requires Instrument	Requires Lab
						Sensitivity	Specificity		
Cue Health	Waived	Y	Molecular	Ant. Nasal	25	99.00%	100.00%	POC Instrument	N
Cepheid	Waived	Y	Molecular	Ant. Nasal	45	100.00%	100.00%	POC Instrument	N
Quidel	Waived	Y	Antigen	Ant. Nasal	15	80.00%	100.00%	POC Instrument	N
Spectrum / Soft Cell	Waived	Y	Molecular	Saliva	360	100.00%	100.00%	N	Y
BD Veritor	Waived	Y	Antigen	Ant. Nasal	15	84.00%	100.00%	POC Instrument	N
Everlywell	Waived	Y	Molecular	Ant. Nasal	360	100.00%	100.00%	N	Y
Abbott IDNow	Waived	Y	Molecular	Ant. Nasal	10	94.70%	98.60%	POC Instrument	N
Vault Health	Waived	Y	Molecular	Saliva	360	100.00%	100.00%	N	Y
Premier Biotech	Moderate	Y	Antibody	Venous	15	91.56%	99.50%	N	N
Ortho Clinical	Moderate	Y	Antibody	Serum/Plasma	85	100.00%	100.00%	Lab Instrument	Y
Beckman Coulter	Moderate	Y	Antibody	Serum/Plasma	60	92.70%	99.60%	Lab Instrument	Y
Scanwell Health	High	N	Antibody	Fingerstick	15	91.51%	98.03%	N	N
SD Biosensor Combo	High	N	Antibody	Venous	15	100.00%	98.00%	N	N
BD/Biomedomics v.2	High	N	Antibody	Venous	15	88.66%	90.63%	N	N
SD Biosensor Ag	High	N	Antigen	Nasopharyngeal	30	84.30%	100.00%	N	N

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