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Retrospective clinical evaluation of 4 lateral flow assays for the detection of SARS-CoV-2 IgG

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ABSTRACT

In a Clinical Laboratory Improvement Amendments laboratory setting, we evaluated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) IgG detection with 4 lateral flow immunoassays [LFIAs; 2 iterations from BTNX Inc. ($n = 457$) and 1 each from ACON Laboratories ($n = 200$) and SD BIOSENSOR ($n = 155$)]. In a cohort of primarily hospitalized, reverse-transcription polymerase chain reaction–confirmed coronavirus disease 2019 cases, sensitivity at ≥14 days from symptom onset was: BTNX kit 1, 95%; BTNX kit 2, 91%; ACON, 95%; and SD, 92%. All assays showed good concordance with the Abbott SARS-CoV-2 IgG assay at ≥14 days from symptom onset: BTNX kit 1, 99%; BTNX kit 2, 94%; ACON, 99%; and SD, 100%. Specificity, measured using specimens collected prior to SARS-CoV-2 circulation in the United States and "cross-reactivity challenge" specimens, was 98% for BTNX kit 1 and ACON and 100% for BTNX kit 2 and SD. These results suggest that LFIAs may provide adequate results for rapid detection of SARS-CoV-2.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in 2019 as the causative agent of coronavirus disease 2019 (COVID-19), a pandemic respiratory infection resulting in over 14 million cases and 600,000 deaths between November 2019 and July 2020 (WHO, 2020).

Antibody detection is currently being implemented in many clinical centers to aid in identification of recent disease and to investigate population seroprevalence. Accurate laboratory tests impact clinical decision making, and understanding performance of a test is essential to determination of when to use the test and what the results might mean. For example, specificity is of particular importance in a low-prevalence setting (Farnsworth and Anderson, 2020). Lateral flow immunoassays (LFIAs) are an attractive alternative or supplement to automated enzyme-linked immunosorbent assay and chemiluminescence assays as they require less operator skill and for their potential utility in a point-of-care setting. Here we evaluated 4 LFIAs for the detection of anti–SARS-CoV-2 IgG in clinical samples.

2. Materials and methods

2.1. Patient population and clinical specimens

Deidentified, presumptive positive specimens ($n = 352$) from 62 individuals with reverse-transcription polymerase chain reaction (RT-PCR)–confirmed COVID-19 were kindly shared by the Department of Laboratory Medicine at the University of Washington School of Medicine (Seattle, WA) with limited metadata, such as Abbott SARS-CoV-2 IgG immunoassay results and the number of days since symptom onset. These consisted of 250 plasma, 77 serum, and 21 whole blood specimens (a further 4 unknown specimens were assumed to be either serum or plasma); were received frozen; and underwent either 1 or 2 freeze–thaw cycles prior to testing. Specificity specimens were obtained from 2 sources: 74 excess clinical serum specimens collected and stored in 2018, and 31 "cross-reactivity challenge" specimens collected between March and April 2020. Among these 105 specimens, there were 27 from individuals with a history of seasonal coronavirus infection (as determined by a syndromic respiratory PCR test) within 3 years prior to collection (HKU1, $n = 13$; NL63, $n = 6$; OC43, $n = 6$; 229E, $n = 2$); 2 specimens reactive for rheumatoid factor; 1 reactive for HIV-1 antibody, HAV total antibody, HBV core total antibody and surface antibody, and

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RPR; and 1 reactive for HCV antibody and HSV2 antibody (Table 1). These specimens were tested after 0, 1, or 2 freeze–thaw cycles.

2.2. LFIAs

Rapid Response™ COVID-19 Test Cassette (BTNX Inc.): We tested 2 different iterations of this kit, hereafter referred to as BTNX kit 1 and BTNX kit 2. LFIAs were performed according to the manufacturer's instructions. Briefly, for BTNX kit 1, 10 μL serum, plasma, or whole blood was transferred to the sample well, followed by 1 drop of assay buffer; results were read and interpreted after 10–15 min. For BTNX kit 2, 5 μL serum, plasma, or whole blood was transferred to the sample well, followed by 2 drops of assay buffer; results were read after 15 min.

SARS-COV-2 IgG/IgM Rapid Test (ACON Laboratories): For this assay, hereafter referred to as ACON, 10 μL serum or plasma, or 15 μL whole blood was transferred to the specimen well, and then 2 drops of buffer were added to the buffer well; results were read after 10–15 min.

Standard Q COVID-19 IgM/IgG Duo (SD BIOSENSOR): This kit is supplied as individual IgM and IgG cartridges; only the IgG cartridges were evaluated in this study and are hereafter referred to as SD. For this assay, 10 μL serum, plasma, or whole blood was transferred to the specimen well, and then 2 to 3 drops of buffer were added to the buffer well; results were read and interpreted after 10–15 min.

Results for all assays were interpreted by 2 readers (KM, TG) and photographed for reference, with the exception of the SD assay, for which the first 30 assays were interpreted by 1 reader only and not photographed. Both readers were essentially blinded in that the sample metadata (time to disease onset and Abbott results) were not revealed until reading was complete. Images of discrepant specimens were read by a third independent and blinded individual (FG), and the consensus between 2 readers was recorded as the final result. A representative image of a positive result on all 4 assays is shown in Fig. 1.

Table 1
Specimens selected in this study for their potential to contain cross-reactive antibodies, where time elapsed refers to the time between PCR detection of the virus (CR1–27) or other potentially interfering substance (CR28–31) and collection of the blood specimen used in this study.

Sample ID	Interfering substance	Time elapsed (d)
CR01	History of coronavirus HKU1 infection	28
CR02	History of coronavirus HKU1 infection	46
CR03	History of coronavirus HKU1 infection	74
CR04	History of coronavirus HKU1 infection	82
CR05	History of coronavirus HKU1 infection	84
CR06	History of coronavirus HKU1 infection	85
CR07	History of coronavirus HKU1 infection	96
CR08	History of coronavirus HKU1 infection	108
CR09	History of coronavirus HKU1 infection	108
CR10	History of coronavirus HKU1 infection	116
CR11	History of coronavirus HKU1 infection	120
CR12	History of coronavirus HKU1 infection	127
CR13	History of coronavirus HKU1 infection	146
CR14	History of coronavirus NL63 infection	1
CR15	History of coronavirus NL63 infection	19
CR16	History of coronavirus NL63 infection	53
CR17	History of coronavirus NL63 infection	411
CR18	History of coronavirus NL63 infection	452
CR19	History of coronavirus NL63 infection	530
CR20	History of coronavirus OC43 infection	103
CR21	History of coronavirus OC43 infection	241
CR22	History of coronavirus OC43 infection	370
CR23	History of coronavirus OC43 infection	440
CR24	History of coronavirus OC43 infection	863
CR25	History of coronavirus OC43 infection	1159
CR26	History of coronavirus 229E infection	118
CR27	History of coronavirus 229E infection	448
CR28	Rheumatoid result of 63	0
CR29	Rheumatoid result of 27	0
CR30	HSV2 Ab, HCV Ab	0
CR31	HIV-1 Ab, HAV total, HBc total, HBsAb, RPR(1:4)	0

2.3. IgM detection

All assays tested also offered IgM detection. The SD IgM cartridge was not evaluated here, but ACON and both BTNX kits included IgM in the same cartridge; however, as IgM results were variable across all assays, we opted to focus on IgG for the purpose of this evaluation. IgM results are available in Supplementary Table S1.

3. Results

3.1. BTNX sensitivity

Sensitivity of the BTNX assays was evaluated using specimens from a primarily hospitalized cohort of individuals with RT-PCR–confirmed COVID-19 (Seattle cohort, $n = 352$) and stratified by the number of days since symptom onset. Sensitivity of BTNX kit 1 at <7 days since symptom onset ($n = 154$) was 16% (95% CI: 10–22%); at 7–13 days ($n = 103$), it was 48% (95% CI: 38–58%); and at ≥14 ($n = 95$) days, it was 95% (95% CI: 88–98%). Sensitivity of BTNX kit 2 at the same time points was 13% (95% CI: 8–19%), 50% (95% CI: 40–60%), and 91% (95% CI: 83–96%), respectively.

We then compared assay performance to that of the Abbott SARS-CoV-2 IgG assay, which holds and Emergency Use Authorization (EUA) from the FDA and for which optical density (OD) values and interpretations for 268 of these specimens. For a number of the patients represented by these samples, >1 sample result was available from the same date of collection. When this occurred, the mean OD value was determined and assigned to all samples collected that day. We reviewed the sample-specific OD and mean OD for 157 specimens for which both values were available and found that taking the mean did not alter the interpretation in any case; therefore, we opted to use the mean data for comparison with LFIAs. Overall agreement with the Abbott assay was 95% [Cohen's Kappa, 0.90 (95% CI: 0.85–0.96)] for BTNX kit 1 and 92% [Cohen's Kappa, 0.84 (95% CI: 0.77–0.90)] for BTNX kit 2.

3.2. Sensitivity at ≥14 days since symptom onset

Based on our observation that BTNX kit performance was substantially better for specimens collected ≥14 days after symptom onset and to focus on a sample set in which most patients would be expected to have seroconverted, sensitivity was subsequently addressed for the remaining kits only on specimens collected ≥14 days after symptom onset ($n = 95$, only 50 of these were tested using the SD assay). This amounted to 95% (95% CI: 88–98%) and 92% (95% CI: 81–98%) sensitivity for ACON and SD, respectively. LFIA results are summarized in Table 2 and listed in full in Supplementary Table S1.

Abbott results were available for 83 of the 95 specimens collected ≥14 days after symptom onset (43 of the 50 tested by SD), and agreement was as follows: BTNX kit 1, 99% (95% CI: 93–100%); BTNX kit 2, 94% (95% CI: 86–98%); ACON, 99% (95% CI: 93–100%); and SD, 100% (95% CI: 92–100%).

3.3. Specificity

As all samples in the Seattle cohort were from laboratory or clinically confirmed COVID-19 cases, a different set of specimens was used to assess specificity ($n = 105$), including 74 collected prior to recognized circulation of SARS-CoV-2 in the United States and 31 "cross-reactivity challenge specimens" from individuals with a history of seasonal coronavirus infection or other potentially cross-reactive antibodies (Table 1). Two false-positive IgG results were observed with BTNX kit 1, amounting to 98% (95% CI: 93–100%) specificity. Of note, 1 additional specimen generated a pink line (Supplementary Fig. S1), where a purple-colored line is the expected result. This was recorded as invalid rather than a positive result since it was not consistent with the operating parameters

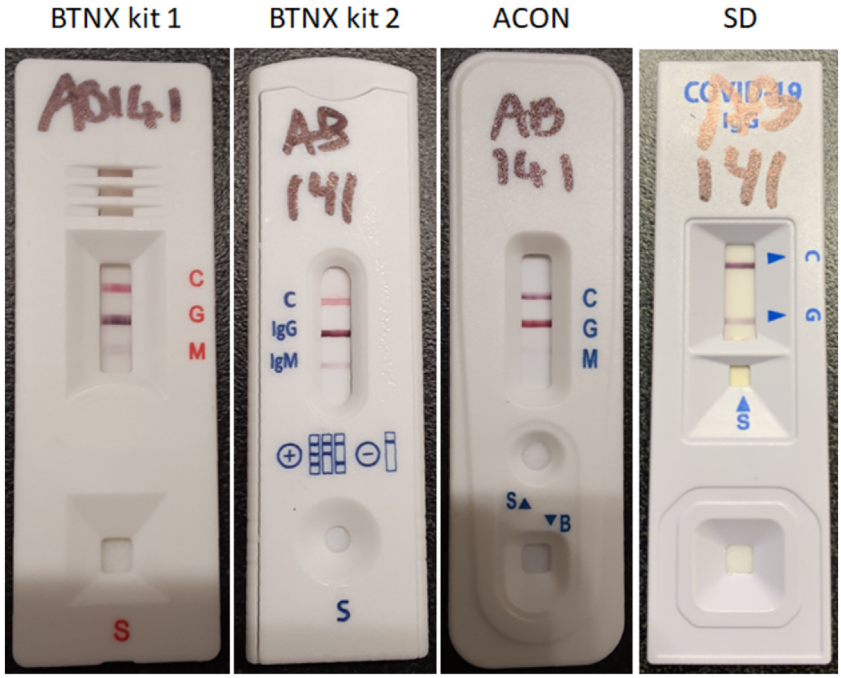

Fig. 1. A plasma sample from an RT-PCR–confirmed COVID-19 case collected 14 days after symptom onset and tested on (left to right) Rapid Response™ COVID-19 Test Cassette (BTNX Inc.) Kit 1, Rapid Response™ COVID-19 Test Cassette (BTNX Inc.) Kit 2, SARS-COV-2 IgG/IgM Rapid Test (ACON Laboratories), and Standard Q COVID-19 IgM/IgG Duo (SD BIOSENSOR).

of the assay. None of the 31 "cross-reactivity challenge specimens" generated a positive IgG signal in this assay. The ACON assay also generated 2 false-positive results, one of which was from a patient with a recent history of coronavirus HKU1 infection and the other was from a patient whose serum was reactive for HIV-1, HAV, HBV, and HCV antibodies. This assay therefore also achieved 98% (95% CI: 93–100%) specificity. False-positive results are summarized in Supplementary Table S2. BTNX kit 2 and the SD assay demonstrated 100% (95% CI: 97–100%) specificity.

4. Discussion

As many manufacturers apply for EUA for COVID-19 serology assays from the FDA, it is becoming apparent that assay performance characteristics are variable (Tang et al., 2020, Theel et al., 2020a). At the time of writing, 29 EUAs had been issued for serology tests; of these, 8 are LFIAs (FDA, 2020). Furthermore, although a number of LFIAs have been evaluated in the literature, some have been used in the context of seroprevalence studies without available peer-reviewed data on their performance. Clinical evaluations of serologic assays for SARS-CoV-2 have been primarily focused on automated assays. Here we evaluated 4 LFIAs for their capacity to detect anti–SARS-CoV-2 IgG in retrospective serum, plasma, and whole blood specimens, focusing on sensitivity at ≥14 days after symptom onset in an inpatient cohort and on specificity.

The sensitivity of the LFIAs was evaluated against the Abbott SARS-CoV-2 IgG EUA assay, for which several peer-reviewed studies have reported acceptable performance (Bryan et al., 2020, Tang et al., 2020, Theel et al., 2020b). Although 8 Abbott-positive specimens were negative on "BTNX kit 1," all but 1 were collected <14 days after symptom onset. Further, 4 of them were collected from a single patient between 1 and 2 days post symptom onset; another specimen collected from this same patient 2 days after symptom onset generated a positive result. Similarly, for the remaining 4 false-negative specimens (3 patients), an additional specimen drawn from the same patients on the same day tested positive. Although it is surprising that an antibody response should be seen at all as early as 1 day into the disease course, it should be noted that this was a predominantly hospitalized and older cohort (Bryan et al., 2020), which may account for potentially incomplete clinical histories in some cases. Also, it has been documented that the infection may be asymptomatic for 1–2 weeks, so an immune response may be well under way by the time of symptom onset. Some specimens from patients who were PCR positive were negative by all assays, suggesting that they had not yet generated detectable levels of antibodies to the viral antigens in the kits. It may take up to 21 days or

Table 2
Summarized performance characteristics of 4 SARS-CoV-2 IgG LFIAs.

Assay	Sensitivity≥14 d from onset[a] (95% CI; BTNX & ACON, $n = 95$; SD, $n = 50$)	Agreement with Abbott SARS-CoV-2 IgG assay (95% CI; BTNX & ACON, $n = 81$; SD, $n = 43$)	Specificity ≥14 d from onset (95% CI; $n = 105$))
Rapid Response™ COVID-19 Test Cassette (BTNX Inc.) Kit 1	95% (88–98%)	99% (93–100%)	98% (93–100%)
Rapid Response™ COVID-19 Test Cassette (BTNX Inc.) Kit 2	91% (83–96%)	94% (86–98%)	100% (97–100%)
SARS-COV-2 IgG/IgM Rapid Test (ACON Laboratories)	95% (88–98%)	99% (93–100%)	98% (93–100%)
Standard Q COVID-19 IgM/IgG Duo (SD BIOSENSOR)	92% (81–98%)	100% (92–100%)	100% (97–100%)

[a] Where a "true positive" is a specimen collected ≥14 days after symptom onset from an RT-PCR–confirmed COVID-19 case.

more for some patients to develop a detectable antibody response (Yongchen et al., 2020).

In some cases, the LFIA tests detected a positive result sooner in a serial sampling series than the Abbott test did. Though these represent clinically positive results, against the Abbott assay, they would be "false positives." Of the samples generating "false-positive" results with BTNX kit 1, 3 were collected from a single patient 1 and 2 days after onset of symptoms and with a PCR Ct of 29 (Panther Fusion® SARS-CoV-2 Assay); this patient went on to seroconvert on the Abbott assay 10 days later. Another of the "false-positive" specimens, collected 10 days after onset of symptoms, was associated with an Abbott OD value of 0.96 (manufacturer cutoff is 1.4); however, a specimen collected the following day from this patient was positive on the Abbott assay (OD, 2.33). A recent study has suggested that it may be beneficial to report OD ratios of 0.8–1.5 on this assay as inconclusive with a recommendation for repeat testing (Bryan et al., 2020). The remaining "false-positive" specimen was collected on the day of symptom onset, and a specimen collected 4 days later was positive on the Abbott assay. These early "false-positive" results may be the result of reactivity with low-avidity IgG, which is not detected by Abbott.

Our approach to efficiently evaluate specificity was to test a set of prepandemic stored samples and then target a set of samples that contain potentially cross-reactive substances based on seasonal CoV or common interfering substances for serologic assays. The resulting specificity data from our sample set are promising, though somewhat limited in number. In particular, for 3 of the 4 assays tested, we did not observe any false-positive IgG results from specimens from patients with a known history of seasonal coronavirus infection; these antibodies have been detected in a high proportion of individuals aged over 50 years (Gorse et al., 2010), and cross-reactivity has been reported with other assays (Demey et al., 2020). One specimen from a patient with a recent history of coronavirus HKU1 infection tested positive on the ACON assay; however, 12 additional specimens from individuals with a history of HKU1 infection did not cross-react in this assay. We did observe false–IgM positive results with all assays where this was tested, but given the questionable clinical significance of IgM detection (Farnsworth and Anderson, 2020; Landry, 2016), the propensity for both antibodies to become detectable within a similar time frame, and the variability over the serial samples included in our data set, we opted to evaluate the performance of IgG detection in these assays only. False positivity due to autoantibodies has been reported for some SARS-CoV-2 serology assays (Theel et al., 2020a); in our study, samples positive for rheumatoid factor generated positive IgM results on both assays, but IgG remained negative.

One potential use for these assays might be to confirm antibody production in patients with resolved symptoms independent of disease detection by a SARS-CoV-2 PCR assay or not. The results of this study of sera from a primarily hospitalized population show that the sensitivity of IgG detection at 14 days or more post symptom onset was 95% in 2 cases (BTNX kit 1 and ACON). When compared directly with Abbott results, sensitivity increased to 99% for both of these assays; similarly, BTNX kit 2 and SD sensitivity was 94% and 100%, respectively. These LFIA tests show good performance for a 15-min test that is very easy to perform; however, BTNX kit 1 and ACON were the only assays to generate false-positive IgG results, supporting the theory that assays providing higher sensitivity may come with a compromise in specificity. Nonetheless, 3 of the kits tested did not show any false positives in a sample set that included a diverse representation of potential cross-reactivity, and specificity for any assay did not fall below 98%. Additional studies will be needed to determine if this measure of sensitivity holds true for more mild disease and whether sensitivity may increase (or decrease) past 14 days. Other studies have shown improved sensitivity after 17 days from symptom onset (Bryan et al., 2020). Although no serologic test is perfect, these results are encouraging that rapid and simple tests can provide an adequate level of sensitivity and specificity. Importantly, several other LFIAs tested by our group showed poor sensitivity and/or specificity (data not shown), indicating the importance of rigorous validation prior to implementation in any setting. It is likely that all tests will have a measurable false-positivity rate, but our results suggest that a substantial number of samples from patients with a history of seasonal CoV or even other viral infections will be required to better define the rate of false positivity. Even if some tests maintain a high (>99%) specificity, the individual patient may be best served by an orthogonal approach to testing, whereby 2 methods that target different antigens (whether 2 LFIAs or an LFIA followed by an enzyme immunoassay or chemiluminescence assay) are used to increase positive predictive value for predicting true exposure to SARS-CoV-2. However, manufacturers are only obliged to disclose the nature of their assay target(s) upon EUA issuance, so the role of the many pending assays in this approach is currently unclear. Of the assays tested in this study, only the target for the SD assay (nucleocapsid) was known. The sensitivity of the LFIAs characterized herein suggests that such an approach would have only a minor impact on clinical sensitivity overall by using 2 assays. This concept is supported by the fact that, of the false negatives, 4 samples were not detected by any of the assays, demonstrating that most positive samples were detected by all assays.

One strength of the study is that, among the specificity sample set, we included 27 samples from patients who had recently experienced seasonal CoV. Although additional studies are required to focus on other patient groups and sample types, the sensitivity sample set in this study was already larger than the data listed for 10 of 13 EUA-approved assays, and the specificity sample set was similar to 4 of 13 EUA-approved assays, current as of June 8, 2020 (FDA, 2020). The primary weaknesses include the positive samples from a primarily hospitalized cohort, the retrospective nature of samples (including freeze/thaw), and the lack of fingerstick blood samples, for which many of these assays are designed. In a pandemic, reliable information is essential to public health responses and individual health care decisions. These results suggest that, with further investigation/data/study/evaluation, LFIAs could potentially be used to meet that need, particularly in low-resource settings or those with limited access to health care. Importantly, it must be noted that detection of IgG does not mean that neutralizing antibodies are present. There are not yet sufficient data in the literature to determine whether detection of IgG may (or may not) correlate with immunity or protection of future exposure to SARS-CoV-2.

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Appendix A. Supplementary data

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