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Article

The Coronavirus Disease 2019 Spatial Care Path: Home, Community, and Emergency Diagnostic Portals

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Abstract: ***Goals:*** To use visual logistics for interpreting COVID-19 molecular and rapid antigen test (RAgT) performance, determine prevalence boundaries where risk exceeds expectations, and evaluate benefits of recursive testing along home, community, and emergency spatial care paths.

Methods: Mathematica/open access software helped graph relationships, compare performance patterns, and perform recursive computations.

Results: Tiered sensitivity/specificity comprise: T1) 90%/95%; T2) 95%/97.5%; and T3) 100%/≥99%, respectively. In emergency medicine, median RAgT performance peaks at 13.2% prevalence, then falls below T1, generating risky prevalence boundaries. RAgTs in pediatric ERs/EDs parallel this pattern with asymptomatic worse than symptomatic performance. In communities, RAgTs display large uncertainty with median prevalence boundary of 14.8% for 1/20 missed diagnoses, and at prevalence >33.3-36.9% risk 10% false omissions for symptomatic subjects. Recursive testing improves home RAgT performance. Home molecular tests elevate performance above T1, but lack adequate validation.

Conclusions: Widespread RAgT availability encourages self-testing. Asymptomatic RAgT and PCR-based saliva testing present the highest chance of missed diagnoses. Home testing twice, once just before mingling, and molecular-based self-testing help avoid false omissions. Community and ER/ED RAgTs can identify contagiousness in low prevalence (<22%). Real-world trials of performance, cost-effectiveness, and public health impact could identify home molecular diagnostics as the optimal diagnostic portal.

Keywords: Emergency Use Authorization (EUA), endemic; false omission rate (R_{FO}), home testing; point-of-care testing (POCT), positive predictive value geometric mean-squared (PV GM^2), prevalence boundary; recursive protocol; tier; and visual logistics

1. Introduction

The main goal is to facilitate informed selection of Coronavirus disease 19 (COVID-19) diagnostics when faced with the multi-dimensional challenges of fluctuating endemic disease, increasing prevalence, and variably accessible testing options with complex performance patterns. Another goal is to minimize false omissions, that is, missed diagnoses that unknowingly elevate risk, create local recurrences, and adversely interrupt personal life, community activities, and work productivity.

Emergence of highly contagious Omicron, BA.2, and other variants; proliferation of COVID-19 commercial diagnostics authorized with limited clinical validation; distribution of one billion rapid antigen tests (RAgTs) **[1,2]**; the new White House "test (in pharmacies) and treat" program **[3]**; and relaxed preventative measures, such as safe spacing and masking, call for analysis of COVID-19 test performance along spatial care paths where people choose their own testing options, that is, "diagnostic portals." A spatial care path is the most efficient route taken by individuals and patients when receiving care in

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the healthcare small-world network of home, community, and emergency medicine settings **[4,5,6]**.

Prevalence, the percentage of a population affected with COVID-19 at a given time, can vary unpredictably in different locales, because of severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) variants, super spreaders, asymptomatic carriers, migrating hotspots, episodic re-openings, incomplete testing, delayed reporting, and other factors, such as erratic sampling and marginal reliability of rushed-to-market COVID-19 tests. Clinical performance depends on whether there are symptoms or not, the patient's viral load, and the timing, location, and quality of the environment, specimen collection (e.g., saliva, and anterior nasal, mid-turbinate, or nasopharyngeal swab), and testing method.

Nonetheless, a surge of clinical evaluations published during the three years paints a fairly clear picture of what to expect. Expectations are at the heart of public acceptance and empowerment. Americans can choose from an array of self-testing options, use COVID-19 tests mailed to them free by the government, and engage different diagnostic portals. Future public health practices will hinge on fundamental understanding of how point-of-need testing meets or defeats attempts to keep families safe, temper contagiousness of new variants, safeguard schools and workplaces, and transition smoothy forward.

2. Methods and Materials

2.1. Emergency Use Authorizations

Assays should be well balanced, that is, achieve both high sensitivity and high specificity. Adverse patterns identify tests that do not perform well, but have received Food and Drug Administration (FDA) Emergency Use Authorization (EUA). Positive percent agreement (PPA) and negative percent agreement (NPA) data were extracted from FDA lists of EUAs **[7]** for home RAgTs and home LAMP (loop-mediated isothermal amplification) tests collated up to the beginning of January 2022. Supplemental Digital Content **Table S1** lists EUA PPA and NPA claims. Donato et al. **[8]** provided the only independent clinical evaluation of sensitivity and specificity for a LAMP molecular home self-test found during searches.

2.2. Clinical Evaluations

A total of 82 clinical studies were tabulated. **Table 1** summarizes performance metrics for the primary study groups (left column) and supporting tabulations (right column). Papers generated by PubMed, other searches, and bibliographies of systematic reviews and meta-analyses comprised a) 34 clinical evaluations **[9-42]** of the use of RAgTs in communities (see **Table S2**); b) 30 clinical evaluations **[43-72]** of RAgTs applied in emergency medicine (emergency rooms and emergency departments), including 9 with results for pediatric patients **[58,65-72]** (**Table S3**); and c) 18 clinical evaluations **[73-90]** that reported results for PCR-based testing of saliva in community groups of strictly asymptomatic subjects (**Table S4**). No human subjects were involved in this research.

2.3. Sensitivity and Specificity Metrics

Sensitivity and specificity metrics from community (**Table S2**) and emergency medicine evaluations (**Table S3**) were subdivided into symptomatic and asymptomatic groups (see **Table 1**). Merging raw data was not practical in light of heterogeneity, missing elements, unbalanced designs, and inconsistent reporting in the clinical studies. Some studies were reported prior to peer review by medRxiv and preliminarily in various journals. In essence, each study generated results reflected in sensitivity and specificity median performance for each clinical setting.

2.4. Bayesian Mathematics and Performance Tiers

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Please refer to open access papers by Kost **[91-93]** in the *Archives of Pathology & Laboratory Medicine* for descriptions of mathematical methods, visual logistics, computational design, and open access software. **Table S5** lists Bayesian equations used to generate the graphics displayed in this paper. **Table 2** presents the mathematical design criteria for the three tiers, which are intended to systematically harmonize Bayesian post hoc performance criteria. The design criteria include simultaneously the performance level, sensitivity, specificity, target prevalence boundary, and false omission rate, R_{FO}, which reflects risk of missed diagnoses.

2.5. Prevalence Boundaries

A prevalence boundary is defined as the prevalence at which the rate of false omissions, R_{FO}, exceeds a specified risk tolerance, such as 5% (1 in 20 diagnoses missed) or 10% (1 in 10 missed). Please note that RFO = 1- NPV [**Eq. 20**]. Prevalence boundary is calculated using **Eq. 26** in **Table S5** and is apparent where the RFO curve intersects the horizontal line demarcating risk tolerance.

The sensitivity needed to achieve a desired prevalence boundary given the specificity, RFO, and prevailing prevalence can be calculated using **Eqs. 27a** and **27b** (newly derived). For example, if the prevalence is 50.6% and you do not want to miss more than 1 in 20 diagnoses of COVID-19 (RFO = 5%), then given a specificity of 97.5%, **Eq. 26a** predicts you will need a test with at least 95% sensitivity, that is, Tier 2 performance (see **Table 2**).

2.6. Pattern Recognition

Visual logistics reveal performance patterns and diagnostic pitfalls over the entire range of prevalence. The approach to pattern recognition presented here, called "predictive value geometric mean-squared (PV GM2)," is strictly visual **[91-93]**. The PV GM2 curve represents a distinguishing "fingerprint" of performance, and thus far in this research, no two fingerprints have coincided. PV GM2 curves visualize how low (≤20%), moderate (20-70%), and high (≥70%) prevalence affect diagnostic performance in a single continuous graphic.

Point values of PV GM2 at fixed prevalence should not be compared because of potential duplicity of the values at different levels of prevalence. Unrealistic comparisons (e.g., test sensitivity 10% and specificity 100%) should be avoided as they produce meaningless curves. The point of PV GM2 visualization is to differentiate performance patterns for tests achieving at least Tier 1 sensitivity and specificity criteria (see **Table 2**), or if below Tier 1 ("subtier"), then to understand why and where performance fails and crosses the Tier 1 threshold.

2.7. Recursion

The recursive formulas for positive predictive value (PPV) [**Eq. 22a**] and negative predictive value (NPV) [**Eq. 22b**] allow calculations of predictive value geometric mean-squared (PV GM2) and RFO performance for repeat testing. When testing only twice with the same assay, single equations can be derived to graph recursive PV GM2 and RFO versus prevalence from 0 to 100% and to conveniently determine graphically the recursive prevalence boundaries at user-defined risk levels of 5% and 10% for missed diagnoses.

3. Results

Figure 1 illustrates patterns of low, high, and median performance documented by evaluations of RAgTs conducted in communities of several countries and states in the United States. RAgTs display large uncertainty with a median prevalence boundary of 14.8% for one in twenty missed diagnoses (RFO 5%). Median sensitivity of 69.85% (range 30.6-97.6%) explains the rapid fall off of PV GM2 due to increasing false negatives as prevalence increases, while median specificity achieves Tier 3. **Figure 2** compares performance

for asymptomatic and symptomatic subjects, the latter showing peak performance at 9% prevalence and a prevalence boundary of 21.7% (at 5% RFO). Median sensitivity for symptomatic subjects was 81.0%. For automated instrument antigen tests, it is 73% (see **Tables 1** and **S2**).

Figure 3 presents patterns of RAgT performance for evaluations conducted in emergency medicine settings [emergency rooms (ERs) and emergency departments (EDs)] (see **Tables 1** and **S3**). Median sensitivity of 68.79% and specificity of 99.5% generate peak performance at 13.2% prevalence. The prevalence boundary for RFO of 5% was 14.4%, almost identical to that seen in **Figure 1**. **Figure 4** compares performance for symptomatic and asymptomatic general populations and children seen in ERs and EDs, with the former marginally better than the latter. The right column of the inset table lists prevalence at peak performance.

There were no evaluations conducted directly in homes for EUA tests with real-world data generated by laypersons who perform the self-testing. Therefore, **Figures 5** and **6** illustrate performance based on manufacturer claims in information for users (IFUs) documents. **Figure 5** also illustrates the theoretical improvement in performance achievable by repeat testing, typically within three days, as described in IFUs. Manufacturers made no claims regarding recursive testing. As can be seen in **Figure 5**, repeat testing pushes performance up to Tier 2. **Figure 6** shows individual performance for three home molecular (LAMP) self-tests, as claimed by manufacturers. One independently conducted clinical evaluation by Donato et al. **[8]** was found. Real-world evidence revealed Tier 1 performance (curve "**CCE**") versus the claim of Tier 2.

Figure 7 summarizes the foregoing results from a risk perspective by plotting RFO versus prevalence with the threshold of a missed diagnosis at 1 in 10 (RFO 10%). Recall, RFO = 1 – NPV. Interestingly, the curves group into clusters for asymptomatic (purple) and symptomatic (red) subjects, while the Donato et al. **[8]** evaluation of home molecular testing (curve "**HMDx**") demonstrated a Tier 1 prevalence boundary of 56.9%. Even at a relatively high 10% risk of missed diagnoses, prevalence boundaries for asymptomatic subjects are low (17.5-23.2%), including that for self-collected saliva specimens obtained in community sites from asymptomatic subjects with PCR-based testing performed later, typically within 24-72 hours in reference laboratories (see **Tables 1** and **S4**).

4. Discussion

4.1. Missed Diagnoses

SARS-CoV-2 prevalence in South African blood donors skyrocketed to 71% even before the Omicron-driven wave arrived **[94]**. This variant peaked in the United States, only to be followed by the BA.2 variant. Omicron is sweeping Southeast Asia. For example, Thailand has reported over 50,000 new cases per day, and Vietnam, 120,000. These outbreaks bump prevalence to levels requiring Tier 2 performance to avoid excessive false negatives.

Mathematical transformation of pre-test to post-test probability of COVID-19 **[92,93]** allows computation of R_{FO}, the false omission rate [**Eq. 20, Table S5**], and determination of the prevalence boundary (PB) [**Eq. 26**]. Shallow PBs limit the clinical usefulness of RAgTs, because of missed diagnoses. If one knows test specificity, sets the R_{FO} threshold (e.g., 5% or 10%), and establishes the PB appropriate for local prevalence, then **Eq. 27a** can be used to calculate the minimum test sensitivity required. Frequent false omissions result in stealth spread of disease.

4.2. Transparency

Unfortunately, there is no way of singling out infectious patients who have false negative test results without repeat testing or additional evaluation. Using quantitative high sensitivity synchrotron X-ray fluorescence imaging, Koller et al. **[95]** showed qualitative visual read-outs miss immobilized antigen-antibody-labeled conjugate complexes of

SARS-CoV-2 signals on lateral flow detection devices. On the other hand, one report showed that ~92% of patients infected with SARS-CoV-2, but missed by antigen testing, contained no viable virus **[96]**. Even the performance of a so-called "ultra-sensitive" antigen test, after exclusion of samples with PCR cycle threshold >35, hovered around Tier 2 for PPA and below it for NPA **[97]**.

There is no explanation for why the PPA and NPA of assays documented in FDA EUAs have not progressively improved. However, the FDA has not required improvement. Liberal FDA approval seems to have diminished competition. One wonders what will become of subtier rapid antigen tests in a competitive market following the end of the "EUA era." People purchasing test kits or ordering them free from COVIDtests.gov should receive disclosure of specificity (to rule-in COVID-19) and sensitivity (to rule it out) documented in clinical evaluations, and may need interactive apps to access prevailing prevalence.

The "…successful implementation of rapid antigen testing protocols must closely consider technical, pre-analytical, analytical and clinical assay performance and interpret and verify test results depending on the pretest-probability of SARS-CoV-2 infection" **[98]**. With that advice, the International Federation of Clinical Chemistry (IFCC) COVID-19 Task Force underscored the need for careful analysis of how prevalence impacts antigen test results in different clinical settings. *Consumer Reports* and other public advocacy groups may eventually compare and rank commercially available point-of-care antigen and saliva tests for the public.

4.3. Public Health at Points of Need

The death toll of the pandemic, including excess deaths from neglect, now is estimated to be 18.2 million **[99]**. The COVID-19 crisis has confirmed and expanded worldwide what we learned during Ebola virus disease outbreaks in West Africa. There is unequivocal need for point-of-care testing **[4-6,100-105]**. People in the United States now have access to COVID-19 RAgTs and molecular diagnostics online, by mail, and in neighborhood stores. With ubiquitous access comes responsibility — on the part of academics, public health educational institutions, professional societies, governments, industry, and global organizations to promote high quality testing.

The CORONADx Project in the European Union **[106]** will produce affordable "PATHAG," ultra-rapid COVID-19 antigen test strips for first-line screening; "PATHPOD," portable LAMP detection for mobile clinics and community health centers; and "PATHLOCK," kit detection using CRISPR-Cas13 technology. This initiative will add to the massive expansion of point-of-care strategies and promote higher quality molecular self-testing **[1,2,104,105]**. Ready access to rapid testing along spatial care paths from home to hospital raises public expectations for controlling transmission, combatting COVID-19, and forestalling future pandemics.

Children, teens, and young adults, even if vaccinated, may quietly spread disease, especially now that the more infectious variants are elevating community prevalence. Complicating matters, hospitals in some limited resource countries administer fake vaccinations (injecting water) for monitory gain **[107]**. Nonetheless, the CDC views vaccination rates as indicators of pandemic status worldwide **[108]**, a reasonable position confirmed by Omicron surges in Hong Kong and China where vaccination rates are low and vaccines less effective.

Vaccination attenuates the severity of disease but does not necessarily eliminate SARS-CoV-2 infection. Thus, individuals and their medical providers face the daunting challenge of guessing local and regional prevalence. Public health officials can help by periodically documenting prevalence and by encouraging self-testing in communities and directly within homes. Pattern recognition by means of PV GM2 and R_{FO} curves allows healthcare providers to quickly tailor the quality of testing to needs.

4.4. Focus and Standardization

RAgTs now are ubiquitous worldwide. They enable people to test frequently and inexpensively wherever they wish. Progressive "normalization" increases demand for convenient, fast, and inexpensive test results for decision making in various settings comprising public gatherings, communities, homes, schools, workplaces, factories, convalescent care, prisons, university campuses, sports events, travel, airports, rural regions, and limited-resource settings abroad.

Figures 2, **4**, and **7** show RAgTs detect SARS-CoV-2 infections in symptomatic subjects more effectively than asymptomatic, for whom community screening using PCR-based saliva testing offers no significant diagnostic advantage (see **Figure 7**). Asymptomatic RAgT and PCR-based saliva testing present the highest risk of missing diagnoses when highly contagious new variants increase prevalence.

Repeat rapid antigen home testing with the second test just before mingling is theoretically sound (see **Figure 5**) and is encouraged in commercial products containing two tests for screening, but has not been validated. Home molecular testing one time shows promise (see "**HMDx"** in **Figure 7**). Controlled studies using some of the nationally distributed free tests could determine the efficacy of home self-testing, and should encompass both RAgT and LAMP assays.

Weaknesses in COVID-19 rapid antigen test performance, even for products introduced more than one year after the FDA first started granting COVID-19 EUAs, call for standardization, or at least a process for attaining consistency and improving sensitivity. The contrast in performance based on FDA EUA PPA and NPA metrics versus real-world sensitivity and specificity from clinical investigations (**Figures 1-4**) demands multicenter studies with diverse populations, well defined clinical settings, different age groups, and large sample sizes.

5. Conclusions

Widespread availability of RAgTs encourages self-testing. People receiving millions of RAgTs for self-testing need guidance. If public health educational institutions and practitioners adapt, learn, teach, and incorporate proven point-of-care strategies, they will better mitigate variant surges and the future outbreaks **[105,109-111]**. RAgTs facilitate transitioning risk avoidance to risk management, especially in limited-resource settings where people cannot afford extended lockdowns, expensive tests, and loss of employment. For those, we recommend mobile testing in vans and inexpensive sample collection kiosks at sites of need **[112]**.

Subtier tests should be improved or retired from FDA EUA status, because of poor performance, uncertainty, and false omissions that increase exponentially with increasing prevalence. Every step beyond a prevalence boundary magnifies chances of missing a diagnosis (see **Figure 7**). Tier 3, with its 100% sensitivity, could eliminate false omissions and prevalence boundaries. However, Tier 3 appears out of reach for current RAgTs. The FDA should tighten authorization criteria and shift the evaluation paradigm from template-based to clinical proof.

Tier 2 performance represents an attainable, practical, and sustainable standard of excellence, in view of the fact that several EUA manufacturers claim that performance threshold (see supplemental **Figure 1S**). The scheme in **Table 1** can be used to establish constraints on 95% confidence limits and reduce uncertainty. Supportive actions the FDA should take comprise a) tightening authorization thresholds and integrating prevalence boundaries, b) increasing sample sizes to generate robust confidence intervals, c) requiring comparison of symptomatic versus asymptomatic patients, d) validating environmental limits of reagents, e) publishing post-market follow-up of performance.

Testing at home and in the community make sense. With acute symptoms, community and ER/ED RAgTs can mitigate spread by helping to identify immediate contagiousness in low (<22%) to moderate (20-40%) prevalence. Real-world trials of repeat testing, diagnostic cost-effectiveness, and public health impact could identify home molecular diagnostics as an optimal diagnostic portal for self-testing and rapid decision making at

most levels of prevalence. Point-of-care testing has, and will continue to provide a valuable resource for crisis response.

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FIGURES

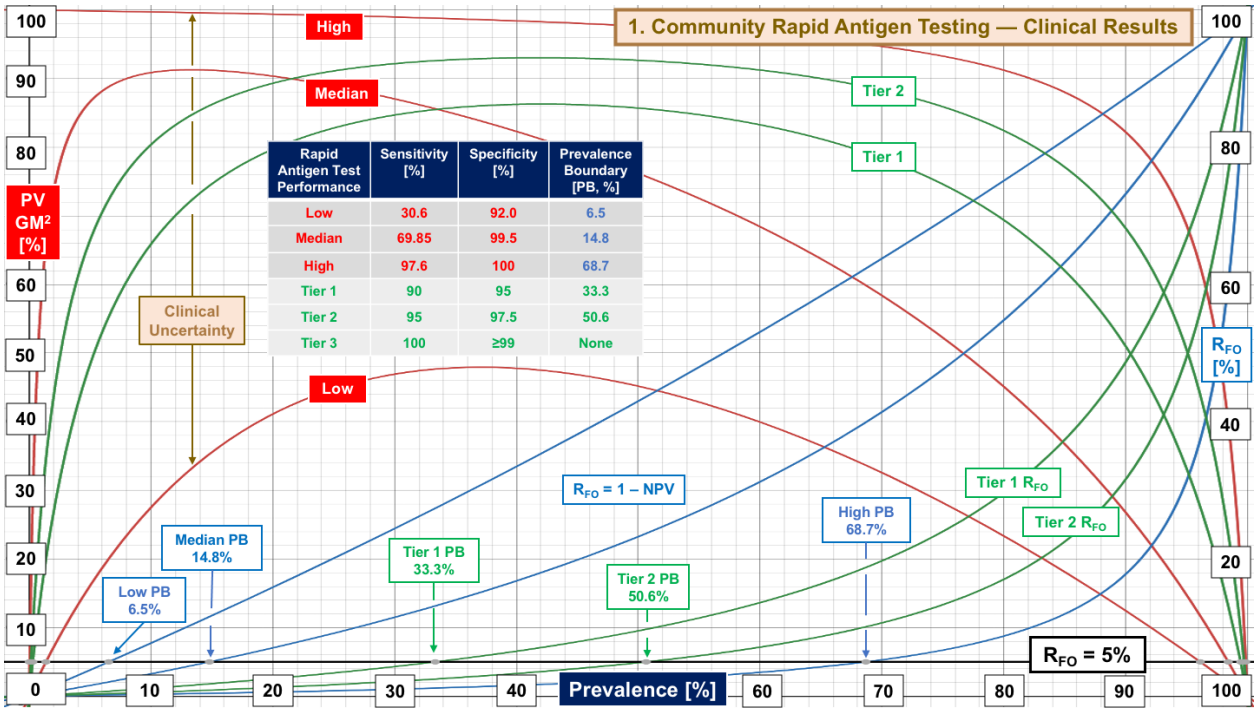

Figure 1. Performance of rapid antigen testing in community settings.

Predictive value geometric mean-squared curves reflect performance (left axis). R_{FO} is the false omission rate (right axis). Curves are plotted for low, median, and high sensitivity/specificity from clinical studies conducted in community settings. Tiers 1 and 2 are plotted in green. The black horizontal line is the risk level of 5%. Prevalence boundaries (PBs) are points at which the risk of a missed diagnosis exceeds 1 in 20.

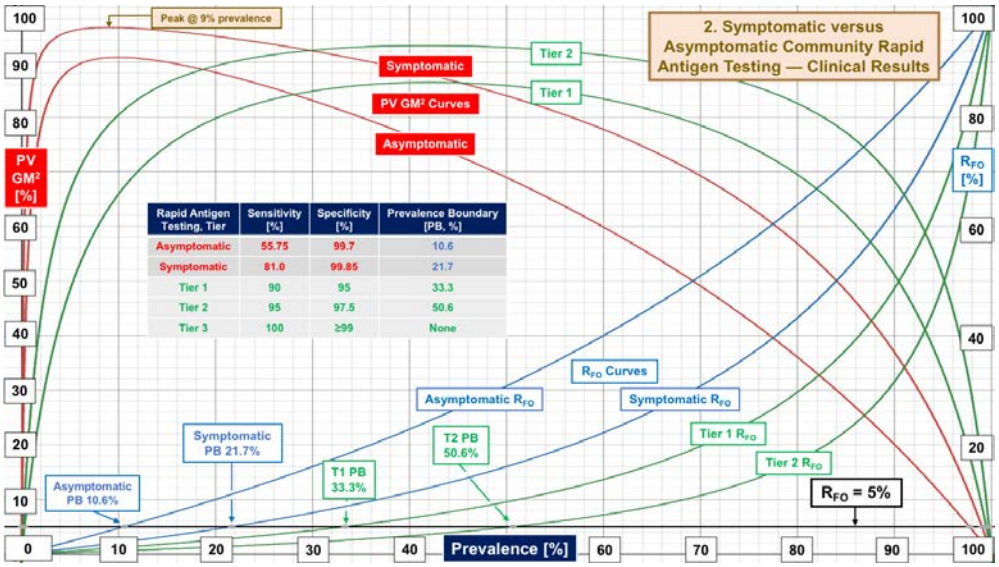

Figure 2. Comparison of symptomatic versus asymptomatic community rapid antigen testing performance based on evidence.

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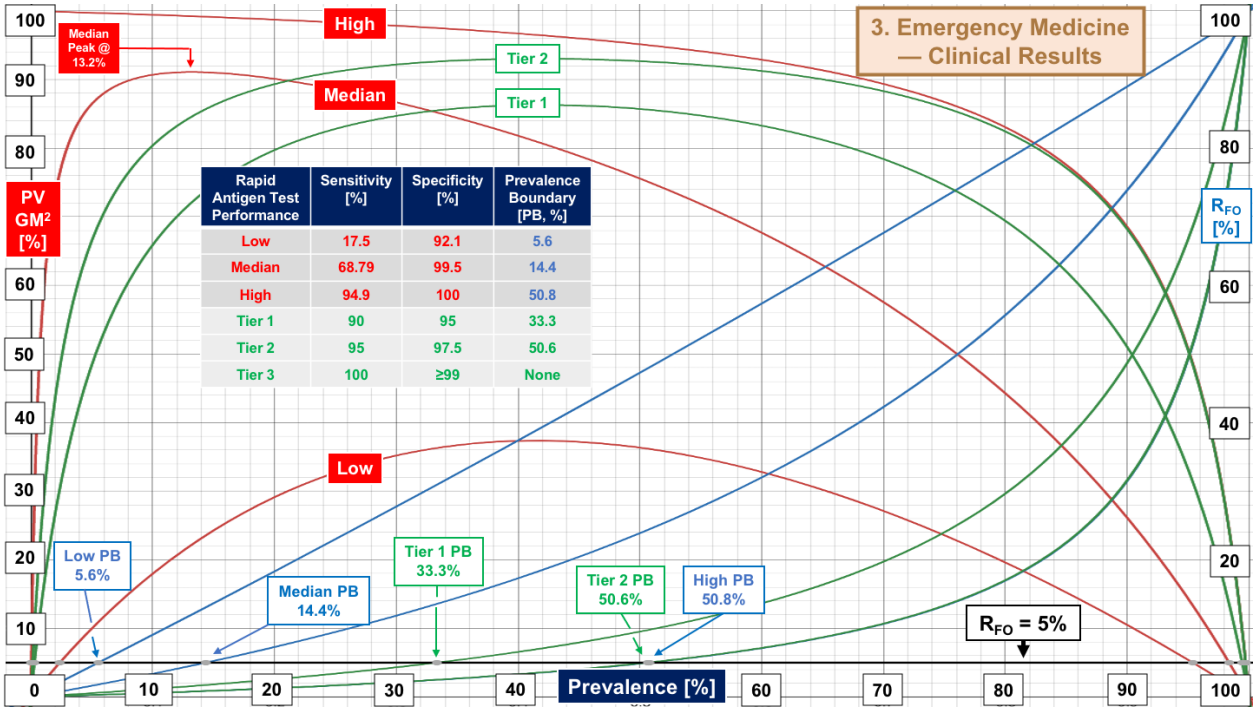

Figure 3. Real-world performance of rapid antigen testing in emergency medicine.

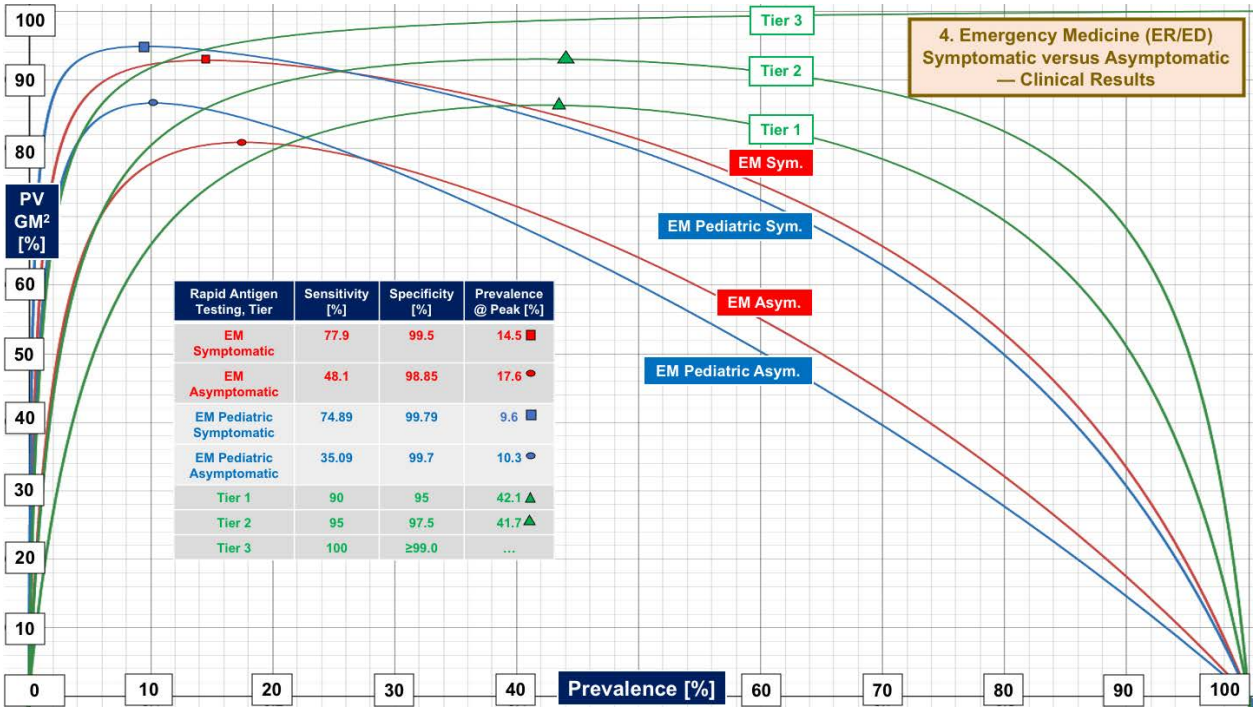

Figure 4. Comparison of symptomatic versus asymptomatic rapid antigen performance in emergency medicine.

Blue lines show performance for pediatric patients presenting to emergence rooms (ERs) and emergency departments (EDs). See the legend in the inset table for prevalence at points of peak performance.

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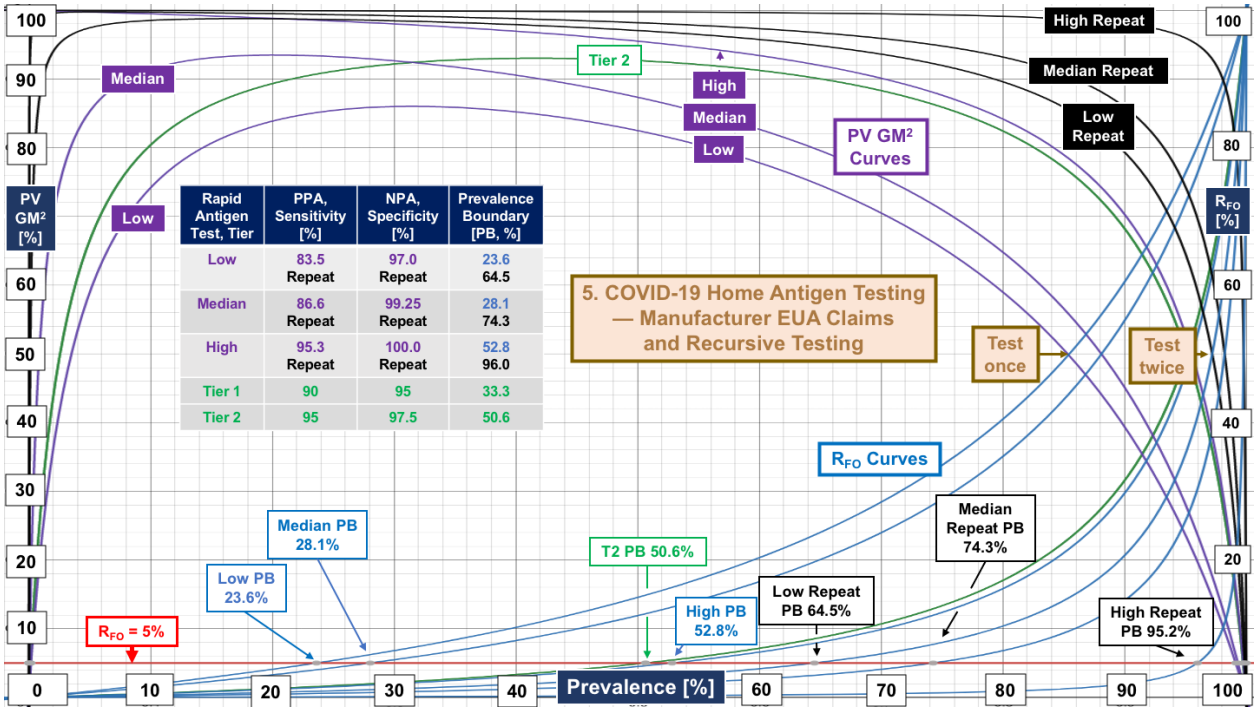

Figure 5. Performance of rapid antigen testing for home self-testing based on manufacturer claims in FDA EUA authorizations.

Theoretical analysis of manufacturer claims shows that repeat testing yields higher performance and prevalence boundaries. Median recursive performance achieves Tier 2. The median recursive prevalence boundary of 74.3% reflects a reasonable minimum for Omicron, BA.2, and other emerging variants.

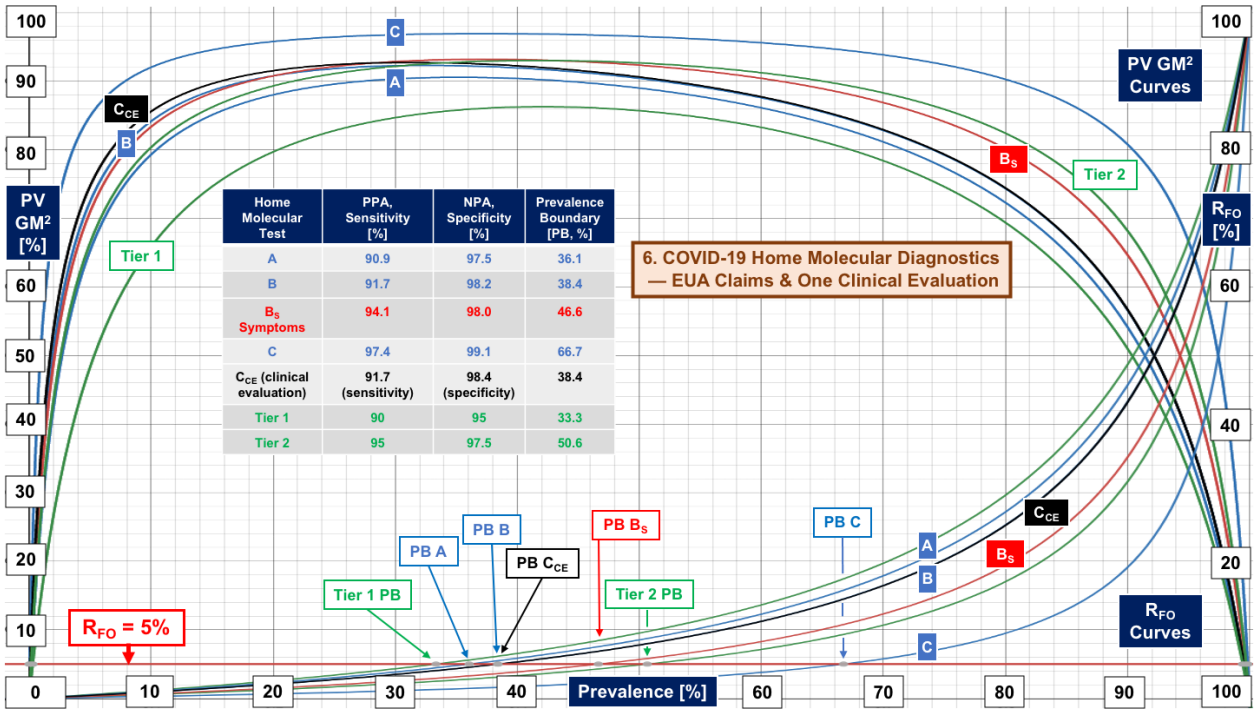

Figure 6. Performance of molecular diagnostics for home self-testing.

In the case of home molecular diagnostics, one independent clinical evaluation, shown by the "C_{CE}" curves, achieved Tier 1 performance.

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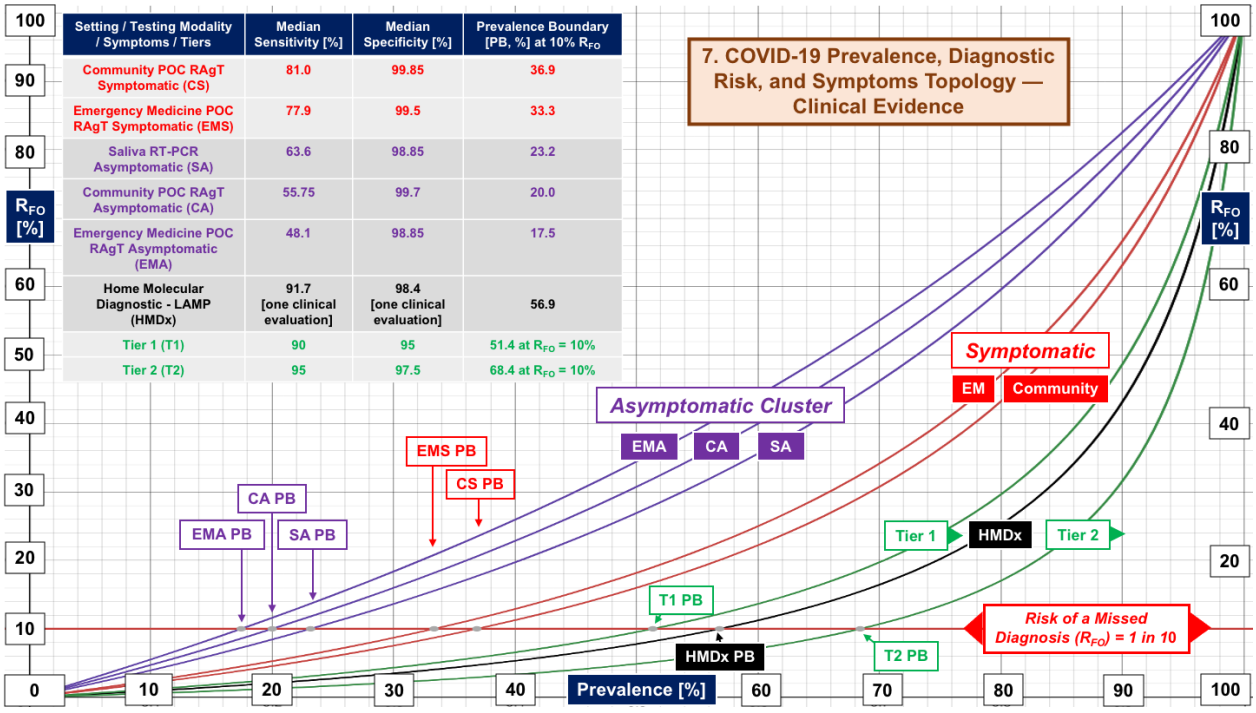

Figure 7. False omission rate topology for asymptomatic and symptomatic subjects.

The purple cluster shows performance for asymptomatic subjects in emergency medicine (EMA) and community (CA) settings, while the red cluster reflects results for symptomatic subjects. Saliva testing for asymptomatic subjects (SA, purple), with specimen collection at points of need and PCR analysis performed in laboratories, did not differ substantially from rapid antigen testing. "**HMDx**" represents one clinical evaluation of molecular self-testing, which achieved performance between Tier 1 and Tier 2. In this case the risk of a missed diagnosis (R_{FO}) is 10%, shown by the red horizontal line.

Tables

Table 1. Performance Metrics for Home, Community, and Emergency Medicine COVID-19 Testing.

CLINICAL SPACE	MEDIAN [N, RANGE]	MEDIAN [N, RANGE]	DATA SOURCE
Home Self-Tests			**Supplemental Table S1**
Rapid antigen tests	PPA 86.6 [12, 83.5-95.3]	NPA 99.25 [12, 97-100]	Manufacturer FDA EUA claim (not substantiated)
Isothermal (LAMP) molecular tests	PPA 91.7 [3, 90.9-97.4]	NPA 98.2 [3, 97.5-99.1]	Manufacturer FDA EUA claim (not substantiated)
Isothermal (LAMP) molecular test	Sensitivity 91.7 [1, CI NR]	Specificity 98.4 [1, CI NR]	One independent clinical evaluation, see Donato et al.[8]

Community RAgTs	Sensitivity	Specificity	Supplemental Table S2
Overall	69.85 [24, 30.6-97.6]	99.5 [24, 92-100]	Performance evaluations
Symptomatic	81.0 [19, 47.7-96.5]	99.85 [16, 85-100]	Symptomatic subjects
Asymptomatic	55.75 [20, 37-88]	99.70 [16, 97.8-100]	Asymptomatic subjects
Automated antigen tests-overall	62.3 [3, 43.3-100]	99.5 [3, 94.8-99.9]	Evaluations using automated laboratory instruments (small set)
-symptomatic	73 [3, 68.5-88.9]	100 [3,100]	Symptomatic subjects for above

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Emergency Medicine RAgTs	Sensitivity	Specificity	Supplemental Table S3
EM Overall	68.79 [20,17.5-94.9]	99.5 [20, 92.1-100]	ER and ED evaluations
Symptomatic	77.9 [15, 43.3-95.8]	99.5 [14, 88.2-100]	Symptomatic EM subjects
Asymptomatic	48.1 [11, 28.6-92.1]	98.85 [10, 92.3-100]	Asymptomatic EM subjects
Pediatric EM	71.3 [10, 42.9-94.1]	99.55 [10, 91.9-100]	Pediatric ER/ED patients only
Ped. Symptomatic	74.89 [6, 45.4-87.9]	99.79 [6, 98.5-100]	Symptomatic EM children
Ped. Asymptomatic	35.09 [2,27.27-42.9]	99.7 [2, 99.4-100]	Asymptomatic EM children

Saliva Testing	Sensitivity	Specificity	Supplemental Table S4
Asymptomatic, molecular diagnostics	63.6 [19, 16.8-95]	98.85 [14, 95-100]	Community evaluations with strictly asymptomatic subjects

Abbreviations: CI, 95% confidence interval; ED, emergency department; EM, emergency medicine; ER, emergency room; EUA, Emergency Use Authorization; FDA, Food and Drug Administration; LAMP, reverse transcription loop-mediated isothermal amplification; NR, not reported; PPA, positive percent agreement; NPA, negative percent agreement; Ped., pediatric; POC, point of care; and RAgTs, rapid antigen tests.

Table 2. Performance Tiers with Coordinated and Integrated False Omission Rates and Prevalence Boundaries Bracketing Community Immunity from 50% to 85%.

Tier	Performance Level	Sensitivity, %	Specificity, %	Target Prevalence Boundary [Actual] at R_{FO} of 5%	20%	10%
1	**Low**	90	95	33% (33.3)	50% (51.4)	70% (70.3)
2	Marginal	95	97.5	50% (50.6)	70% (68.4)	85% (83.0)
3	High	100	≥ 99	No Boundary	No Boundary	No Boundary

Abbreviation: R_{FO}, false omission rate.

Supplment

Table S1. COVID-19 Tests with FDA Emergency Use Authorization for Home Self-testing.

Category of Test, Notables	Tier (without repetition), Sample Size	Company, EUA Latest Date LOA [Earliest Date LOA], Product Name	Company PPA (%) Claim [CI, Δ]	Company NPA (%) Claim [CI, Δ]	Assay Method, Specimen Type, Age, Time Interval Protocol for Specimen Collection, and Notes
Part I. Antigen Tests	*Sub-Tier (8)*				
Lowest PPA of 83.5%	N = 350	Quidel Corp. 10/21/21 [3/31/21] Quickview At-Home OTC COVID-19 Test	**83.5** [74.9-89.6, Δ = 14.7]	**99.2** [97.2-99.8, Δ = 2.6]	Lateral flow, visual read, NCP Ag. AN. ≥14 years or adult-collected ≥2 years. OTC. Home testing, serial screening ≥24 & ≤36 hours between tests.
Smallest Δ uncertainty of 13.8% for the PPA 95% CI	N = 460	Abbott Diagnostics 1/7/22 [3/31/21] BinaxNow COVID-19 Antigen SelfTEST (OTC)	**84.6** [76.8-90.6, Δ =13.8]	**98.5** [96.6-99.5, Δ = 2.9]	SelfTEST: Lateral flow, visual read, NCP Ag. AN. ≥15 years or adult-collected ≥2 years. Self-swab and self-test 2 times ≥24, ≤48 hours apart. Home testing. PPA & NPA established from single test ≤7 days from symptom onset.
Largest sample size, smallest Δ uncertainty of 1% for the NPA 95% CI	N = 597	BD (Becton Dickinson) 11/23/21 [8/24/21] Veritor At-Home COVID-19 Test	**84.6** [70.3-92.8, Δ = 22.5]	**99.8** [99-100, Δ = 1]	Chromatographic, digital immunoassay, NCP Ag. Smartphone read using Scanwell Health App. Anterior nares. ≥14 years or adult-collected ≥2 years within 7 days. Home testing. With or without symptoms

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					when test twice ≥24 & ≤48 hours between tests. OTC.
	N = 165 (19 children added 9/21)	Orasure 1/27/22 [6/4/21] InteliSwab COVID-19 Rapid Test (OTC)	**85** [74-92, Δ = 21]	**98** [93-100, Δ = 6]	Lateral flow, visual read, NCP Ag. AN Ag. ≥18 years or children≥2 years if adult-collected. OTC. Home testing, serial 2-test screening ≥24 & ≤36 hours between tests.
NPA 100%, FP 0, and PPV 100%.	N = 257	InBios 1/25/22 [11/22/21] SCoV-2 Ag Detect Rapid Self-Test	**85.71** [70.62-93.74, Δ = 23.12]	**100** [98.30-100.00, Δ = 1.70]	Lateral flow, visual read, NCP Ag. AN. Home testing, serial screening ≥14 years or adult-collected ≥2 years within 5 days of symptoms. With or without symptoms when test twice ≥24 & ≤48 hours between tests. OTC.
	N = 268	Siemens 2/9/22 [12/29/21] CLINITEST Rapid COVID-19 Ag Self-Test	**86.5** [79.6-91.3, Δ = 11.7]	**99.3** [95.9-100, Δ = 4.1]	Lateral flow, visual read. NCP Ag. Anterior nares. OTC. Home testing, serial screening ≥14 years or adult-collected ≥2 years within 7 days of symptoms. With or without symptoms when test twice ≥24 & ≤48 hours between tests.
Lot COVGCCM0008 was recalled due to FPs 12/28/21.	N = 492	Celltrion DiaTrust COVID-19 Ag Home Test 10/21/21 [10/21/21]	**86.7** [73.8-93.7, Δ = 19.9]	**99.8** [98.7-100.0, Δ = 1.3]	Lateral flow, visual read. OTC. Mid-turbinate swab. Home testing, serial screening "twice over two or three days" with ≥24 & ≤48 hours between tests with or without symptoms. Subjects ≥14 years old.
Largest Δ uncertainty of 25% for the PPA 95% CI	N = 153	AccessBio 1/22/22 [8/2/21] CareStart COVID-19 Antigen Home Test	**87** [70-95, Δ = 25]	**98** [93-99, Δ = 6]	Lateral flow, visual read, NCP Ag. OTC. AN. ≥14 years or adult-collected, ≥2 years. Home testing, serial screening, With or without symptoms when test twice ≥24 & ≤48 hours between tests.
	Tier 1 *(3)*				
NPA 100%, FP 0, and PPV 100%.	N = 172	Acon Laboratories 10/19/21 [10/4/21] Flowflex COVID-19 Antigen Home Test	**93** [81-99, Δ = 18]	**100** [97-100, Δ = 3]	Lateral flow, visual read, NCP Ag. OTC. AN. ≥14 years or adult-collected, ≥2 years. Performed once <7 days of symptom onset or without symptoms or other epidemiological reasons.
Largest Δ uncertainty of 6.2% for the NPA 95% CI	N = 139	iHealth Labs 12/22/21 [11/5/21] COVID-19 Antigen Rapid Test	**94.3** [81.4-98.4, Δ = 17.0]	**98.1** [93.3-99.5, Δ = 6.2]	Lateral flow, visual read, home testing, serial screening. OTC. AN. <7 days of symptoms onset for 15 years, adult-collected ≥2 years. Without symptoms performed twice >24, <48 hours between tests.
First FDA EUA. High PPA and lowest NPA, i.e., "flip" phenomena.	N =198	Ellume Ltd. COVID-19 Home Test 2/11/21 [12/15/20]	**95** [82-99, Δ = 17]	**97** [93-99, Δ = 6]	Lateral flow, fluorescence, instrument read, NCP Ag. OTC. Mid-turbinate nasal swab. Self-collected. ≥16 years, or adult-collected, ≥2 years. Home testing, screening. Smartphone assisted. *FP recall of >2(10)[6] products 2/24/21 through 8/11/21.*
	Tier 2 *(1)*				
Highest PPA. Smallest sample size. NPA 100%, FP 0, and PPV 100%.	N = 128	SDBiosensor 1/5/22 [12/24/21] COVID-19 At-Home Test (Roche Diagnostics)	**95.3** [84.5-98.7, Δ = 14.2]	**100** [95.7-100, Δ = 4.3]	Lateral flow, visual read, serial screening. OTC. AN. Self-collected ≥14 years, adult-assisted ≥2 years, <6 days with symptoms. If without perform twice >24, <48 hours between tests. NCP. "Negative results do not rule out SARS-CoV-2."
Statistics					
Median, range [low-high]	**N = 227.5** [128-597]		**86.6** [83.5-95.3, Δ_M = 11.8]	**99.25** [97-100, Δ_M = 3]	Median performance is sub-tier. Highest PPA and NPA achieve Tier 2.
Mean [SD]	**281.6** [157.9]		**88.43** [4.55]	**98.98** [1.02]	

Part II. Molecular Diagnostics, Details	**Tier, Sample Size, and Cost**	**Company, Product, EUA LOA Date [Earliest Date]**	**Company PPA (%) Claim [CI, Δ]**	**Company NPA (%) Claim [CI, Δ]**	**Specimen Type, Age, and Time Interval/ Protocol for Specimen Collection [plus notes]**
	Tier 1 *(2)*				
RT-LAMP and lateral flow strip. ORF1ab region of	N = 112	Detect COVID-19 Molecular Non-prescription Home Test	**90.9** [76.4-96.9, Δ = 20.5]	**97.5** [91.2-99.3, Δ = 8.1]	AN swab. Self-collected ≥14 or adult assisted ≥2 years. Without symptoms performed twice >24, <48 hours between

the SARS-CoV-2 genome.	Test & processing hub $75.	1/12/22 [10/28/21]			tests. Apparent FPs due to subject misinterpretation; app modified to reduce this error. Testing time 55-65 minutes.
RT-LAMP. Non-overlapping regions of the N gene.	N = 404 Overall N = 101 (1) N = 303 (2) Single-use test kit $75.	Lucira CHECK-IT COVID-19 Test Kit 4/9/21 [4/9/21]	**91.7** [85.6-95.8, Δ = 10.2] (1) 94.1 [85.5-98.4] (2) 90.1 [81.5-95.6]	**98.2** [95.8-99.4, Δ = 3.6] (1) 98.0 [89.4-99.9] (2) 98.2 [95.5-99.5]	AN swab. Symptomatic (1) and asymptomatic (2). PPAs exceed Tier 1 threshold of 90%. NPAs meet the Tier 2 threshold of 97.5%. Testing time 30 minutes.
	***Tier 2** (1)*				
"Isothermal nucleic acid amplification test." Nucleocapsid N region of the SARS-CoV-2 virus.[8]	N = 271 Overall N = 138 (1) N = 133 (2) Test $61.75 to $65 each. Reader $249.	Cue Health COVID-19 Test for Home and OTC Use. 2/9/22 [3/5/21]	**97.4** [86.5-99.5, Δ = 13.0] (1) 96.4 [82.3-99.4] (2) 100 [72.2-100]	**99.1** [96.9-99.8, Δ = 2.9] (1) 98.2 [93.6-99.5] (2) 100 [97.0-100]	AN swab. Self-collected adult or assisted ≥2 years. Symptomatic (1) and asymptomatic (2). Testing time 20 minutes. A clinical evaluation of 292 outpatients in a community drive through showed sensitivity of 91.7% and specificity of 98.4% for S and A (with recent exposure) adult subjects.[8]
Statistics					
Median, range [low-high]	**N = 271** [112-404]		**91.7** [90.9-97.4, Δ_M = 6.5]	**98.2** [97.5-99.1, Δ_M = 1.6]	Median and mean performance are both Tier 1.
Mean [SD]	**262.3** [146.2]		**93.3** [3.54]	**98.3** [0.80]	

Abbreviations: Δ, magnitude in % of the 95% CI, i.e. high minus low limits; Δ_M, span of the median range; Ag, antigen; A, asymptomatic; AN, anterior nares; CI, 95% confidence interval with upper and lower bounds in percent; COVID-19, coronavirus disease 2019; EUA, Emergency Use Authorization; FDA, Food and Drug Administration (USA); RT-LAMP, reverse transcription loop-mediated isothermal amplification; LOA, letter of authorization; NA, not applicable; NCP, nucleocapsid protein; NPA, negative percent agreement; O, overall; OTC, over the counter; PPA, positive percent agreement; PPV, positive predictive value; and S, symptomatic.

Notes: a) Tier sensitivity/specificity (%) comprise: 1) 90/ 95; 2) 95/ 97.5; and 3) 100/ ≥99. b) Data are reported as they appear in FDA EUA authorization letters and Information for Users under "In Virto Diagnostic EUAs – Antigen Diagnostic Tests for SARS-CoV-2, Home Testing posted before the end of 2021. c) Prescription, telehealth, and home collection EUAs are not listed. d) SD Biosensor "Standard Q COVID-19 Ag Home Testing" was recalled January 31, 2022.

Table S2. COVID-19 Antigen Test Performance for Symptomatic and Asymptomatic Subjects in Community Settings.

Tier (N), Author, Journal, Year, & Modality	Sensitivity (%) [95% CI] (ranked)	Specificity (%) [95% CI]]	Antigen Assay	Sample Size (N), Sites, and Notes
Part I. Point-of-Care Testing				
Sub-tier (29)				
Alghounaim *Frontiers Med* 2021	**30.6** [19.6-43.7] [O] 77.8 [40-97.2] [S]	**98.8** [97.8-99.4] [O] 94.7 [74-99.9] [S]	Standard Q RAgT, SD Biosensor. ONP swabs.	N=972. Community screening 10 days, 28 symptomatic. "Most infections (77.4%) were asymptomatic." Kuwait.
Garcia-Finana *BMJ* 2021	**40** [28.5-52.4] [A]	**99.9** [99.8-99.99] [A]	Innova SARS-CoV-2 Ag rapid LFT.	N=5,869. Asymptomatic at 48 sites, 200 each in Liverpool, UK.
Allan-Blitz *J Clin Micro* 2021	**47.5** [39.1-56.1] [O] 47.7 [35.2-60.5] [S] 54.4 [39.0-69.1] [A]	**100** [99.3-100] [O] 100 [98.7-100] [S] 99.8 [98.7-100] [A]	BinaxNOW COVID-19 rapid Ag Card, Abbott. AN swabs. Results for AN PCR.	N=834 [O], 276 [S], & 422 [A]. Four publicly accessible testing sites across Florida.
Mungomklang *Am J Trop Med Hyg* 2021	**47.97** [36.10-59.96] [A]	**99.71** [99.15-99.94] [A]	"Rapid SARS-CoV-2 antigen test." NP swabs.	N=1,100. Asympto-matic migrant workers during case finding in Samut Sakhon, Thailand.
Jakobsen *J Pathol Micro Immuno Scand* 2021	**48.5** [NR] [O] 56.2 [NR] Ct<33 63.9 [NR] Ct<30	**100** [NR] [O] 100 [NR] Ct<33 100 [NR] Ct<30	Standard Q COVID-19 Ag Test. AN swabs.	N=7,074. Low 0.9% prevalence public test center, Copenhagen, Denmark.
Prince-Guerra *MMWR 2021* **Almendares** *J Clin Micro* 2021	**52.5** [46.7-58.3] [O] 64.2 [56.7-71.3] [S] 39.6 [26.4-54.0] [A]	**99.9** [99.7-100.0] [O] 100 [99.4-100.0] [S] 99.8 [99.5-100.0] [A]	BinaxNOW COVID-19 Ag Card. AN swabs.	N=3,419 with 827 symptomatic & 1,968 asymptomatic. Two community-based testing sites in Arizona.
Stohr *Clin Micro Infect* 2021	**55.6** [50-5-60.7] [O] 49.1 [41.7-56.5] (1) 61.5 [54.6-68.3] (2)	**99.8** [99.6-99.9] [O] 99.9 [99.7-100] (1) 99.7 [99.4-99.9] (2)	(1) BD Veritor System for Rapid Detection of SARS-CoV-2 (VRD). (2) Roche SARS-CoV-2 Ag detection test. Nasa; swabs.	N=3,201. N=1,595 (1) & 1,606 (2). Testing kits obtained from a MHS community center, Netherlands, then self-testing performed at home.
Frediani *Nature Sci Report* 2021	**57** [37-76] (1 < 7 days) [O] **74** [64-82] (2 < 7 days) [O]	**100** [79-100] (1 < 7 days) [O] **99** [97-100] (2 < 7 days) [O]	BinaxNOW COVID-19 rapid Ag Test. AN swab.	Assessment of self-administration. N=44 self- or parent-collected (1) & 297 staff-collected (2).
Pollock NR *Open Forum Infect Dis* 2021	**57.7** [51.1-64.1] [O] 84.3 [71.4-93.0] [S < 7 days] & 50.0 [41.0-59.0] [A] adults. 85.7 [42.1-99.6] [S < 7 days] & 51.4 [34.4-68.1] [A] children.	**98.3** [97.5-99.0] [O] 97.5 [92.8-99.5] [S < 7 days] & 99.1 [98.3-99.6] [A] adults. 85.0 [62.1-96.8] [S < 7 days] & 97.8 [94.5-99.4] [A] children.	Access Bio CareStart COVID-19 Antigen Test	N=1,498, 1,245 adults & 253 children. Sensitivity 79.6% for Ct≤30. FP were 21/234 tests. Community testing site in MA.
Pilarowski *J Infect Dis* 2021	**57.7** [36.9-76.6] [O] 93.3 [68.1-99.8] when Ct≤30.	**100** [99.6-100] [O] 99.9 [99.4-99.9] when Ct≤30.	BinaxNOW COVID-19 rapid Ag Test. Nasal swab by technician.	N=878. Public plaza in San Francisco, California, over 3 days, symptomatic and asymptomatic (40%).
Boum *Lancet* 2021	**58** [53-64] [O] 80.0 [71.0-88.0] [S first 7 days] 37.0 [27.0-48.0] [A]	**94** [88-97] [O] NR	SD Biosensor, South Korea. NP swabs. (Data from table on page 1,094.)	N=1,090 [O]. Community screening in Cameroon.
Drevinek *Epid Mikrobiol Immuno* 2020	**66.4** [59.9-72.2] [O] 73.8 [66.7-79.9] [S] 43.6 [31.4-56.7] [A]	**100** [99.0-100] [O] NR NR	PanBio Ag Test, Abbott. NP swabs.	N=591. Large-scale testing, single site, Prague, Czech Republic. Symptomatic (290) and asymptomatic (301) subjects.
Pollreis *PLoS ONE* 2021	**67.6** [50.2-81.9] [O] 50.0 [6.8-93.2] [A subset]	**100.0** [97.9-100.0] [O] 100.0 [89.4-100.0] [A subset]	BinaxNOW COVID- 19 Test Ag Card. Nasal swabs.	N=214. Local public health district, rural population, Idaho (1). N=14 asymptomatic

				subset (2). 82.7 % symptomatic.
Jakobsen *medRxiv* 2021	**69.7** [NR] [O] 78.8 [NR] [S] 49.2 [NR] [A]	**99.5** [NR] [O] 98.9 [NR] [S] 99.6 [NR] [A]	Standard Q COVID-19 Ag Test. OP swabs.	N=4,697. 705 self-reported S & 3,008, A. Public test center, Copenhagen, Denmark.
Nalumansi *In J Infect Dis* 2021	**70.0** [60-79] [O] (More likely positive with qRT-PCR Ct 29, then sensitivity of 92%.)	**92** [87-96] [O]	Standard Q COVID-19 Ag Test. NP swabs.	N=262. Males (89%) 14% of whom were symptomatic at treatment centers in Uganda.
Fernandez-Montero *eClin Med* 2021	**71.43** [56.74-83.42] [A]	**99.68** [99.37-99.86] [A]	SARS-CoV-2 Rapid Antigen Test, Roche Diagnostics.	N=2,542. Asymptomatic adults, semi-closed community, Univ. of Navarra, Spain.
Gremmels *eClin Med* 2021	**72.6** [64.5-79.9] [Utrecht, S] 81.0 [69.0-89.8] [Aruba, S]	**100** [99.7-100] [Utrecht, S] 100 [99.7-100] [Aruba, S]	Panbio COVID-19 Ag Rapid Test, Abbott. NP swabs.	U: N=1,367 in Utrecht, Netherlands. N=208 in Aruba. COVID-19. 16+ years at community testing centers.
Jian *Int J Infect Dis* 2021	**76.39** [64.91-85.60] [O]	**99.26** [98.78-99.58] [O]	COVID-19 Antigen Rapid Test, Eternal Materials, Taipei, Taiwan. NP swabs.	N=2,096. High-throughput community testing site in Wanhua District of Taipei, Taiwan. Both S & A.
Shah	**77.2** [72.4-81.6] [O] 81.4 [76.8-85.5] (Or) 78.6 [73.4-83.3] [S] 68.8 [53.7-81.3] [A]	**99.6** [99.2-99.8] [O] 99.6 [99.2-99.8] (Or) 99.8 [99.2-100.0] [S] 99.4 [98.6-99.8] [A]	BinaxNOW COVID-19 rapid Ag Test. Nasal swab. 2nd swab at 30 minutes for repeat testing same day.	N=2,110. Overall & repeat (Or). 1,188 S & 877 A in community testing site in Wisconsin.
Pollock NR *J Clin Micro* 2021	**77.4** [72.2-82.1] [O] 96.5 [90.0-99.3] [S < 7 days] & 70.2 [56.6-81.6] [A] adults. 84.6 [65.1-95.6] [S<7 days] & 65.4 [55.6-74.4] [A] children.	**99.4** [99.0-99.7] [O] 100 [98.6-100.0] [S< 7 days] & 99.6 [98.9-99.9] [A] adults. 100 [94.5-100.0] [S<7 days] & 99.0 [98.0-99.6] [A] children.	BinaxNOW COVID-19 Ag Card. 20 tests per hour.	N=2,308 with 1,380 adults (71% A) & 928 children (89% A). FP were 12/2,308 tests. Community testing site in Massachusetts.
Ford *J Ped Infect Dis Soc* 2021	**80.8** [75.9-85.1] [O] (Adults) 73.0 [55.9-86.2] (C) 75.9 [56.5-89.7] [SC] 57.1 [18.4-90.1] [AC]	**99.9** [99.5-100] [O] (Adults) 100 [98.1-100] (C) 100 [NR][SC] NR	BinaxNOW COVID-19 rapid Ag Test. Nasal swab.	N=1,807 adults. N=217 children (C). Self-collected at community public testing site in Wisconsin.
Nsoga *PLoS ONE* 2021	**81** [74.2-86.6] [O]	**99.1** [96.9-99.9] [O]	Panbio COVID-19 Ag Rapid Test, Abbott. OP swabs.	N=402. Screening center in Geneva, Switzerland. "Most had symptoms."
Siddiqui *Microbiol Spectrum* 2021	**81 [**75-86] [O] 87 [80-91) [S] 71 [61-80] [A] 82 [66-91] [AE] 64 [51-76] [ANE]	**99.8** [100-100] (sic) [O] >99 [NR] all groups	BinaxNOW COVID-19 rapid Ag Test. Nasal swab.	N=6,099. Overall, symptomatic, & asymptomatic. Self-referred walk-up testing site.
Drain *Am J Clin Pathol* 2021	**82.1** [64.4-92.1] [A]	**100** [98.1-100] [A]	LumiraDx SARS-CoV-2 Ag Test. AN swabs.	N=222. Asymptoma- tic adults & children at five clinic- & community-based sites in the US.
Shrestha *Kathmandu Univ Med J* 2020	**85** [NA] [A, day 5]	**100** [NA] [A, day 5]	"An Ag test kit for COVID-19."	N=113. High risk close contacts in quarantine in province 3, Kathmandu, Nepal.
Chiu *Microbiol Spectr* 2021	**85.3** [75.6-91.6] [S < 5 days] 82.7 [72.6-89.6] self-collected. 84.2 [69.6-92.6] [A]	**94.9** [91.6-96.9] [S < 5 days] 96.4 [93.4-98.0] self-collected. 99.9 [99.9-100] [A]	INDICAID COVID-19 rapid antigen test, PHASE Sci. Intl. AN swabs. 20 minute test.	N=349 symptomatic in California communities & 22,994 asymptomatic in Hong Kong outbreak screening centers.
Stokes *Eur J Clin Micro Infect Dis* 2021	**86.1** [81.3-90.0] [S < 7 days]	**99.9** [99.5-100] [S < 7 days]	Panbio COVID-19 Ag Rapid Test, Abbott. NP swabs.	N=1,641. Sympto- matic subjects < 7 days, community assessment centers.
Agarwal *J Infect Dev Ctries* 2021	**89.7** [72.6-97.8] [O]	**99.5** [NR] [O]	Standard Q COVID-19 Ag test. Nasal swabs.	N=467. Fever clinic in north India. 2 AFP. Compared to TrueNat, POC chip-based real-time portable PCR.
Tier 1 (2)				

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Kerneis *Eur J Clin Micro Infect Dis* 2021	**94** [86-98] [O] 95 [87-99] [S] 88 [64-99] [A]	**99** [98-99] [O] 98 [96-99] [S] 99 [98-100] [A]	Standard Q COVID-19 Ag test. NP swabs.	N=1,109 with 459 symptomatic & 650 asymptomatic. Paris community screening centers.
Van der Moeren *PLoS ONE* 2021	**94.1** [71.1-100] [S] 78.9 [70.6-85.7] in qRT-PCR positive prequalified subjects	**100** [98.9-100] [S]	BD Veritor System for Rapid Detection of SARS-CoV-2 (VRD). NP swabs.	N=352. Municipal Health Service test centers in the Netherlands. Symptomatic.
Tier 2 (1)				
Drain *Infect Dis Ther* 2021	**97.5** [87.1-99.6] [O] NP swab (Tier 2) **97.6** [91.6-99.3] [O] N swab (Tier 2)	**97.7** [94.7-99.0] [O] NP swab (Tier 2) **96.6** [92.7-98.4] [O] N swab (Tier 1)	LumiraDx SARS-CoV-2 antigen test.	N=512. Children & adults (81% S) in ten clinic- & community-based settings in US & UK cities.

Statistics	**Median [N, Range]**	**Median [N, Range]**
Overall [O]	**69.85 [24, 30.6-97.6]**	**99.5 [24, 92-100]**
Symptomatic [S]	**81.0 [19, 47.7-96.5]**	**99.85 [16, 85-100]**
Asymptomatic [A]	**55.75 [20, 37-88]**	**99.70 [16, 97.8-100]**

Part II. Antigen Automated Instrument Tests				
Alghounaim *Frontiers Med* 2021	**43.3** [30.6-56.8] [O] 88.9 [51.8-99.7] [S]	**99.9** [99.3-100] [O] 100 [80.5-100] [S]	SARS-CoV-2 Ag assay on LIAISON XL, Diasorin. ONP swabs.	N=972. Community screening 10 days, 26 symptomatic. Kuwait.
Drevinek *Epid Mikrobiol Immuno* 2021	**62.3** [55.8-68.4] [O] 68.5 [61.1-75.0] [S]	**99.5** [98.0-99.9] [O] NR	Standard F Ag FIA, SD Biosensor. NP swabs.	N=591. Large-scale testing, single site, Prague, Czech Republic. Symptomatic (290) and asymptomatic (301) subjects.
Van der Moeren *J Clin Virol* 2021	**73** [61.3-82.7] [S]	**100** [97.9-100] [S]	SARS-CoV-2 Ag assay on LIAISON XL LAI, Diasorin. ONP swabs.	N=248. Community-dwelling symptomatic subjects at Municipal Health Service COVID-19 test centers, Netherlands.
Gili *Int J Infect Dis* 2021	**100** [96-100] [O] for screening @ 1.645 pg/mL optimal cutoff. 92.6 [85.4-97.0] in smaller cohort @ 1.24 pg/mL optimal cutoff.	**94.8** [93.6-95.8] [O] For screening @ 1.645 pg/mL optimal cutoff. 90.8 [84.5-95.2] in smaller cohort @ 1.24 pg/mL optimal cutoff.	Lumipulse SARS-CoV-2 antigen assay, benchtop Fujirebio, Tokyo. NP swabs.	N=1738 swabs collected in schools, prisons, elderly care homes, & from hospital healthcare worker surveillance in Italy.

Statistics	**Median [N, Range]**	**Median [N, Range]**
Overall [O]	**62.3 [3, 43.3-100]**	**99.5 [3, 94.8-99.9]**
Symptomatic [S]	**73 [3, 68.5-88.9]**	**100 [3, 100]**
Asymptomatic [A]	**No Data**	**No Data**

Abbreviations: A, asymptomatic; AE, asymptomatic with exposure; Ag, antigen; AN, anterior nasal; ANE, asymptomatic with no exposure; CI, 95% confidence interval; CLEIA, chemiluminescence enzymatic immunoassay; Ct, cycle threshold; FIA, fluorescence immunoassay; FN, false negative; FP, false positive; ID, infectious disease; LFT, lateral flow test; MHS, Municipal Health Services; N, nasal; NA, not available; NP, nasopharyngeal; NR, not reported; O, overall; ONP, oronasopharyngeal; OP, oropharyngeal; PCR, polymerase chain reaction; PPV, positive predictive value; qRT-PCR, quantitative reverse transcription PCR; RAgT, rapid antigen test; S, symptomatic; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; UK, United Kingdom; and US, United States.

Note: Tier sensitivity/specificity (%) comprise: 1) 90/ 95; 2) 95/ 97.5; and 3) 100/ ≥99.

Table S3. COVID-19 Antigen Test Performance in Emergency Medicine.

Category, Author, Journal, and Year	Sensitivity (%) [95% Confidence Interval]	Specificity (%) [95% Confidence Interval]	Antigen Assay/ Specimen/ Testing Details	Sample Size (N) and Descriptive Notes
I. Emergency Medicine (EM)				
Bianco *J Clin Virol* 2021	**90.3** [86.3-93.4] [O] 89.3 [84.2-93.3] [S] 92.1 [85-96.5] [A]	**92.1** [89.7-94.1] [O] 88.2 [72.5-96.7] [S] 92.3 [89.9-94.4] [A]	LumiraDx Platform, UK. Instrumented test runs on a portable, wall outlet or battery-powered multi-assay desktop platform. Nasal swab.	N = 907. Adult and pediatric patients in EDs and occupational medicine during the 2nd peak of the Italian pandemic.
Burdino *J Virol Meth* 2021	**89.6** [NR] from Table 1. In text: 90.1 [86.2-93.1]	**99.4** [NR] from Table 1. In text: 99.4 [98.6-99.8]	LumiraDx SARS-CoV-2 Ag Test. Nasal swab.	N = 1,232. Patients referred to the ER in a tertiary care hospital in Turin, Italy.
Caruana *Microorganisms* 2021	**41.2** b-d [O] **48.3** a [O] 43.3 b-d [S] 52.2 a [S] 33 a-d [A]	**99.5** a **99.7** b [O] **99.5** c **99.7** d [O] 99 a, 99.5 b-d [S] 100 a, b, d [A] 99.5 c [A]	4 RAgTs evaluated: a) Exdia, b) Standard Q RAgT, c) Panbio, & d) BD Veritor.	N = 532 with S (293) and A (239). RAgT performed by lab technicians in the ER. (No CIs reported for sensitivity & specificity.)
Caruana *New Microbes New Infect* 2021	**28.6** [NR] [A]	**98.2** [NR] [A]	Standard Q COVID-19 Rapid Antigen Test, SD Biosensor/Roche. NP swabs.	N = 116. Asymptomatic ED patients screened on admission to Morges, Switzerland community hospital. 2 FP results. PPV 50%.
Cento *Viruses* 2021	**85** [82-89] 91 [86-95] for samples with Ct≤29.	**97** [96-98]	LumiraDx SARS-CoV-2 test. NP swab.	N = 960. ER admissions to a tertiary COVID-19 hospital. 50 FN confirmed by RT-PCR.
Cerutti *J Clin Virol* 2020	**70.6** [NR]	**100** [NR]	Standard Q COVID-19 Ag (R-Ag) test, Roche Diagnostics. NP "secretions."	N = 330. Symptomatic patients in ERs of 2 infectious disease reference centers, North Italy.
Ciotti *J Med Virol* 2021	**30.77** [17.02-47.57]	**100** [71.51-100.00]	Ag Respi-Strip test.	N = 50. Mixed ED & infectious diseases ward patients in Rome, Italy.
Holzner *J Med Virol* 2021	**68.87** [±1.86] [O] 69.46 [±2.30] [S] 62.0 [±0.32] [A] All & Ct<30, 80.48	**99.56** [±0.26] [O] 99.51 [±0.34] [S] 97.63 [± 1.03] [A] All & Ct <30, 99.56	Standard Q, Roche Diagnostics	N = 2,375 with S (1,539) & A (836). For 423 S & Ct<30, sensitivity 79.67 [±2.06] & specificity 99.51 [±0.35].
Koelman *Eur J Clin Micro ID* 2021	**65.3** [57.1-72.8]	**100** [96.9-100]	Romed lateral flow immunochromatographic assay, Netherlands	N = 150. ER patients presenting to a teaching hospital in Rotterdam, Netherlands.
Leixner *Intl J Infect Dis* 2021	**69.2** [58.8-78.3] [S] Ct<25, 100.0 Ct<30, 91.8	**99.7** [98.1-100.0] [S]	AMP Rapid Test SARS-CoV-2, Austria. NP Swab.	N = 392. Symptomatic patients presenting to the Edin Vienna, Austria. Median Ct 27.6.
Leli *Intl J Infect Dis* 2021	**68.7** [60-9-75.5] [O] 81 [70.3-88.6] [S] 48.1 [34.5-62] [A]	**95.2** [93.1-96.7] [O] 98.4 [93.9-99.7] [S] 93.8 [90.4-96.1] [A]	LumiraDx SARS-CoV-2 Ag Test. NP Swab. (Median Ct for Ag+ was 23.9, and Ag-, 35.6.)	N = 792. Patients admitted to ED in Alessandra, Italy. Prevalence 21% overall; S (207), 38.2%; & A (377), 14.3%.
Linares *J Clin Virol* 2020	**73.3** [62.2-83.8] [O] 86.5 [75.5-97.5] < 7 days [S] 54.5 [A]	**100** [NR] [NR for S & A]	Panbio COVID-19 Rapid Test Device, Abbottt. Median Ct 23.3. NP swab.	N = 255. Symptomatic (72.1%) & asymptomatic with close contact in the ED & primary care in Madrid.
Loconsole *BioMed Res Intl* 2021	**94.9** [91.9-97.0] [O] 95.8 [92.7-97.7] [S] 91.8 [81.9-97.2] [A]	**97.4** [96.5-98.1] [O] 96.4 [93.7-98.0] [S] 97.8 [96.8-98.3] [A]	Lumipulse CLEIA Ag Test on G1200 automated analyzer, Fujirebio, Tokyo, Japan, in 50-60 minutes.	N = 911 ED patients in Bari, Italy. NP samples processed quantitatively at regional reference laboratory. Not POC testing.
Masia *Open Forum Infect Dis* 2020	**69** [53.3-80.1] For [S], then 95 when Ct≤25; 85 when Ct≤30, & 89 for triad.	**100** [97.2-100]	Panbio COVID-19 Ag Rapid Test Device	N = 223. ED patients in Alicante, Spain. NP swabs. Sample types studied. (Symptom triad is fever, cough, & malaise.)
Merrick *Infect Prev Pract* 2021	**70.7** [65.8-75.2]	**99.1** [98.1-99.6]	Lateral-flow Ag detection using Innova and SureScreen tests. AN swab.	N = 1,422. St. Thomas' ED in central London. PPV of 97.7% and NPV of 86.4% with prevalence of 34.7%. 3 FP and 95 FN results.
Mockel *Biomarkers* 2021	**75.3** [65.8-83.4] [S]	**100** [98.4-100] [S]	AGTEST Roche SD/Biosensor. Deep ONP specimens.	N = 281. Symptomatic adults in four adult EDs in Berlin. FN results (22) occurred in adult ED patients.

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Oh *J Korean Med Sci* 2021	**17.5** [8.8-32] Ct≤30, 26.9 [13.7-46.1] Ct≤25, 41.1 [21.6-64.0]	**100** [95.3-100]	Standard Q COVID-19 Ag Test, SD Biosensor, Suwon, South Korea	N = 118. ED and admitted population. "Clinical applicability for diagnosis higher if applied higher performance tests."
Orsi *J Virol Meth* 2021	**93.3** [83.8-98.2] [S] **86.7** [75.4-94.1] [S] (FIA)	**100** [92.9-100] [S] **100** [92.9-100] [S] (FIA)	FREND COVID-19 Ag Rapid Diagnostic Test & Standard F COVID-19 Ag FIA versus RT-qPCR.	N = 110. Symptomatic patients who accessed the ER. Comparison study performed in laboratory within 8 hours from swab arrival.
Osterman *Med Micro Immuno* 2021	**50.34** [45.71-54.96] **45.41** [40.48-50.43] (FIA)	**97.67** [95.63-98.77] **97.78** [95.68-98.87] (FIA)	SARS-CoV-2. Rapid Antigen Test, Roche Diagnostics, & Standard Q COVID-19 Ag Test FIA versus RT-PCR. N/P swab.	N = 445/386 & 381/360 (FIA). ERs, care units, or employee test centers in Germany. Sensitivity "…markedly lower than reported by manufacturers."
Thell *PLoS ONE* 2021	**77.9** [70.0-84.6] [S] 81.6 [68.0-91.2] when within 7 days	**98.1** [94.6-99.6] [S] 95.9 [86.0-99.5] when within 7 days	SARS-CoV-2 Rapid Antigen Test, Roche Diagnostics. NP swabs.	N = 296. 5 EDs in Austria. Suspected, symptomatic patients. 1% FP & 10.1% FN.
Turcato *J Infection* 2021 Preliminary Report	Preliminary 80.3 [74.9-85.4] [O] 89.9 [85.4-94.4] [S] 50.0 [36.0-63.0] [A]	Preliminary 99.1 [98.6-99.3] [O] 97.6 [96.5-98.5] [S] 99.6 [99.1-99.9] [A]	SD Biosensor SARS-CoV-2 Rapid Antigen Test. NP swab.	N = 3,410. S (991) & A (2,419) patients who required ED evaluation in Merano, Italy. *Preliminary - excluded from statistical summary.*
Turcato *Am J Emer Med* 2022 Final Report	**82.9** [81.0-84.8] [O] 89.8 [88.0-91.5] [S] 63.1 58.4-67.8] [A]	**99.1** [98.8-99.3] [O] 97.6 [97.1-98.1] [S] 99.6 [99.5-99.7] [A]	SD Biosensor SARS-CoV-2 Rapid Antigen Test. NP swab.	N = 3,899. S (1,191) & A (2,708) patients who required ED evaluation in Merano, Italy. 3.3% FN.

EM Statistics	**Median [N, Range]**	**Median [N, Range]**
Overall	**68.79 [20, 17.5-94.9]**	**99.5 [20, 92.1-100]**
Symptomatic	**77.9 [15, 43.3-95.8]**	**99.5 [14, 88.2-100]**
Asymptomatic	**48.1 [11, 28.6-92.1]**	**98.85 [10, 92.3-100]**

II. Pediatric EM (ER & ED)				
Carbonell-Sahuquillo *J Med Virol* 2021	**70.6** [52.2-84.9] [S] (results in text)	**100** [98.9-100] [S]	Panbio COVID-19 Ag Rapid Test Device.	N = 357. Symptomatic ED pediatric patients in Valencia, Spain. Prevalence 15%.
Denina *Intl J Med Sci* 2021	**94.1** [71.3-99.8]	**91.9** [86.9-95.5]	LumiraDx Platform. Nasal swab.	N = 191. Pediatric patients in ED in Turin, Italy with or without symptoms/exposure.
Gonzalez-Donapetry *Ped Infect Dis J* 2021	**77.78** [51.92-92.63] [S]	**100** [98.88-100] [S]	Panbio COVID-19 Ag Rapid Test Device. NP swabs.	N = 440. Hospital Univ. La Paz symptomatic pediatric ED patients who meet COVID-19 criteria.
Jung *Frontiers Pediatrics* 2021	**87.9** [71.8-96.6] [S] Ct>25, 63.6 [30.8-89.1]	**98.5** [96.3-99.6] [S] Ct>25, 99.6 [98.0-100.0]	BIOSYNEX COVID-19 Ag BSS	N = 308. Symptomatic pediatric patients 0-17 years in ED and primary care in France. Prevalence 10.7%
Lanari *Viruses* 2021	**53.8** (1) [35.4-71.4] **86.4** (2) [75.0-93.9]	**99.7** (1) [98.4-100] **98.3** (2) [97.1-99.1]	(1) COVID-19 Ag FIA kit. (2) AFIAS COVID-19 Ag kit. NP swab.	N = 1,146. Pediatric patients admitted to the Emergency Unit of IRCCS-Polyclinic of Sant'Orsola, Bologna.
Mockel *Biomarkers* 2021	**72.0** [53.3-86.7] [S]	**99.4** [97.3-99.9] [S]	AGTEST Roche/SD Biosensor. Deep ONP specimens.	N = 202. Pediatric patients in one ED in Berlin. FN (7) & FP (1) results occurred.
Quentin *Clin Micro Biol Infect* 2021	**69.57** [54.25-82.26] 82.86 [66.35-93.44] [S] 27.27 [6.02-60.97] [A]	**99.89** [99.41-100] 99.77 [98.74-99.99] [S] 100 [99.27-100] [A]	COVID19Speed-Antigen Test, BioSpeedia, France	N = 1,009. Children presenting to the pediatric ED of the Univ. Hosp., Saint-Etienne, France. S (493). A (516) children had the most FN results.
Reichert *Am J Infect Cont* 2021	**42.9** [9.9-81.6] [A] Asymptomatic adults compared: 38.9 [17.3-64.3]	**99.4** [98.6-99.8] [A] Asymptomatic adults compared: 99.7 [98.4-100]	SD Biosensor SARS-CoV-2 Rapid Antigen Test. NP swab.	N = 710. Asymptomatic (x 48 hours) pediatric patients in ED. No known contacts 14 days.
Villaverde J Pediatrics 2021	**45.4** [34.1-57.2] [S]	**99.8** [99.4-99.9] [S]	Panbio COVID-19 Ag Rapid Test Device. NP swabs.	N = 1,620. Pediatric patients with symptoms within 5 days in EDs at 7 medical centers.

Statistics	**Median [N, Range]**	**Median [N, Range]**
Pediatric EM	**71.3 [10, 42.9-94.1]**	**99.55 [10, 91.9-100]**
Symptomatic	**74.89 [6, 45.4-87.9]**	**99.79 [6, 98.5-100]**

Asymptomatic	**35.09 [2, 27.27-42.9]**	**99.7 [2, 99.4-100]**
Not Stated	**77.99 [4, 53.8-94.1]**	**99 [4, 91.9-99.89]**

Abbreviations: A, asymptomatic; Ag, antigen; AN, anterior nasal; CI, 95% confidence interval; CLEIA, chemiluminescence enzymatic immunoassay; Ct, cycle threshold; ED, emergency department; EM, emergency medicine; ER, emergency room; FIA, fluorescence immunoassay; FN, false negative; FP, false positive; NP, nasopharyngeal; NPV, negative predictive value; NR, not reported; O, overall; ONP, oronasopharyngeal; POC, point of care; RT-PCR, reverse transcription-polymerase chain reaction; PPV, positive predictive value; S, symptomatic; and SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

Table S4. COVID-19 Saliva Testing Sensitivity and Specificity Performance in Strictly Asymptomatic Subjects (no mixed populations) — Clinical Evidence.

Author, Journal, & Year	Sensitivity (%) [95% CI] (ranked)	Specificity (%) [95% CI]]	Sample Size (N), Context, & Descriptive Notes	Authors' Conclusions
Nacher *PLoS ONE* 2021	**16.8** [10.1-25.6]	**98.9** [97.7-99.6]	N = 90. Prospectively enrolled asymptomatic with a testing indication in the Amazonian Forest. NPS RT-PCR reference method.	Saliva "…sensitivity–using NP samples as gold standard—went from very poor among asymptomatic patients…"
Nacher *Font Med* 2021	**24** [est. CI, 15-33]	**NR**	N = 39% of 776 = 303 asymptomatic. Reported 46 in Fig. 2. CI estimated from Fig. 2. Sites and mobile testing in French Guiana up to 240 km in the Amazon forest. NPS RT-PCR RM.	**"**The sensitivity (of) saliva samples for asymptomatic persons seemed insufficient… without any temporal indication about the onset of infection…"
Marx *Clin Infect Dis* 2021	**28.5** [8.2-64.1]	**99** [97.0-99.7]	N = 299 asymptomatic. Testing at community testing events and homeless shelters, Denver. NPS RT-PCR RM.	**"**Among asymptomatic participants, sensitivity was low …"
Bosworth *J Clin Virol* 2020	**33** [NR]	NR	N = 15 asymptomatic. Data also reported in Table 1 by Khiabani *Am J Infect Control* 2021. WHO E/RdRp gene RM and other assays.	**"…**saliva as an alternative sample type."
Alkhateeb *Diag Micobiol Infect Dis* 2021	**36** [11-69] 22 [3-60] if low risk	**100** [3-100] 100 [29-100]	N = 12 asymptomatic & 12 at risk, i.e., afebrile & no comorbidities. RT-PCR NPS RM.	"…saliva's low sensitivity in asymptomatic SARS-CoV-2 infections …"
LeGoff *Nature Sci Rep* 2021	**38** [23-55] RT-LAMP **92** [78-98] RT-PCR	**97** [96-98] RT-LAMP **97** [96-98] RT-PCR	N = 1,027 asymptomatic (RT-LAMP) and 978 asymptomatic (RT-PCR), compared to NPS RT-PCR with ≥1 gene targets.	"No difference in RT-LAMP sensitivity… between symptomatic and asymptomatic participants."
Igloi *PLoS ONE* 2021	50.0 [18.7-81.3] (1) 60 [26.2-87.9] (2)	99.1 [96.8-99.9] (1) 99.6 [97.5-99.9] (2)	N = 5 for SD Biosensor SARS-Co-2 saliva RAgT vs. saliva RT-PCR RM (1). N = 6 for NPS RAgT versus saliva RT-PCR RM(2).	Asymptomatic subjects. Not included in statistical analysis, because of small sample sizes and use of RAgT for saliva.
Lopes *Viruses* 2021	**55** [NR] (On p. 7 in text.)	**98.3** [NR] (Calculated from data on p. 6 with corrected matches of 786 and 55% sensitivity.)	N = 821. Asymptomatic patients and healthcare workers with close contacts admitted to hematology ward. RT-PCR NPS RM.	"Symptomatic subjects showed significantly higher viral detection rate … compared with those asymptomatic..."
Fernandez-Gonzalez *J Clin Micro* 2021	**60** [27.4-86.3]	**NR**	N = 208. Self-collection of saliva by outpatient asymptomatic patients. RT-PCR NPS TM.	"…saliva is an acceptable specimen for the detection of SARS-CoV-2 in the community setting ."
Nagura-Ikeda *J Clin Micro* 2020	**63.35** [NR] (median of evaluation comparisons with 4 reference methods)	**NR**	N = 15 asymptomatic. Qiagen RT-qPCR, cobas SARS-CoV2, direct RT-qPCR, and RT-LAMP RMs LDT.	"…RT- qPCR, cobas SARS-CoV-2, RT-qPCR kits, and RT-LAMP showed sufficient clinical sensitivities for selective use in clinical settings and facilities."
Babady *J Mol Diag* 2021	**63.6** [46.6-77.8] (oral rinse)	**96.9** [89.5-99.5] (oral rinse)	N = 285, 224 symptomatic, 35 asymptomatic, & 26 unknown. RT-PCR NPS RM.	"…no difference in detection rate across samples types between symptomatic and asymptomatic participants."

Chau *Clin Infect Dis* 2020	**64** [NR]	NR	N = 11 asymptomatic. Data also reported in Table 1 by Khiabani *Am J Infect Control* 2021. NP-throat swabs with RT-PCR RM.	"Asymptomatic infection is common and can be detected by analysis of saliva."
Herrara *Intl J Infect Dis* 2021	**78.1** [NR] 80.3 [73.6-86.0] if inconclusive results were eliminated.	**98.8** [NR] 99.5 [99.0-99.7] if inconclusive results were eliminated.	N = 2,107. Asymptomatic healthcare and office workers in Mexico City. NPS Rt-PCR RM.	"…saliva is as effective as NP swabs for the identification of SARS-CoV-2-infected asymptomatic patients."
Yokota *Clin Infect Dis* 2021	**87.5** [NR] (Calculated from Table 2 combined raw data.)	**99.8** [NR] (Calculated from Table 2 combined data.)	N = 1,924. Asymptomatic contact tracing & airport. RT-PCR NPS RM.	"…saliva specimens had high sensitivity and specificity."
Kerneis *Eur J Clin Micro Infect Dis* 2021	**88** [69-97] (1) **92** [74-99] (2)	**95** [94-97] (1) **97** [95-98] (2)	N = 812 asymptomatic using MGI-2 saliva procedure (1); & N = 848, Roche reference method (2). Asymptomatic data in Table 3.	"Diagnostic accuracy of…saliva NAAT is similar to NP NAAT, subject to compliance with protocols for saliva."
Vogels *Med (CelPress)* 2021	**89.5** [NR]	**99.9** [NR]	N = 3,779. Asymptomatic & presymptomatic basketball NBA players & staff. Quest BioReference AN/OP swab RM.	Commercial evaluation of SalivaDirect in healthy individuals.
Balaska *Diagnostics* 2021	**90** [94.6-99.6] (Calculated from collated screening data in Table 2.)	**100** [98.1-100] (Calculated from collated screening data in Table 2.)	N = 200. Screening of asymptomatic healthcare workers. Advanta Dx SARS-CoV-2 RT-PCR saliva-based assay evaluation study. NPS NeumoDx or Abbott RT-PCR RMs.	"Fluidigm Advanta Dx RT-PCR saliva-based assay may be a reliable diagnostic tool for… screening asymptomatic healthcare workers."
Rao *Med Virol* 2021	**95** [83.8-100] (Estimated by the authors using a Bayesian latent class model.)	**99.9** [98.9-100] (Estimated by the authors using a Bayesian latent class model.)	N = 562 asymptomatic subjects in a detention center (210) and airport quarantine (352) in Kuala Lumpur, Malaysia. LCM: "Positive results of either test specimen (NP + OP swab) or random saliva was assumed as a perfect gold standard. "	"Self-collected saliva provides accurate surveillance testing of a community." "…estimated sensitivity and specificity of random saliva were higher than NP + OP swabs…."

Statistics	**Median [N, Range]**	**Median [N, Range]**
	63.6 [19, 16.8-95]	**98.85 [14, 95-100]**
	Mean [SD], N	**Mean [SD], N**
	62.9 [26.6], 19	**98.4 [1.6], 14**

Abbreviations: Ag, antigen; CI, 95% confidence interval; LAMP, loop-mediated isothermal amplification; LCM, (Bayesian) latent class model; LDT, lab developed test; NAAT, nucleic acid amplification test; NP, nasopharyngeal; NPS, nasopharyngeal swab; NR, not reported; OP, oropharyngeal; RT-PCR, reverse transcription polymerase chain reaction; RAgT, rapid antigen test; RM, reference method; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; and WHO, World Health Organization.

Table S5. Fundamental Definitions, Derived Equations, Ratios/Rates, Recursive Formulas, Predictive Value Geometric Mean-squared, and Prevalence Boundary.

Eq. No.	Category and Equations	Dep. Var.	Indep. Var.
	Fundamental Definitions		
1	x = Sens = TP/(TP + FN)	x	TP, FN
2	y = Spec = TN/(TN + FP)	y	TN, FP
3	s = PPV = TP/(TP + FP)	s	TP, FP
4	t = NPV = TN/(TN + FN)	t	TN, FN
5	p = Prev = (TP + FN)/N	p	TP, FN, N
6	N = TP + FP + TN + FN	N	TP, FP, TN, FN
	Derived Equations		
7	PPV = [Sens•Prev]/[Sens•Prev + (1-Spec)(1-Prev)], or s = [xp]/[xp + (1-y)(1-p)] — symbolic version of the equation above	s	x, y, p
8	p = [s(y-1)]/[s(x + y - 1) - x]	p	x, y, s
9	x = [s(p-1)(y-1)]/[p(s-1)]	x	y, p, s
10	y = [sp(x-1) + s - px]/[s(1-p)]	y	x, p, s

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11	NPV = [Spec•(1-Prev)]/[Prev•(1–Sens) + Spec•(1–Prev)], or t = [y(1–p)]/[p(1–x) + y(1–p)]	t	x, y, p
12	p = [y(1-t)]/[t(1 - x - y) + y]	p	x, y, t
13	x = [pt + y(1-p)(t-1)]/[pt]	x	y, p, t
14	y = [pt(x-1)]/[t(1-p) – 1 +p]	y	x, p, t
	Ratios		
15	TP/FP = PPV/(1-PPV) = [Sens•Prev]/[(1-Spec)(1-Prev)], or [xp]/[(1-y)(1-p)]	TP/FP Ratio	x, y, p
16	FP/TP = (1-PPV)/PPV = [(1-y)(1-p)]/(xp)	FP/TP Ratio	x, y, p
17	FN/TN = (1-NPV)/NPV = [p(1-x)]/[y(1-p)]	FN/TN Ratio	x, y, p
	Rates		
18	R_{TP} = TP/(TP + FN) = x	R_{TP}	TP, FN
19	R_{FP} = FP/(TN + FP) = 1 – Spec = 1- y	R_{FP}	TN, FP
20	R_{FO} = FN/(TN + FN) = 1 – NPV = 1- t = [p(1-x)]/[p(1-x) + y(1-p)]	R_{FO}	x, y, p
21	R_{POS} = (TP + FP)/N	R_{POS}	TP, FP, N
	Special Cases		
	Recursive formulae for PPV (s_{i+1}) and NPV (t_{i+1})		
22a	s_{i+1} = [xp_i]/[xp_i + (1-y)(1-p_i)], where the index, i = 1, 2, 3…	s_{i+1}	x, y, p_i
22b	t_{i+1} = [y(1-p_i)]/[p_i(1-x) + y(1-p_i)]	t_{i+1}	x, y, p_i
	Prevalence when sensitivity is 100% (i.e., FN = 0)		
23	Prev = 1 – [(1 – N_+/N)/Spec], or p = 1- [(1-$POS_{\%}$)/y]	p	$POS_{\%}$, y
	PPV when sensitivity is 100%		
24	PPV = [Prev]/[Prev + (1-Spec)•(1-Prev)], or s = [p]/[p + (1-y)(1-p)]	s	y, p
	Predictive value geometric mean-squared (range 0 to 1)		
25	PV GM^2 = PPV•NPV = s•t = {[xp]/[xp + (1-y)(1-p)]}• {[y(1–p)]/[p(1–x) + y(1–p)]}	PV GM^2	x, y, p
	Prevalence boundary for a given R_{FO}		
26	PB = {y(1-t)/([(1-x) - (1-t)(1-x-y)]} = [yR_{FO}]/[(1-x) -R_{FO}(1-x-y)]	PB	x, t, R_{FO}
	Sensitivity when given specificity, R_{FO}, and PB		
27a	x = [PB-R_{FO}(y+PB-y•PB)]/[PB(1-R_{FO})]	x	y, R_{FO}, PB
	Sensitivity, given R_{FO} and PB, when specificity (y) is 100%		
27b	x = (PB-R_{FO})/[PB(1-R_{FO})]	x	R_{FO}, PB
	Accuracy (not recommended – see note)		
…	A = (TP + TN)/N = Sens•Prev(dz) + Spec•Prev(no dz)	A	TP, TN, N

Abbreviations

Dep. Var., dependent variable; Indep. Var., independent variable(s)

Eq., equation

i, an index from 1 to 3 or more — the number of testing events

N, total number of people tested

N_+, number of positives (TP + FP) in the tested population

N-, number of negatives (TN + FN) in the tested population

PB, prevalence boundary

$POS_{\%}$, (N_+/N), percent positive of the total number tested (same as R_{POS})

$NEG_{\%}$, (N-/N), percent negative of total number tested

Prev, prevalence (p); Prev(dz), same as p; Prev(no dz), prevalence of no disease

PPV, positive predictive value (s); NPV, negative predictive value (t)

PV GM^2, square of the geometric mean of positive and negative predictive values, (PPV•NPV), expressed as a fraction from 0 to 1

p_{i+1}, p_i, indexed partition prevalence in the recursive formula for PPV and NPV

R_{FO}, the rate of false omissions

R_{FP}, false positive rate, aka false positive alarm — probability that a false alarm will be raised or that a false result will be reported when the true value is negative

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R_{POS}, positivity rate

R_{TP}, true positive rate, the same as sensitivity

Sens, sensitivity (x); Spec, specificity (y)

TP, true positive; FP, false positive; TN, true negative; FN, false negative

Notes

Sens, Spec, PPV, NPV, and Prev are expressed as percentages from 1 to 100%, or as decimal fractions from 0 to 1 by dividing by 100%.

PV GM^2 was created for visual logistics comparisons of performance curves of diagnostic tests, not for point comparisons.

If the denominators of derived equations become indeterminate, then revert to the fundamental definitions, Eqs. 1-6.

The use of the formula for accuracy is not recommended, because of duplicity of values with complementary changes in sensitivity and specificity.

Table S6. Antigen Tests with FDA Emergency Use Authorization Ranked by Positive Percent Agreement.

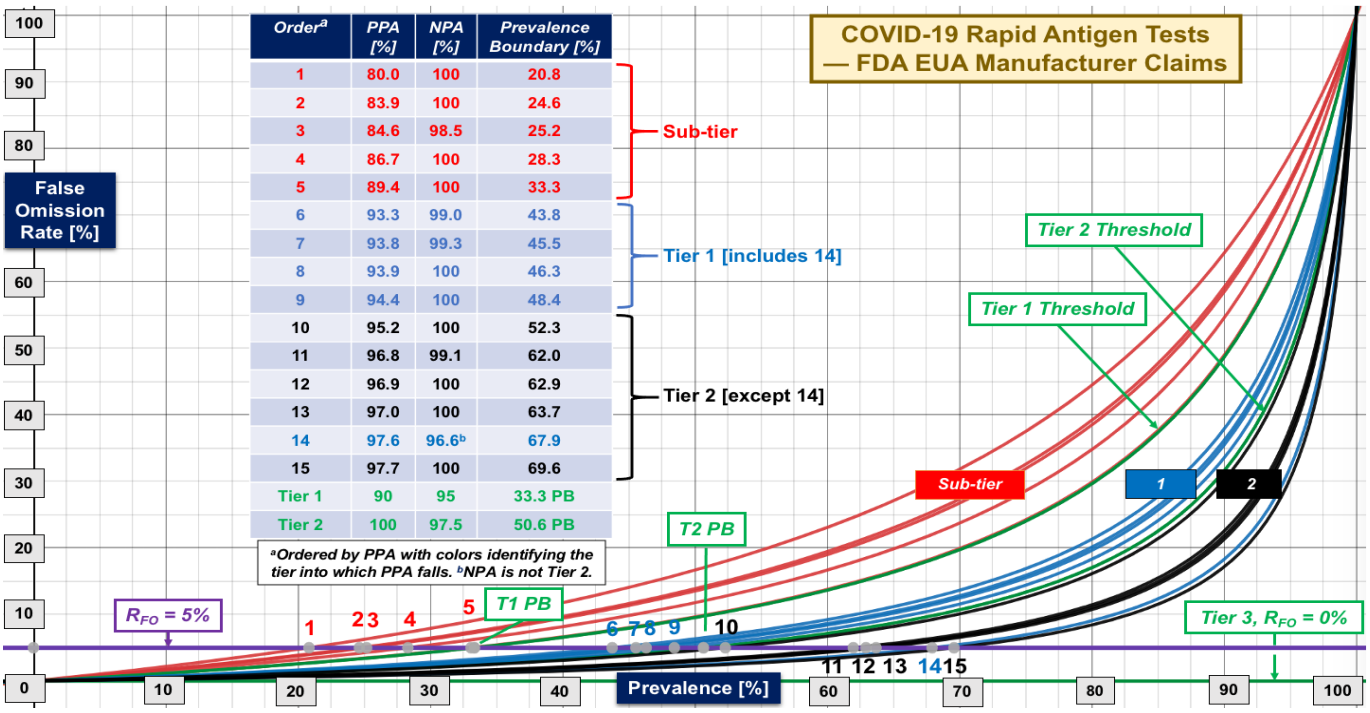
Figure Numbers	Tier, Sample Size	Company, EUA Latest Date [Earliest Date], Product Name	PPA (%) [CI]	NPA (%) [CI]	Assay Method, Specimen Type, Collection, Interval for Procuring Specimen, Protocol [plus notes]
	Sub-Tier				
1, 2, 4	Sub-tier N = 105	Ortho Clinical Diagnostics 3/16/21 [1/11/21] VITROS Reagent Pack	**80.0** [56.6-88.5] *[Lowest PPA]*	**100.0** [95.2-100.0]	Chemiluminescence immunoassay, instrument read; nasopharyngeal swab; healthcare provider; 7 days. [Second FDA EUA study available with PPA 86.2%, NPA 97.7%.]
1, 2, 4	Sub-tier N = 226	Becton Dickinson 4/14/21 [7/2/20] Veritor System	**83.9** [67-93]	**100** [98-100]	Chromatographic digital immunoassay, instrument read, serial screening; nasal swab; healthcare provider; 5 days.
1, 2, 4, 8 [Curve B performance in Fig. 8, without recursion] *See CI analysis*	Sub-tier N = 460	Abbott 4/20/21 [8/26/20] BinaxNow COVID-19 Ag Card	**84.6** [76.8-90.6] (PPA of 97.1% in N=53 small set initially claimed.)	**98.5** [96.6-99.5]	Lateral flow, visual read; anterior nasal swab; healthcare provider; 7 days. Test once with guidance using NAVICA app for return flights [United Airlines]. Same N, PPA, & NPA as self test in Figure 8, curve B (recursive B* not applicable). Note temperature limits of 2-30° C (35.6-86° F) when travelling.
1, 2, 4	Sub-tier N = 502	InBios 5/6/21 SCoV-2 Ag Detect Rapid Test	**86.67** [73.8—93.74]	**100** [98.53-100.00]	Lateral flow, visual read, serial screening; anterior nasal swab; healthcare provider; 5 days if symptoms. If none, test twice, 2-3 days apart, 24-48 hrs.
1, 2, 4	Sub-tier N = 89	Qorvo Biotechnologies 4/13/21 Omnia SARS-CoV-2 Antigen	**89.47** [78.88-95.09]	**100** [89.28-100]	Bulk acoustic wave biosensor, instrument read, cartridges; anterior nasal swab; healthcare provider; 6 days.
	Tier 1				
3, 4	Tier 1	Celltrion 5/11/21 [4/16/21] DiaTrust COVID-19 Ag Rapid Test	**93.33** [78.7-98.2]	**99.03** [94.7-99.8]	Lateral flow, visual read, serial screening; nasopharyngeal swab; healthcare provider; 7 days if symptoms. If none, test twice, 2-3 days, 24-49 hrs.
3, 4	Sub-tier N = 180	Access Bio 4/15/21 [10/8/20] CareStart COVID-19 ANTIGEN	**93.75** [79.85-98.27]	**99.32** [96.27-99.88]	Lateral flow, visual read; nasopharyngeal swab; healthcare provider; 5 days. [PPA 87.18% performance inferior (NPA 100.00%) if anterior nasal swab. See FDA EUA.]
3, 4 *Multiplex*	Tier 1 N = 125	Princeton BioMediTech 2/4/21 Status COVID-19/Flu	**93.9** [83.5-97.9]	**100** [95.2-100.0]	Lateral flow, visual read, multi-analyte; nasopharyngeal swab; healthcare provider; 5 days. [For Influenza A/B metrics, see FDA EUA.]

3, 4	Tier 1 N = 105	Celltrion USA 10/23/2020 Sampinute COVID Ag MIA	**94.4** [80.0-99.0]	**100.0** [88.0-100.0]	Magnetic force-assisted electrochemical sandwich immunoassay; nasopharyngeal swab; healthcare provider; 5 days.
	Tier 2				
3, 4 *Multiplex*	Tier 2 N = 164	Quidel 10/2/20 Sofia 2 Flu + SARS Ag FIA	**95.2** SARS -Cov-2 [84.2-98.7]	**100.0** SARS-Cov-2 [96.9-100.0]	Lateral flow, fluorescence, multi-analyte, instrument read; nasopharyngeal and nasal swabs; healthcare provider; 5 days. [For Influenza A/B metrics, please see FDA EUAs.]
Not plotted—see the other two Quidel tests.	Tier 2 N = 209	Quidel 4/1/21 [5/8/20] Sofia SARS Ag IFA	**96.7** [83.3-99.4]	**100.0** [97.9-100.0]	Lateral low, fluorescence, instrument read on Sofia of Sofia 2 only; nasopharyngeal and nasal swabs; healthcare provider; 5 days if symptoms. If none, test twice, 2-3 days apart, 24-48 hrs.
3, 4	Tier 2 N = 138	Quidel 12/22/20 [12/18/20] Quickview SARS Ag Test	**96.8** [83.8-99.4]	**99.1** 94.9-99.8]	Lateral flow, visual read; anterior nares swab specimen; healthcare provider; 5 days. [Data for fresh specimens.]
3, 4	Tier 2 N = 166	Luminostics 12/7/20 Clip COVID Rapid Ag Test	**96.9** [83.8-99.9]	**100** [97.3-100]	Lateral flow immunoluminescent assay, instrument read; healthcare provider; anterior nasal swab; 5 days
3, 4	Tier 2 N = 141	DiaSorin 3/26/21 LIAISON SARS-CoV-2 Ag	**97.0** [84.7-99.5]	**100** [96.6-100]	Chemiluminescence immunoassay, LIAISON XL analyzer read; nasopharyngeal and direct nasal swab; healthcare provider; 10 days. [Wilson CI]
3, 4	Tier 1* N = 257	LumiraDx UK 4/15/21 [8/18/20] SARS-CoV-2 Ag Test	**97.6** [91.6-99.3]	**96.6*** [92.7-98.4]	Microfluidic immunofluorescence assay, instrument read; nasal swab; healthcare provider; 12 days. [95% Wilson CI]
3, 4	Tier 2 N = 126	Quanterix 1/5/21 Simoa SARS-CoV-2 N Protein Ag Test	**97.7** [92.03-99.72] *[Best PPA]*	**100** [90.75-100.0]	Paramagnetic microbead-based immunoassay; nasopharyngeal swab; healthcare provider; 14 days.

Abbreviations: Ag, antigen; CI, 95% confidence interval with upper and lower bounds in percent; CLIA, Clinical Laboratory Improvement Act; EUA, Emergency Use Authorization; FDA, Food and Drug Administration; FIA/IFA, immunofluorescence assay; MIA, magnetic force-assisted electrochemical sandwich immunoassay; NPA, negative percent agreement; PPA, positive percent agreement; SARS-CoV-2, severe acute re3spiratory syndrome-Coronavirus-2; and UK, United Kingdom.

Notes: a) Tier sensitivity/specificity (%) comprise: 1) 90/95; 2) 95/97.5; and 3) 100/≥99. b) *One exception in the ranking by PPA—the NPA is not Tier 2. c) Boldface PPA and NPA are used for computations underlying performance plots. d) Data are reported exactly as they appear in FDA EUA Instructions for Users.

Supplement Figure



Order[a]	PPA [%]	NPA [%]	Prevalence Boundary [%]
1	80.0	100	20.8
2	83.9	100	24.6
3	84.6	98.5	25.2
4	86.7	100	28.3
5	89.4	100	33.3
6	93.3	99.0	43.8
7	93.8	99.3	45.5
8	93.9	100	46.3
9	94.4	100	48.4
10	95.2	100	52.3
11	96.8	99.1	62.0
12	96.9	100	62.9
13	97.0	100	63.7
14	97.6	96.6[b]	67.9
15	97.7	100	69.6
Tier 1	90	95	33.3 PB
Tier 2	100	97.5	50.6 PB

Figure S1. Rate of False Omissions for FDA EUA COVID-19 Rapid Antigen Tests

The purpose of this figure is to illustrate that manufacturer claims can attain Tier 2 performance. The figure integrates R_{FO} curves for the first 15 RAgTs that received FDA EUAs (see **Table S6**) listed in in order of ascending PPA. If prevalence exceeds the labeled boundaries, then 1 in 20 patients risk unknowingly spreading contagion. The three tiers were designed to allow progressive bracketing of false omission rates. Six of the 15 claims have prevalence boundaries above Tier 2 at 50.6%. These claims strengthen the case for using Tier 2 as an attainable and desirable performance standard for COVID-19 RAgTs. Abbreviations: NPA, negative percent agreement; PB, prevalence boundary; PPA, positive percent agreement; RAgT, rapid antigen test; and R_{FO}, false omission rate.