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DIAGNOSTIC STRATEGIES FOR ENDEMIC CORONAVIRUS DISEASE 2019 (COVID-19): RAPID ANTIGEN TESTS, REPEAT TESTING, AND PREVALENCE BOUNDARIES

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RUNNING TITLE: Diagnostic Strategy for Endemic COVID-19
ABSTRACT

CONTEXT. – Coronavirus disease 2019 (COVID-19) rapid antigen tests generate intrinsically fast, inherently spatial, and immediately actionable results. They quickly confirm COVID-19, but weakly rule out infection. Test performance depends on prevalence and testing protocol. Both affect predictive values.

OBJECTIVES. – To use original mathematics and visual logistics for interpreting COVID-19 rapid antigen test performance patterns, gauge the influence of prevalence, and evaluate repeated testing.

DESIGN. – Mathematica and open access software helped graph relationships, perform recursive computations, and compare performance patterns. PubMed retrieved articles addressing endemic COVID-19.

RESULTS. – Tiered sensitivity/specificity comprise: T1) 90%/95%; T2) 95%/97.5%; and T3) 100%/≥99%, respectively. Performance of self- and home antigen tests with Food and Drug Administration Emergency Use Authorization peaks in low prevalence. Fall-off in performance appears with increasing prevalence because suboptimal sensitivity creates false negatives. The rate of false omissions limits clinical use because of prevalence boundaries based on tolerance for risk. Mathematical analysis supports testing twice to improve predictive values and extend prevalence boundaries nearly to levels of herd immunity.

CONCLUSIONS. – COVID-19 is quickly becoming endemic. Suboptimal sensitivity of rapid antigen tests limits performance in high prevalence. Risk of contagion in packed spaces (e.g., airplanes) might be avoided with dual testing 36 hours apart, allowing time for viral load to increase. Awareness of community prevalence and proof of improved performance with repeated testing will help manage COVID-19 risk, while meeting rapid decision-making needs for highly contagious and new variants (e.g., Delta). New COVID-19 variants call for high quality, low cost, readily accessible, fast, user friendly, and ubiquitous point-of-care testing.
INTRODUCTION

Goals

The goals of this research are to apply mathematical relationships and visual logistics to reveal patterns of coronavirus disease 19 (COVID-19) rapid antigen test (RAgT) performance and to facilitate understanding of predictive values, false omission rates, prevalence boundaries, risk tolerance, and repeat (recursive) testing.

Context

COVID-19 variants, such as the India Delta (B.1.617.2), for which Pfizer (BNT162b2) and Johnson & Johnson vaccines are not as effective compared to effectiveness against the wildtype severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) first detected in Wuhan, China, crop up rapidly and frequently, propelling dynamic surges in contagion that demand early and rapid detection.

In the United States, Delta infections constitute 98.9% of new sequenced cases, according to a Centers for Disease Control and Prevention (CDC) Nowcast projection September 4, 2021. Delta binds strongly to lung cell receptors and must be treated with monoclonal antibodies early on. The virus that caused the first U.S. COVID-19 cases in January 2020 is no longer detected among variants circulating in the country.

About 176.7 million people, or 53.2% of the total U.S. population, have been fully vaccinated as of September 7, 2021. Less forgiving and 8-10 times more transmissible, Delta is outrunning other variants and now accounts for nearly all hospitalizations and deaths in the unvaccinated. This pandemic of the unvaccinated is accelerating as new waves spread widely. The speed of new contagion warrants rapid testing. On September 4, 2021, 536.9 million tests were reported, 41.7 million were positive, and the 7-day positivity rate was 9.77%.^3
The CDC recommends that, “…fully vaccinated people who have come in close contact with someone with suspected or confirmed COVID-19 to be tested three to five days after exposure, and to wear a mask in public indoor settings for fourteen days or until they receive a negative test result.”

As Delta COVID-19 plays out against the background spectra of testing access, vaccination rates, age groups, and community prevalence worldwide, it is placing vulnerable people, such as children, at high risk in the second half of 2021 and early 2022, when a challenging Influenza A/B season is expected. In the United States alone, pediatric cases have skyrocketed recently. Nearly 500 children have died of COVID-19 complications.

Key factors going forward comprise testing frequency, vaccination rates, variant trends, and importantly, prevailing prevalence. This research investigates the benefits of RAgTs using repeat testing, which potentially can make up for low sensitivity and enhance SARS-CoV-2 detection. Access, speed, convenience, and the low cost of RAgT fulfill important needs in the unfolding era of Delta, which is making COVID-19 a dreaded endemic global disease.

**Objectives**

The objectives are a) to use visual logistics to interpret COVID-19 RAgT performance patterns, b) to calibrate performance relative to three sensitivity and specificity tiers, c) to assess performance for home use and self-testing with a repeat (recursive) testing protocol, d) to understand the significance of false omission rates and prevalence boundaries, and as highly infectious variants become entrenched worldwide, e) to recommend strategies for the use of RAgTs in risk reduction and management.

**METHODS**

**Overview**
Table 1 presents the mathematical design criteria for the three tiers, which are intended to systematically harmonize Bayesian post hoc performance of COVID-19 diagnostics. The design criteria include simultaneously the performance level, sensitivity, specificity, target prevalence boundary, and false omission rate, $R_{FO}$, which reflects risk for missed diagnosis at user-defined tolerance levels of 5%, 10%, and 20%. Please refer to open access papers by Kost in the *Archives of Pathology & Laboratory Medicine* for descriptions of mathematical methods, visual logistics, computational design and software, and human ethics.

**Rapid Antigen Tests**

Antigen tests considered for inclusion here received Food and Drug Administration (FDA) Emergency Use Authorization (EUA) status in 2020 continuing through May 2021 when the CDC allowed vaccinated people to remove masks in public, creating controversy and broader demand for rapid detection of SARS-CoV-2. Then subsequently in July 2021, the CDC reversed its masks off decision, and recommended more testing when Delta became a dominant threat.

It is not the intent to analyze all FDA EUA or Conformité Européenne (CE) Mark RAgTs, but instead to select popular ones for self- and home testing (Table 2), and then graph performance and illustrate the effects of repeat (recursive) testing as a continuous function of prevalence from 0 to 100%, the first such report.

**Mathematical Foundations**

**Equation Set.** — The Supplemental Digital Content (the supplemental digital content can be found at the end of article) provides an updated equation set. Eqs. 7 through 14 are used to calculate continuous positive predictive value (PPV) and negative predictive value (NPV), plus associated parameters through rearrangement of variables.
Recursive formulas for PPV [Eq. 22a] and NPV [Eq. 22b] allow calculation of predictive values for repeat testing, which ideally should be performed with different test designs, so-called orthogonal testing. When testing only twice with the same assay, a single equation can be derived to simplify recursive graphing for prevalence 0 to 100%.

**Transformation of Pre-test Probability (Prevalence) to Post-test Probability.** — A proof in Kost with intermediate steps detailed, demonstrates how sensitivity and specificity modulate the pre-test probability of COVID-19 to generate post-test probability for a negative test, the false omission rate, or $R_{FO}$ [Eq. 20]. The proof is summarized here, where TP is true positive; FP, false positive; TN, true negative; and FN, false negative.

We use this transformation: Pre-test probability $\rightarrow$ Pre-test odds $\rightarrow$ Likelihood ratio $\rightarrow$ Post-test odds $\rightarrow$ Post-test probability. Pre-test odds = [Pre-test probability]/[1 – (Pre-test probability)]

$= p/(1 - p)$ where $p$ is the prevalence. Therefore, $p/(1 - p) = (TP + FN)/(TN + FP)$, which is equivalent to the ratio, $[+ COVID-19]:[- COVID-19]$.

Multiplying the pre-test odds by the likelihood ratio for a negative test generates the post-test odds of a negative test for COVID-19. For a negative test, the likelihood ratio is $(1 - x)/y = [FN/TN][(TN + FP)/(TP + FN)]$, where $x$ is sensitivity and $y$, specificity. Next, we calculate $[p/(1-p)] \cdot [(1-x)/y] = FN/TN$.

Since the post-test probability is $[Post-test odds]/[1 + (Post-test odds)]$, the post-test probability is $[FN/(TN + FN)]$. However, $FN/(TN + FN)$ is the false omission rate. Therefore, the post-test probability = $R_{FO}$, but $R_{FO} = 1 - NPV$, so the post-test probability is 1 - NPV.

**Prevalence Boundary.** — The prevalence boundary is defined as the prevalence at which $R_{FO}$ exceeds a specified risk tolerance, such as 5% (1 in 20 diagnoses missed), 10% (1 in 10 missed), or 20% (1 in 5 missed).
The prevalence boundary is calculated using Eq. 26 and apparent where the R_{FO} curve intersects the horizontal line demarcating risk tolerance. Precedent for R_{FO} = 5% is found in a report of reverse-transcriptase polymerase chain reaction (RT-PCR) step-wise testing for ruling out COVID-19 devised by Raschke et al.\textsuperscript{10} and published in the Archives.

RESULTS

Figure 1 presents the logic of repeat (recursive) testing. First round testing uses community prevalence (left) to generate the post hoc Bayesian viewpoint of PPV and NPV. Then, for the second round the partitioned new prevalences are the PPV for the COVID-19 TP set and 1- NPV for the COVID-19 FN set, as shown on the right and derived at the bottom of the figure, respectively. For the populations as a whole, those who have COVID-19 are the sum of TPs and FNs. Those without the disease are the sum of TNs and FPs.

Figure 2 applies these concepts to the three performance tiers designed based on the performance criteria in Table 1. This figure plots PPV and NPV (green) as functions of prevalence and the corresponding false omission rates (black) for each tier. With a risk tolerance of 5%, the prevalence boundary for Tier 1 is 33.3% and for Tier 2, 50.6%. Tier 3 has no prevalence boundary because sensitivity is 100% and hence, there are no false negatives. That is, NPV =1, and thus, R_{FO} = 1 – NPV = 0.

Figure 3 illustrates the effects of repeat testing on two RAgTs with FDA EUA status (the top two listed in Table 2). The negative percent agreement (NPA) of 99.2\% underlying curve A (purple) and NPA of 98.5\% for curve B (blue) found in FDA EUA Information for Users (IFU) documents reflect high specificity that pushes PPV performance into upper Tier 2 and 3 levels where it peaks in low prevalence.
Theoretical analysis shows that repeat testing improves performance, such that the PPV curves for A* and B* appear almost perfect. However, performance based on repeat testing has not been proven in clinical trials. Additionally, the manufacturers include disclaimers for repeat testing in FDA EUA IFUs. Positive percent agreement (PPA) and NPA evaluation data supporting repeat testing were not included in FDA EUAs.

Figure 4 illustrates the NPV, false omission rates ($R_{FO}$), and prevalence boundaries (PB) for the same two tests illustrated in Figure 3 and listed in the upper section of Table 2. Penalties for poor sensitivity, documented in FDA EUA IFUs as PPA of 83.5% for A and 84.6% for B, come into play. The PPAs (analogue of sensitivity) for both tests are substantially below Tier 1, i.e., “subtier.” That causes test performance to fall off quickly and significantly as prevalence increases.

However, repeat testing pushes the prevalence boundary forward from 24.0% to 65.6% for A*, and from 25.2% to 68.3% for B*, nearly reaching levels of community immunity (herd immunity), which starts at about 70%. However, for the Delta variant, the prevalence boundary may have to reach as high as 85% or more (if attainable). Repeat test performance is indicated by the second box on the right in Figure 4. Rapid antigen tests achieving Tier 2 performance through recursive testing will have high impact in the ranges of prevalence where risk avoidance and management are needed the most.

From a clinical standpoint, testing once with low sensitivity RAgTs will generate high rates of false negatives as prevalence increases. With one test, the $R_{FO}$ becomes unacceptably risky, because missed diagnoses may lead to stealth spread of SARS-CoV-2. To maintain a $R_{FO}$ of 5% (horizontal red line toward the bottom of Figure 4), that is, to avoid missing more than 1 in 20 diagnoses of SARS-CoV-2 infection, repeat testing “jumps” performance over the Tier 1
and 2 prevalence boundaries of 33.3% and 50.6%, respectively, to make the RAgTs safer to use, but not as safe as Tier 3, for which NPV is 100% and $R_{FO}$ is zero.

**DISCUSSION**

**Guidelines**

In May 2021, the Infectious Disease Society of America (IDSA) issued guidelines\textsuperscript{11,12} for RAgTs as follows: a) for symptomatic individuals suspected of having COVID-19, use standard nucleic acid amplification testing (NAAT); b) for asymptomatic individuals with risk for exposure to SARS-CoV-2 infection, use a single standard NAAT; c) for asymptomatic individuals with risk for exposure, use a single standard NAAT rather than two consecutive RAgTs; d) in asymptomatic individuals with risk for exposure, the IDSA panel is neither for or against using a *single* RAgT over no testing; e) in asymptomatic individuals with risk for exposure, the IDSA panel is neither for or against using a *repeat* RAgT over no testing.

These IDSA guidelines have merit. However, future editions must be based on detailed analysis of prevalence in relation to performance metrics, both FDA actions and clinical evaluations. The prevalence-based performance mappings in Figures 3 and 4 extend the IDSA guidelines to help create practical strategies for RAgTs. The IDSA panel should recommend minimum sensitivity and specificity metrics for RAgTs, such as Tier 2. It should facilitate clinical evidence for or against repeat RAgTs, provide a logic model for improving the quality of RAgTs, and create a roadmap with instructions for the FDA, manufacturers, and clinical investigators to follow.

**Repetition**

False omission rates and prevalence boundaries *must be* taken into account, especially when the sensitivity of RAgTs falls below 90% (i.e., subtier), because missed diagnoses increase
exponentially as prevalence increases. Transformation of pre-test to post-test probability of COVID-19 allows computation of the false omission rate, $R_{FO}$, and determination of the prevalence boundary, $PB$, which creates significant limitation to the clinical use of an antigen test for decision making.

*Figures 3 and 4* illustrate the theoretical merits of repeat testing. Repetition of testing takes advantage of the Bayesian transformation to improve post hoc knowledge of the presence or absence of COVID-19. In other words, it improves the yield of the test at the cost of duplicating time, effort, and reagents. Manufacturers who include disclaimers for repeat testing in FDA EUA IFU documents should provide clinical proof of the effectiveness and efficacy of the dual testing approach.

The theoretically derived hypothesis of improved performance when testing twice needs proof by conducting large multicenter clinical evaluations with diversified populations, including children. Such reports could not be found in the literature. No clinical research funds were allocated or recommended for RAgT clinical evaluations in the President’s national strategy for COVID-19.13 Unfortunately, there is no way of singling out infectious patients of any age who have false negative RAgT results without repeat or additional testing (e.g., molecular diagnostics).

**Quality**

We do not know why the PPA and NPA of assays documented in FDA EUAs have not progressively improved over the past year, as inspection of recent FDA EUAs shows.9 However, the FDA has not required improvement. Liberal FDA authorization seems to have diminished competition to produce high performance tests. Uncertainty compounds the poor performance of low sensitivity RAgTs over the range of prevalence.7,8 Please see Kost8 for the mathematics and
visual logistics of uncertainty. Repeat testing can compensate for poor performance but can only partially alleviate uncertainty in test results.

One wonders what will become of subtier and Tier 1 tests in a competitive market following the end of the “EUA era,” if it actually ends. A Clinical Laboratory and Standards Institute (CLSI) whitepaper\textsuperscript{14} addressed this EUA lifecycle issue but did not adequately analyze poor performers. CLSI emphasized quality control and like others,\textsuperscript{15} training, which underscores the importance of clear user instructions in RAgT kits. However, ultimately the FDA needs to tighten authorization criteria and unless improved substantially to Tier 2 or higher quality, retire EUAs for subtier and probably also marginal RAgTs in Tier 1.

**Endemic COVID-19**

There is unequivocal need for point-of-care testing of highly infectious diseases.\textsuperscript{5,16-23} Public health educators should teach point-of-care testing.\textsuperscript{24,25} Public health investment in RAgTs for COVID-19 is warranted to reduce human loss. In 2020 as a result of the pandemic, life expectancy in the United States dropped 1.87 years, 8.5 times the average decrease in peer countries, and deceases in life expectancy in Hispanic and non-Hispanic Black people were about 2-3 times greater than in the non-Hispanic White population.\textsuperscript{26}

With ubiquitous access to testing comes responsibility on the part of academics, public health institutions, professional societies, governments, industry, and global organizations to promote high quality testing, appropriate use, user training, and periodic public reporting of community prevalence. Prevalence is underestimated because of incomplete data and undiagnosed cases.\textsuperscript{27} The CDC estimates that by end-May 2021, 120.2 million Americans had been infected.\textsuperscript{28} That would be 120.2/332.7 million, or 36.1\% of the United States population.
Viral infections that behave like COVID-19 eventually become endemic. Endemic means regularly found among a particular people or geospatially in a certain area, locality, or region. So far, the topic of endemic COVID-19 has received limited clinical and academic attention, probably because of insufficient testing as variants race ahead undetected. Annas et al.\textsuperscript{29} showed the value of vaccination and isolation for forestalling endemic COVID-19 in a limited-resource setting. Lazizi et al.\textsuperscript{30} pointed to safeguards that allow resumption of elective surgery, while Zaman et al.\textsuperscript{31} highlighted the importance of diagnostic testing during endemic COVID-19.

Lum et al.\textsuperscript{32} emphasized vigilance to detect endemic COVD-19 and ramp up for surges. McGuinness et al.\textsuperscript{33} noted the importance of prevalence. Patterson et al.\textsuperscript{34} recommended that “policymakers use lessons (learned) … to develop appropriate risk assessments and control plans for now-endemic COVID-19, and for future pandemics.” Clearly, optimal diagnostic strategies need to be integral to risk assessments and control plans. Strategy-based policy will be valuable in the race for survival, especially in limited-resource settings where Delta is changing the risk landscape.

**Empowerment**

People in the United States can purchase COVID-19 RAgTs online and in neighborhood stores, although supplies are temporally depleted. **Figure 5** portrays the accessibility, speed, convenience, and simple process steps of a RAgT. Instructions in English and Spanish are user friendly. From purchasing the test kit, which was available on the shelf at a local pharmacy and then biking home, until observing the first negative result was 30 minutes. A second test is recommended three days (at least 36 hours) following an initial negative result. If the first result is positive, then immediate medical evaluation and isolation are in order.
Point-of-care testing is empowering individuals to take the steps necessary to care for themselves in the face of burgeoning populations, diminishing resources, infectious outbreaks, limited hospital access, packed emergency rooms, depleted oxygen supplies, and endemic Delta COVID-19. People purchasing test kits with their own funds for their own purposes should receive disclosure of performance metrics, ideally derived from large and diverse multicenter studies and presented as easily interpretable visual logistics.

In social settings, public gatherings, homes, schools, workplaces, factories, convalescent care, prisons, education, sports events, travel, airports, rural regions, and limited-resource settings abroad, RAgTs are easing the difficulty of transitioning risk avoidance to risk management. This is especially important in limited-resource settings where many people live hand-to-mouth and cannot afford extended lockdowns, expensive molecular diagnostics, long delays in results, and loss of employment, not to mention more than one month in quarantine if tested positive.35

**CONCLUSIONS AND DIAGNOSTIC STRATEGIES**

**Standardizing Performance**

Weaknesses in COVID-19 RAgT 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. PPA and NPA data originate from manufacturers, who typically have conducted limited evaluations. Well populated multicenter studies with diverse population are needed to establish performance in clinical practice.

Every step over a prevalence boundary magnifies chances of missing a diagnosis of SARS-CoV-2 infection (see Figure 4). Tier 3, with its 100% sensitivity, could eliminate false
omissions and prevalence boundaries. However, Tier 3 appears out of reach for current RAgT technologies. Therefore, repeat testing offers a solution that improves performance substantially and advances prevalence boundaries to levels that are practical, even approaching herd immunity.

**Self-testing Twice**

Repeat (recursive) antigen testing is supported by theoretical analysis (see Figure 3 & 4) but lacks clinical proof. Repeat testing after thirty-six hours allows time for viral incubation and an increase in viral load that potentially diminishes false negatives in infected persons. High Delta viral loads can be expected to improve RAgT performance. Clinical evidence of correlation with viral load would support the efficacy of repeat testing and help justify use of RAgTs.

If intrinsic (Tier 2 sensitivity) and extrinsic (repeat testing) enhancements are incorporated, higher performance will garner benefits. Communities could avail themselves of self-testing and home kits to detect COVID-19 quickly. Dual testing reagents, swabs for sample collection, a timed assay development interval, and a thirty-six hour repeat testing protocol are included in some commercial test kits (see Figure 5).

A major U.S. airline is promoting RAgT kits that can be carried in luggage, and then before returning from international travel, used to credential the internet-guided, self-swabbing traveler who obtains a single favorable negative test result valid for boarding the flight home. Two negative results spaced thirty-six hours apart would be more convincing of lack of SARS-CoV-2 infection. Sequential self-testing protocols will empower people to be responsible for their own health and for the safety of others.

**Strategies for Endemic COVID-19**
COVID-19 is propelling expansion of point-of-care strategies worldwide. The White House national strategy for COVID-19 recommended rapid point-of-care antigen testing without qualification in regard to prevalence level or clinical validation that would reveal performance in community settings.

Table 3 presents multidimensional strategies for rapid antigen testing and importantly, also for improving its performance. This table is based on the synthesis of public health recommendations, peer-reviewed literature, external sources including industry, focus group surveys abroad, findings in this paper, and the views of the author and academic colleagues.

Point-of-care testing represents a valuable pandemic response with the striking advantage of accessibility that allows people to confirm SARS-CoV-2 infection at the earliest possible moment in their homes, workplaces, or gatherings. From home to hospital, ready access raises public expectations for controlling transmission, combatting Delta COVID-19, and forestalling future pandemics. We should prepare now.

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Table 1. Design Scheme for Performance Tiers with Layered 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: |
|------|-------------------|----------------|----------------|-----------------------------------------------|
| 1    | Low               | 90             | 95             | 5% 50% 70% [33.3] [51.4] [70.3]                 |
| 2    | Marginal          | 95             | 97.5           | 10% 70% 85% [50.6] [68.4] [83.0]                |
| 3    | High              | 100            | ≥99            | 20% No Boundary No Boundary No Boundary          |
Table 2. Antigen Tests for Non-Prescription Home and Self-test Use with FDA Emergency Use Authorization

| Figure Numbers, Curves, Color | Tier (without repetition), Sample Size | Company, EUA Latest Date LOA [Earliest Date LOA], Product Name | PPA (%) [CI] | NPA (%) [CI] | Assay Method, Specimen Type, Age, and Time Interval/Protocol for Specimen Collection [plus notes] |
|-----------------------------|--------------------------------------|---------------------------------------------------------------|--------------|--------------|---------------------------------------------------------------------------------------------------|
| **Sub-Tier**                |                                      |                                                               |              |              |                                                                                                  |
| 3 & 4                      | N = 350                              | Quidel Corp. 3/31/21 [3/21/21] Quickview At-Home OTC COVID-19 Test | **83.5** [74.9-89.6] | **99.2** [97.2-99.8] | Lateral flow, visual read, NCP Ag. Anterior nares swab specimen. ≥14 yrs. ≤6 days. OTC. Home testing, serial screening. [Also, for home use ≥8 yrs by prescription.] |
| 3 & 4                      | N = 460                              | Abbott Diagnostics 8/10/21 [3/31/21] BinaxNow COVID-19 Antigen Self Test | **84.6** [76.8-90.6] | **98.5** [96.6-99.5] | Lateral flow, visual read, NCP Ag. Anterior nasal (nares) swab. ≥15 yrs. Test 2 times, ≥36 hrs apart. OTC. Self-swab and self-test. Home testing. [PPA & NPA established from single test ≤7 days from symptom onset.] |
| **Tier 1**                 |                                      |                                                               |              |              |                                                                                                  |
| NA                         | N = 198                              | Ellume Ltd. COVID-19 Home Test 2/11/21 [12/15/20]               | **95** [82-99] | **97** [93-99] | Lateral flow, fluorescence, instrument read, NCP Ags. Mid-turbinate nasal swab, self-collected. ≥16 years or ≥2 yrs with adult assist. All-comer subjects. OTC. Home testing, screening. Smartphone assisted. [For a comparison of asymptomatic vs. symptomatic subjects, please see Fig. 8 in Kost, reference 2.] |
Abbreviations: Ag, antigen; 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); LOA, letter of authorization; NA, not applicable; NCP, nucleocapsid protein; NPA, negative percent agreement; OTC, over the counter; and PPA, positive percent agreement.

Notes: Tier sensitivity/specificity (%) comprise: 1) 90/95; 2) 95/97.5; and 3) 100/≥99. Data are reported exactly as they appear in FDA EUA Letter and Instructions for Users documents.
Table 3. Rapid Antigen Testing Strategies: A Standard of Care for Endemic COVID-19

| Objectives                      | Recommended guidelines                                                                 |
|---------------------------------|-----------------------------------------------------------------------------------------|
| Optimize Rapid Testing          | Predictive value performance patterns suggest Tier 2 (PPA 95%, NPA 97.5%) should become the minimum performance threshold for RAgTs. |
|                                 | Consider the current community prevalence and its impact on test results, especially in the high range of prevalence. |
|                                 | Self- and home test using a RAgT kit as soon as signs or symptoms arise and within the first 3 to 5 days for optimal detection of SARS-CoV-2. |
|                                 | When self- and home testing, repeat the test at 36 hours and follow the protocol specified by the manufacturer. Repeat testing will improve the performance of low and sub-tier tests. |
|                                 | Establish performance metrics (e.g., PPA, NPA, CI, and LOD) in diverse large multicenter populations with a full range of SARS-CoV-2 viral loads. Explicitly characterize the reference method (e.g., Ct brackets). |
|                                 | Harmonize preanalytical and assay methods. Do not compare to an inferior test. |
| Manage Risk, Therapy, and Burden | Decide on risk tolerance for COVID-19 false negatives (e.g., 5% or 10%). That is, establish the R_{FO}. If 5%, then 1 in 20 diagnoses will be missed. If 10%, then 1 in 10 diagnoses will be missed. |
|                                 | Beware the prevalence boundary beyond which risk exceeds the R_{FO}. Determine whether the specific RAgT used is compatible with the prevailing community prevalence and the level of risk tolerance. |
|                                 | Testing twice extends the prevalence boundary, which should not be crossed, and decreases risk. |
|                                 | If signs and symptoms are present and the RAgT is negative, find a PCR molecular diagnostic, test immediately with the higher sensitivity PCR assay, and seek medical attention if positive. |
|                                 | Use rapid testing to partition emergency room patients into those with and without COVID-19, accelerate monoclonal Ab therapy, and reduce the burden on intensive care units. |
|                                 | Identify Delta infection quickly to spare lives, including children, for whom Monday and... |
| **Thursday RAgTs** 36 hours apart when in school theoretically will be superior (pending clinical proof) to once per week saliva testing. | **Assure Access and Close Resilience Gaps**
Maintain access to widespread free community testing in order to quickly detect breakthrough infections, identify variant surges, and close gaps in community resilience.

Delta viral loads can be 1,000 times higher, which increases transmissibility up to 10-fold, but also improves the effectiveness of RAgTs for this variant.

Move mobile testing vans to communities most in need and make use of tests offered (e.g., RAgT, PCR, antibody, and multiplex COVID-19/Influenza A/B) during surges in positivity rates to close community resilience gaps.

Raise the bar for unvaccinated persons in social groups, the workplace, and gatherings by implementing the best selection of point-of-care approaches to confirm that there are no active infections with SARS-CoV-2 or its variants. |
| **Avoid Exposure, Vulnerability, and Shared Risk**
When RAgT results are negative in the presence of COVID-19 symptoms and signs, rapid response multiplex molecular diagnostics will help clarify the differential diagnosis, whether quarantine or isolation is needed, and the treatment plan.

If an event, especially those indoors, is highly critical or involves potential exposure of numerous persons, then use a RAgT kit with repeat testing or a PCR molecular diagnostic within 72 hours of the event.

Test quickly with a RAgT or rapid response PCR assay upon presentation to the emergency room, pre-operative screening, admission to intensive care, or other shared facilities to protect medical staff and vulnerable patients. Delays incur costs. Speed creates value. |
| **Perform, Teach, Pray, and Play**
When in unique settings, such as musicians performing, teachers teaching, or worshipers praying, screen temperatures, and deploy sequential RAgTs before engaging activities.

Implement frequent testing in schools and summer camps along with required masks and hand-washing during the day, plus temperature checks each morning, before assemblies, and prior to competitive sports.

If exposed to variants, test frequently. For example, require members of large orchestras or other performing groups to self- or home testing before rehearsals and performances to protect themselves and audiences. |
| **Travel Safely**
Recognize that international airline travel may require a negative PCR molecular assay or RAgT |
result within 72 hours of departure and before return or travel to the United States.

Purchase packs of RAgT kits before departure, then before returning to the United States, follow airline consultant instructions for web-guided self-testing and documenting of results.

Depending on local public health policy, implement quarantine entry and exit testing using antigen assays or PCR molecular diagnostics accompanied by reasonable durations of isolation.

| Empower without Intimidating | Test free of charge everywhere, anytime. Test at home, when traveling, or any place in the world, and use the results to avoid and manage risk, not to punish. |
|-----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                             | When a person is not vaccinated, test weekly with a PCR assay or twice per week using a dual test RAgT kit if in the workplace, university, or similar environments. |
|                             | Avoid stigmatizing positive test results by requiring unnecessary prolonged quarantine or shameful detention. Do not use test results to intimidate. Instead, optimize human resources. |
|                             | End quarantine when test results turn negative. Allow work and other activities to resume with minimal personal and economic loss. |
|                             | Create a positive and reassuring social milieu, a point of care culture of self-motivated frequent testing, so that empowered individuals can stop variant outbreaks and avoid spread to highly vulnerable people. |
|                             | Expect COVID-19 to become endemic worldwide. Adapt by vaccinating, testing, and empowering. Diagnostic testing allow us to calibrate and manage our own personal risk. |

**Abbreviations:** Ab, antibody; CI, confidence interval; COVID-19, coronavirus disease 2019; Ct, cycle threshold; NPA, negative percent agreement; PPA, positive percent agreement; PCR, polymerase chain reaction; RAgT, rapid antigen test; $R_{FO}$, rate of false omission; and SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
Figure 1. The Logic of Recursive Prevalence.

Community prevalence (left) allows calculation of the positive predictive value (PPV) and negative predictive value (NPV) for the first RAgT. Then, using the post hoc Bayesian viewpoint, the second test uses the prevalence derived from the first round. Second round prevalences are PPV and 1- NPV, feeding forward on the top and derived at the bottom.

Abbreviations: COVID-19, coronavirus disease 2019; FP, false positive; FN, false negative; TP, true positive; and TN, true negative.

Figure 2. Illustration of Performance Characteristics for Tiers 1, 2, and 3.

This figure illustrates positive and negative predictive values as functions of prevailing prevalence for the three performance tiers. False omission rates determine prevalence boundaries given the risk tolerance level of 5%, the red horizontal line toward the bottom. Abbreviations: PPV, positive predictive value; NPV, negative predictive value; and $R_{FO}$, false omission rate.

Figure 3. Theoretical clinical improvement in performance with a recursive protocol for self-testing.

This figure illustrates the improvement in positive predictive value (PPV) with repeat testing. The inset table lists FDA EUA metrics for two rapid antigen tests. The curves with asterisks reflect the theoretical effect of second round testing. Performance is good improving to excellent because of high NPA (specificity equivalent) in FDA EUA Information for Users. Abbreviations: FDA, Food and Drug Administration; EUA, Emergency Use Authorization; NPA, negative percent agreement; PPA, positive percent agreement; PPV, positive predictive value.

Figure 4. Negative Predictive Values, False Omission Rates, and Prevalence Boundaries for Repeat Rapid Antigen Testing.
This figure illustrates the theoretical improvement in performance for recursive testing (A* & B*) using the same two RAgTs analyzed in Figure 3. The curves with asterisks are derived from Eqs. 22a and 22b (see supplemental Table 1). Repeat testing pushes the NPV curves into the Tier 2 performance zone and advances the prevalence boundaries substantially, making the tests more practical and useful. Manufacturer FDA IFUs (information for users) include a disclaimer for repeat testing. Abbreviations: FDA, Food and Drug Administration; IFU, information for users; NPA, negative percent agreement; NPV, negative predictive value; PB, prevalence boundary; PPA, positive percent agreement; and R_FO, false omission rate.

**Figure 5. Access, Speed, and Process Steps for Self-testing in a Small Community.**

Few analytical processing steps make it quick and easy for families to protect themselves during variant surges. To improve performance, take advantage of recursion and repeat the test. This strategy for detecting SARS-CoV-2 reflects the new normal of diagnostic testing at points of need for endemic COVID-19. Abbreviations: COVID-19, coronavirus disease 2019; and SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
Positive Predictive Value  
\[ PPV = \frac{TP}{TP + FP} \]

Negative Predictive Value  
\[ NPV = \frac{TN}{TN + FN} \]

Use 1 - NPV to find FN COVID-19 among all negatives.

\[ \text{COVID-19 FN/All negatives} = \frac{FN}{TN + FN} = \frac{TN + FN - TN}{TN + FN} = 1 - \frac{TN}{TN + FN} = 1 - NPV \]
Performance Tiers — Green
False Omission Rates ($R_{FO}$) for Tiers — Black
$R_{FO}$ Tolerance Limit, 5% — Red

Prevalence boundaries for Tier 1 and 2 performance levels at the false omission rate, $R_{FO}$, of 5%.

Tier 1 $R_{FO}$ = 5%
Tier 2 $R_{FO}$
Tier 3 $R_{FO}$ = 0
| Home & Self Antigen Tests | PPA [%] | NPA [%] |
|---------------------------|---------|---------|
| A                         | 83.5    | 99.2    |
| A*                       | Test twice | Test twice |
| B                         | 84.6    | 98.5    |
| B*                       | Test twice | Test twice |

*Potential enhanced performance when the subject tests twice.*
| Rapid Antigen Test | PPA [%] | NPA [%] | Prevalence Boundary [PB, %] |
|--------------------|---------|---------|----------------------------|
| A                  | 83.5    | 99.2    | 24.0  65.6                 |
| A*                 | Repeat  | Repeat  | 24.0  65.6                 |
| B                  | 84.6    | 98.5    | 25.2  68.3                 |
| B*                 | Repeat  | Repeat  | 25.2  68.3                 |

| Tier | Sensitivity [%] | Specificity [%] | PB [%] |
|------|-----------------|-----------------|-------|
| T1   | 90              | 95              | 33.3  |
| T2   | 95              | 97.5            | 50.6  |
| T3   | 100             | ≥99             | None  |

NPA A, B

RFO = 1 - NPV

A, B

PB A 25.2%

PB B 33.3%

PB T1 50.6%

PB T2 65.6%

PB A* 65.6%

PB B* 68.3%

RFO = 5%
PURCHASE AT NEIGHBORHOOD PHARMACY

TEST AT HOME

Davis, California, USA

STUDY INSTRUCTIONS

OPEN TEST CARD & SWAB PACKAGE

ADD REAGENT TO TEST CARD

SET TIMER FOR THE DURATION OF DEVELOPMENT

TEST 2 TIMES 36 HRS APART

READ RESULT — TOTAL TIME < 30 MIN

START TIMER

OBSERVE REACTION

POSITIVE CONTROL

NEGATIVE COVID-19 ANTIGEN

SWAB NOSE BY YOURSELF

INSERT SWAB

READ AT 15-30 MINUTES

WAIT 15 MINUTES

START TIMER

WEAR REAGENT TO TEST CARD

ADD REAGENT TO TEST CARD

TEST 2 TIMES 36 HRS APART

READ RESULT — TOTAL TIME < 30 MIN

START TIMER

OBSERVE REACTION

POSITIVE CONTROL

NEGATIVE COVID-19 ANTIGEN

SWAB NOSE BY YOURSELF

INSERT SWAB

READ AT 15-30 MINUTES

WAIT 15 MINUTES

START TIMER

OBSERVE REACTION

POSITIVE CONTROL

NEGATIVE COVID-19 ANTIGEN

SWAB NOSE BY YOURSELF

INSERT SWAB

READ AT 15-30 MINUTES

WAIT 15 MINUTES

START TIMER

OBSERVE REACTION

POSITIVE CONTROL

NEGATIVE COVID-19 ANTIGEN
### SUPPLEMENTAL DIGITAL CONTENT

**Table 1. Fundamental Definitions, Derived Equations, Ratios/Rates, Recursive Formulas, and Prevalence Boundary**

[The Supplemental Digital Content was not copyedited by *Archives of Pathology & Laboratory Medicine*.]

| Eq. No. | Category & equations | Dep. Var. | Indep. Var. |
|---------|----------------------|-----------|-------------|
| **Fundamental Definitions** | | | |
| 1 | \( x = \text{Sens} = \frac{TP}{TP + FN} \) | x | TP, FN |
| 2 | \( y = \text{Spec} = \frac{TN}{TN + FP} \) | y | TN, FP |
| 3 | \( s = \text{PPV} = \frac{TP}{TP + FP} \) | s | TN, FP |
| 4 | \( t = \text{NPV} = \frac{TN}{TN + FN} \) | t | TN, FN |
| 5 | \( p = \text{Prev} = \frac{(TP + FN)}{N} \) | p | TP, FN, N |
| 6 | \( N = TP + FP + TN + FN \) | N | TP, FP, TN, FN |
| **Derived Equations** | | | |
| 7 | \( PPV = \frac{[\text{Sens}\cdot\text{Prev}]}{[\text{Sens}\cdot\text{Prev} + (1-\text{Spec})(1-\text{Prev})]} \), or \( s = \frac{[xp]}{[xp + (1-y)(1-p)]} \) — symbolic version of the equation above | s | x, y, p |
| 8 | \( p = \frac{[s(y-1)]}{[s(x+y-1) - x]} \) | p | x, y, s |
| 9 | \( x = \frac{[s(p-1)(y-1)]}{[p(s-1)]} \) | x | y, p, s |
| 10 | \( y = \frac{[sp(x-1) + s - px]}{[s(1-p)]} \) | y | x, p, s |
| 11 | \( NPV = \frac{[\text{Spec}\cdot(1-\text{Prev})]/[\text{Prev}\cdot(1-\text{Sens}) + \text{Spec}\cdot(1-\text{Prev})]}{[\text{Spec}\cdot(1-\text{Prev})]/[\text{Prev}\cdot(1-\text{Sens}) + \text{Spec}\cdot(1-\text{Prev})]} \), or \( t = \frac{[y(1-p)]}{[p(1-x) + y(1-p)]} \) | t | x, y, p |
| 12 | \( p = \frac{[y(1-t)]}{[t(1-x-y) + y]} \) | p | x, y, t |
| 13 | \( x = \frac{[pt + y(1-p)(t-1)]}{[pt]} \) | x | y, p, t |
| 14 | \( y = \frac{[pt(x-1)]}{[t(1-p) - 1 + p]} \) | y | x, p, t |
| **Ratios** | | | |
| 15 | \( \frac{TP}{FP} = PPV/(1-PPV) = \frac{[\text{Sens}\cdot\text{Prev}]/[(1-\text{Spec})(1-\text{Prev})]}{[\text{Sens}\cdot\text{Prev}]/[(1-\text{Spec})(1-\text{Prev})]} \), or \( \frac{TP}{FP} = \frac{TP}{FP} \) Ratio | TP/FP | x, y, p |
| 16 | \( \frac{FP}{TP} = (1-PPV)/PPV = \frac{[(1-y)(1-p)]}{(xp)} \) | FP/TP | x, y, p |
| 17 | \( \frac{FN}{TN} = (1-NPV)/NPV = \frac{[p(1-x)]}{[y(1-p)]} \) | FN/TN | x, y, p |
| **Rates** | | | |
| 18 | \( R_{TP} = \frac{TP}{(TP + FN)} = x \) | R_{TP} | TP, FN |
| 19 | \( R_{FP} = \frac{FP}{(TN + FP)} = 1 - \text{Spec} = 1 - y \) | R_{FP} | TN, FP |
| 20 | \( R_{FO} = \frac{FN/(TN + FN)}{1 - NPV} = 1 - t = \frac{[p(1-x)]}{[p(1-x) + y(1-p)]} \) | 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 \[ s_{i+1} = \frac{xp_i}{xp_i + (1-y)(1-p_i)} \] where the index, \( i = 1, 2, 3 \ldots \)

22b \[ t_{i+1} = \frac{y(1-p_i)}{[p(1-x) + y(1-p_i)]} \]

Prevalence when sensitivity is 100% (i.e., \( FN = 0 \))

23 \[ \text{Prev} = 1 - \left( \frac{1 - N+/N}{\text{Spec}} \right), \text{ or } p = 1 - \frac{1 - \text{POS\%}}{y} \]

PPV when sensitivity is 100%

24 \[ \text{PPV} = \frac{[\text{Prev}]/[\text{Prev} + (1-\text{Spec})(1-\text{Prev})], \text{ or } s = \frac{p}{[p + (1-y)(1-p)]} \}

Predictive value geometric mean squared (range 0 to 1)

25 \[ \text{PV GM}^2 = \text{PPV}\text{•NPV} = s\text{•}t = \left\{ \frac{xp}{xp + (1-y)(1-p)} \right\} \times \left\{ \frac{y(1-p)}{[p(1-x) + y(1-p)]} \right\} \]

Prevalence boundary for a given \( R_{FO} \)

26 \[ \text{PB} = \frac{[y(1-t)][(1-x) - (1-t)(1-x-y)]}{y[R_{FO}][(1-x) - R_{FO}(1-x-y)]} \]

Accuracy (not recommended – see note)

\[ A = \frac{(\text{TP + TN})}{N} = \text{Sens}\text{•Prev(dz) + Spec\text{•Prev(no dz)}} \]

### Abbreviations

- Dep. Var., dependent variable; Indep. Var., independent variable(s)
- Eq., equation; i, 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
- \( p_{i+1}, p_i \), partition prevalences in the recursive formula for PPV and NPV
- \( R_{FO} \), false omission rate
- \( R_{FP} \), 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
- \( R_{POS} \), 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%.
- If denominators of derived equations become indeterminate, then revert to the fundamental definitions, Eq. 1-7.
- The formula for accuracy is not recommended, because of duplicity of values with complementary changes in sensitivity and specificity.