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Letter to the Editor

The Coronavirus Disease 2019 Grand Challenge: Setting Expectations and Future Directions for Community and Home Testing

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Running Title: Mitigating Endemic COVID-19 in Communities & Homes
To the Editor.—Judging effectiveness, managing positives, modifying quarantines, and advising regarding negatives\textsuperscript{1} require realistic expectations of coronavirus disease 2019 (COVID-19) rapid antigen tests (RAgTs), because their performance is limited. The government is supplying one billion of these to Americans (at COVIDtests.gov), empowering people to discover if they are infected by performing self-testing. Will schools and workplaces accept the results, perhaps by requiring photographic or telehealth proof? Hopefully officials will embrace this advance in point-of-care testing, including home molecular diagnostics (Table 1), and determine its impact for a world striving to mitigate the effects of endemic Omicron, avoid lengthy quarantines, and limit lockdowns.

The authors of recent commentary\textsuperscript{2} state, “For symptomatic patients, antigen testing achieves sensitivities ranging from 85 to 97%,” supported by two references. Further, “…for asymptomatic testing sensitivity decreases to about 74%.” However, from the start of the pandemic through the end of 2021 thirty-four publications reveal a different story. For community settings, such as drive-ups, city plaza kiosks, walk-ups, and screening centers, testing symptomatic subjects generated median RAgT sensitivity of 81.0\% (range 47.7-96.5\%) and when asymptomatic, 55.75\% (range 37-88\%). Mixed asymptomatic/symptomatic populations had median sensitivity of 69.85\% (range 30.6-97.6\%). These medians differ substantially from the sensitivities cited in the commentary,\textsuperscript{2} while specificity medians (symptomatic, 99.85\%; asymptomatic, 99.70\%; and mixed, 99.5\%) were in line with it.

Collating manufacturer Emergency Use Authorization (EUA) claims for home RAgTs showed a median of 86.6\% (range 85.3-95.3\%) for positive percent agreement (PPA) and 99.25\% (97-100\%) for negative percent agreement (NPA). While the US Food and Drug Administration (FDA) publishes EUA PPA and NPA performance metrics in “Information for
Users,” manufacturer claims typically are based on small populations that may not reflect real-world results in homes across the nation. Receiving test kits at residences implies they are for home self-testing. Searches failed to uncover validations of home RAgTs in actual peoples’ hands.

Since vaccination will not stop Omicron infections, episodic increases in local or regional prevalence will lead to RAgT false omissions. Kost\textsuperscript{3} demonstrated that as prevalence increases repeat testing can compensate for the fall-off in performance due to the poor sensitivity of RAgTs. Brands containing two tests enable repeats (\(>24\) but \(<48\) hours) that improve chances of detecting infectivity. My shipment from COVIDtests.gov contained two kits, that is, four tests, so repeat testing will not be practical for most families. Omicron vaccine-breakthrough infections do not show elevated infectious viral titers in nasopharyngeal swabs compared to Delta,\textsuperscript{4} but persistent infectivity heightens Omicron transmission. COVID-19 tests should be validated for Omicron and labeled as such on packaging for consumers.

Since the performance of RAgTs generally is limited, we should consider alternatives during this national experiment. Manufacturers of reverse-transcription loop-mediated isothermal amplification (RT-LAMP) home tests boast PPAs ranging from 90.9 to 97.4\%, with NPAs from 97.5 to 99.1\% (\textbf{Table 1}). The commentary\textsuperscript{2} did not highlight these home molecular diagnostics or their better performance, which could obviate repeating RAgTs. However, the downside of home molecular diagnostics is their higher cost. Therefore, they should be part of the subsidized national distribution. Additionally, their performance in homes should be studied systematically and compared to the performance of RAgTs.

Multidisciplinary public health teams can collaborate in a “Grand Challenge” to study the impact and cost-effectiveness of RAgT, RT-LAMP, and other diagnostic technologies as they
emerge for self-testing by partitioning part of the government supply of COVID-19 tests into studies of performance conducted in diversely populated geospatial regions.\textsuperscript{5} Fact-based point-of-care social innovations will bring higher diagnostic standards, so we can be guardians of our own health, the well-being of our families, and the safety of communities where we live, now and in future public health crises.

References

Table 1. Molecular Diagnostics Tests with FDA Emergency Use Authorization for Home Self-testing.

<table>
<thead>
<tr>
<th>Molecular Method Details</th>
<th>Tier, Sample Size, and Cost</th>
<th>Company, Product, EUA LOA Date [Earliest Date]</th>
<th>Company PPA (%) Claim [CI, ∆]</th>
<th>Company NPA (%) Claim [CI, ∆]</th>
<th>Specimen Type, Age, and Time Interval/ Protocol for Specimen Collection [plus notes]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tier 1</strong></td>
<td></td>
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<tr>
<td>RT-LAMP and lateral flow strip. ORF1ab region of the SARS-CoV-2 genome.</td>
<td>N = 112 Test &amp; processing hub $75.</td>
<td>Detect COVID-19 Molecular Non-prescription Home Test 1/12/22 [10/28/21]</td>
<td><strong>90.9</strong> [76.4-96.9, ∆ = 20.5]</td>
<td><strong>97.5</strong> [91.2-99.3, ∆ = 8.1]</td>
<td>AN swab. Self-collected ≥14 or adult assisted ≥2 years. Without symptoms performed twice &gt;24, &lt;48 hours between tests. Apparent FPs due to subject misinterpretation; app modified to reduce this error. Testing time 55-65 minutes.</td>
</tr>
<tr>
<td>RT-LAMP. Non-overlapping regions of the N gene.</td>
<td>N = 404 Overall N = 101 (1) N = 303 (2) Single-use test kit $75.</td>
<td>Lucira CHECK-IT COVID-19 Test Kit 4/9/21 [4/9/21]</td>
<td><strong>91.7</strong> [85.6-95.8, ∆ = 10.2]</td>
<td><strong>98.2</strong> [95.8-99.4, ∆ = 3.6]</td>
<td>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.</td>
</tr>
<tr>
<td>“Isothermal nucleic acid amplification test.” Nucleocapsid N region of the SARS-CoV-2 virus.</td>
<td>N = 271 Overall N = 138 (1) N = 133 (2) Test $61.75 to $65 each. Reader $249.</td>
<td>Cue Health COVID-19 Test for Home and OTC Use 2/9/22 [3/5/21]</td>
<td><strong>97.4</strong> [86.5-99.5, ∆ = 13.0]</td>
<td><strong>99.1</strong> [96.9-99.8, ∆ = 2.9]</td>
<td>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 symptomatic and asymptomatic (with recent exposure) adult subjects.</td>
</tr>
</tbody>
</table>

Abbreviations: ∆, magnitude in % of the 95% CI, i.e. high minus low CI limits; 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); FP, false positive; RT-LAMP, reverse transcriptase loop-mediated isothermal amplification; NPA, negative prediction accuracy; PPA, positive prediction accuracy; ∆, magnitude in % of the 95% CI.
transcription loop-mediated isothermal amplification; LOA, letter of authorization; NPA, negative percent agreement; ORF1ab, overlapping open reading frame that encodes polyproteins PP1ab and PP1a; OTC, over the counter; PPA, positive percent agreement; and SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Notes: Tier sensitivity/specificity (%) comprise: 1) 90/95; 2) 95/97.5; and 3) 100/≥99. Data are reported as they appeared in FDA EUA “Instructions for Users, In Vitro Diagnostics EUAs – Molecular Diagnostics Tests for SARS-CoV-2” on 2/15/22. Home testing EUAs are listed. Home collection and prescription home testing EUAs are not listed.