# Emergency Use Authorization and Antigen Diagnostic Tests for COVID-19

## Challenges and Future Trends


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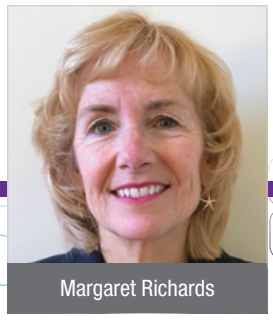
### In Vitro Diagnostic EUAs for COVID-19

Since the US Department of Health and Human Services Secretary declared COVID-19 a public health emergency on February 4, 2020, the US Food and Drug Administration (FDA) has issued numerous Emergency Use Authorizations (EUAs) for in vitro diagnostic devices (IVDs) to detect various targets of current or past COVID-19 infection.

An EUA is one of several tools the FDA has used to quickly make certain medical products available during the COVID-19 pandemic. In emergencies, the FDA can issue an EUA to provide access to medical products that may be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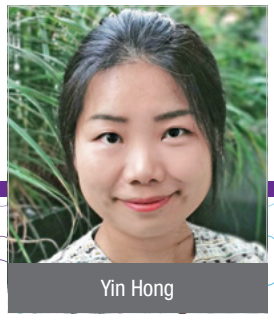
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Table 1. In Vitro Diagnostic (IVD) EUAs[2]

| Type of IVD | Number of Authorized Tests as of April 27, 2021 | Purpose |
|---|---|---|
| Molecular Diagnostic Test | 241 | Detection of SARS-CoV-2 nucleic acid for current infection; sample collection devices for molecular testing |
| Molecular Laboratory Developed Test | 32 | Detection of SARS-CoV-2 nucleic acid for current infection |
| Antigen Diagnostic Test | 23 | Detection of SARS-CoV-2 antigen for current infection |
| Serology Test | 76 | Detection of SARS-CoV-2 antibodies for past infection |
| Tests for Management of COVID-19 Patients | 3 | Detection of biomarkers for patients diagnosed with COVID-19 |
| **TOTAL** | **375** | |

used when there are no adequate, approved, or available options.[1] The EUA process is different than an FDA approval or clearance. Under an EUA, the FDA makes a product available to the public based on the best available evidence, without waiting for all the evidence that would be needed for full approval.[1] EUAs remain in effect until the emergency declaration ends.

The amount of EUA activity for IVDs in the past year is stunning, as shown in Table 1.

The greatest number of IVD EUAs are associated with molecular diagnostic tests (n=241). We chose to take a closer look at antigen diagnostic tests, however, because they hold the most public health promise in terms of speed, ease of administration, reasonable sensitivity and specificity, and cost.

## Antigen Diagnostic Tests

Antigen diagnostic tests identify the SARS-CoV-2 nucleocapsid protein antigen. Currently, the molecular diagnostic test using real-time reverse transcriptase-polymerase chain reaction (RT-PCR) remains the "gold standard" for the diagnosis of COVID-19 due to its high sensitivity and specificity to detect viral RNA.[3] However, RT-PCRs often require longer turnaround times and must be processed by trained laboratory staff with higher associated costs for the test kit and equipment.[4] Antigen diagnostic tests, which require minimal training and equipment, have faster processing times and lower costs. Table 2 compares the antigen diagnostic test to the standard RT-PCR.

A total of 23 antigen diagnostic tests have been authorized by the FDA as of April 27, 2021 (See Table 3). Samples from nasopharyngeal or nasal swabs can be collected and

Table 2. Antigen Diagnostic Test vs. Standard RT-PCR[5,6]

| Characteristic | Antigen Diagnostic Tests | Standard RT-PCR Tests |
|---|---|---|
| Wait Time | ~ 15 minutes processing | ~ 2–6 hours processing, 2–4 days if samples need to be shipped |
| Cost | Low ($5–$10 per test) | High (test kit up to $200 plus shipping, lab equipment, staff, etc.) |
| Staff Required | Healthcare provider or self–/other–collected | Healthcare provider and highly trained laboratory staff |
| Sample Types | NP or NS if collected by healthcare provider; NS if home use | NP preferred, but NS, saliva, and other tissue samples are, or will become, available |
| Sensitivity and Specificity | High specificity; sensitivity drops with medium or low viral load | High sensitivity and specificity |

NP: nasopharyngeal swab; NS: nasal swab

Table 3. List of EUAs for Antigen Diagnostic Tests as of April 27, 2021[2]

| Intended Use | Number of Antigen Test EUAs | Sample Type | Reading Method | Days Since Symptom Onset | Total Samples Tested | % Positivity (test positive proportion) | PPA | NPA |
|---|---|---|---|---|---|---|---|---|
| Lab Use (H/M) Prescription | 5 | NP NS | Instrument read | 0–5, 0-7, or 0–14 days | 72–141 | 22.7%–69.8% | 80%–97.7% | 100% |
| POC Use Prescription with or without serial screening | 12 | NP NS | Instrument read; Visual read | 0–5, 0-7, or 0–12 days or without symptoms | 92–460 | 13.7%–42.4% | 84%–97.6% | 96.6%–100% |
| Home Use Prescription | 2 | NS | Visual read | 0–6 or 0–7 days | 52–161 | 28.6%–46.2% | 84.8%–91.7% | 99.1%–100% |
| Home Use OTC screening or serial screening | 4 | NS | Instrument read; Visual read | With or without symptoms | 52–350 | 18.7%–46.2% | 83.5%–95% | 99.2%–100% |

PPA: Positive Percent Agreement; NPA: Negative Percent Agreement; NP: nasopharyngeal swab; NS: nasal swab; Lab: Laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. §263a, that meet requirements to perform moderate (M), high (H), or waived (W) complexity tests; POC (Point of Care): Patient care settings operating under a CLIA Certificate of Waiver; OTC: Over the Counter

processed by healthcare providers for point-of-care (POC) use or self-/other-administration in home use. Some antigen tests require a prescription and symptoms, whereas others are made available over-the-counter (OTC) with symptoms optional. Some tests are for adults only whereas others can be used for ages two and older.

## EUA for Antigen Diagnostic Test

For antigen diagnostic test developers requesting an EUA, the FDA recommends several validation studies to determine the test's clinical and analytical performance. The FDA website has two templates, one for an antigen diagnostic test for laboratory and POC use and one for home use,[2] that include some of the validation studies needed for analytical performance (See Figure 1). For clinical performance, a usability study is recommended for the POC claim to demonstrate that healthcare providers can perform the test from the instructions given in the test kit. This is also recommended for home use to demonstrate that an individual can perform the test accurately, either self-collected or other-collected, depending on the intended use.

Clinical evaluation is done to compare the performance of the antigen test versus a comparator RT-PCR test authorized by the FDA.[7] Performance is assessed as Positive Percent Agreement (PPA) and Negative Percent Agreement (NPA), percentages that are similar in concept to sensitivity and specificity, respectively. As there is no current reference standard available, PPA and NPA are used instead of sensitivity and specificity because the latter assume a reference standard.

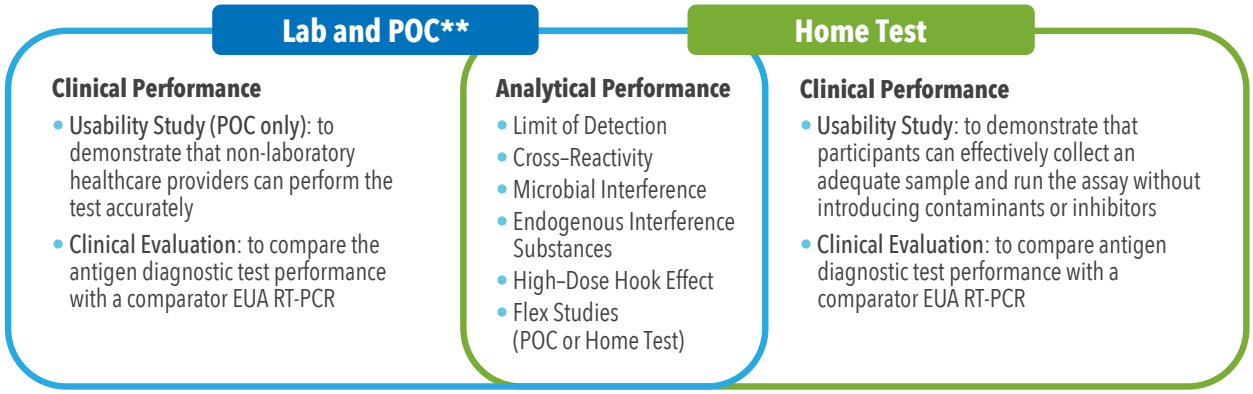
A PPA of ≥ 80% is required for laboratory-based POC and home use tests that are prescription only. For OTC home use, a PPA ≥ 90% and an NPA ≥ 99% are required for both asymptomatic and symptomatic individuals.

## Challenges

In general, antigen tests have high specificity (NPA), but relatively moderate sensitivity (PPA) compared to an RT-PCR (See Table 2). The sensitivity of antigen tests drops in samples with RT-PCR cycle threshold (Ct) values > 30, which are samples with medium to low viral loads.[8] A Ct value is the cycle of amplification at which the fluorescence crosses the threshold to become positive and viral load and Ct threshold values are inversely correlated. Simply put, the higher the viral load the lower the Ct value and vice versa. Although more data are required, higher viral load is thought to be related to higher transmissibility[9] and risk of intubation and mortality.[10] An antigen test may identify individuals with higher viral load who are most likely to infect others. Viral loads correlate well with date of diagnosis and/or symptom onset; they are the highest within 1-5 days of infection and decline thereafter.[9]

Interestingly and importantly, viral load does *not* seem to correlate with any one COVID-19 symptom or symptom constellation. Those who are asymptomatic but have a positive test can nonetheless have a high viral load (and transmit disease), which is one of the characteristics of COVID-19 that has made it difficult to manage. As the pandemic begins to wane globally, rapid antigen tests on both symptomatic and asymptomatic persons for screening purposes could be particularly useful.

**Figure 1.** Validation Studies Recommended for Antigen Diagnostic EUAs*




* This list covers the main validation studies recommended in the EUA templates and some studies may not be applicable in certain conditions. For a complete list of validation studies, please refer to the FDA website.[2]

** Laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. §263a, that meet requirements to perform high or moderate complexity tests; Patient care settings operating under a CLIA Certificate of Waiver.

## Future Trends

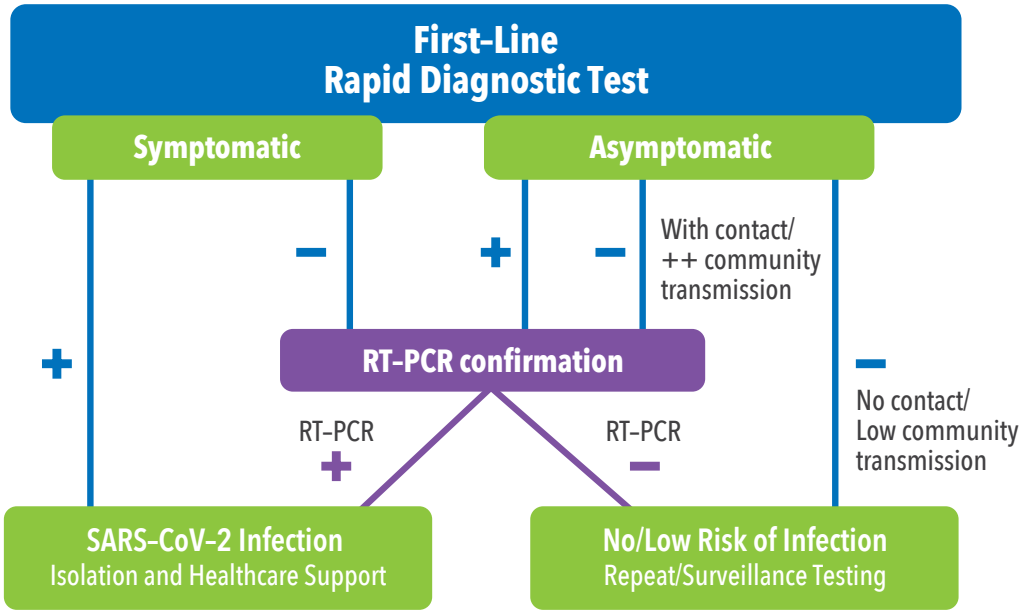
Although an antigen diagnostic test is not as sensitive as an RT-PCR, it can be very useful from a public health perspective. Situations of public health import include:

- Persons with limited access to a standard RT-PCR
- Individuals not meeting RT-PCR testing criteria
- Home-use/screening (when COVID-19 exposure is suspected or known, especially with underlying conditions or susceptibility)
- Community settings such as universities or workspaces where large numbers of people gather regularly and need to be tested often

One study has shown that frequent mass testing using rapid tests as part of a screening program might be more cost-effective than a standard testing approach.[11] To date, only four rapid antigen tests and two rapid molecular tests have received an EUA for OTC use (symptomatic and asymptomatic individuals, screening, or serial screening). Various testing algorithms have been proposed by health authorities using rapid tests as first-line screening under certain conditions and, depending on the screening result, branching out into different decisions involving RT-PCR test confirmation, isolation, surveillance testing, etc.

Figure 2 shows one test flow. Other test flows have been devised by regulatory and health authority agencies around the globe.

**Figure 2.** COVID-19 Diagnostic Test Flow Chart[6,12,13]



The beauty of a rapid diagnostic first-line test is the ability to scale mass testing with low cost and rapid response. An approach that involves RT-PCR testing first-line is potentially expensive and can cause delays. The fact that these rapid tests have moderate sensitivity and high specificity is an advantage. There are few false positives (due to high specificity) and more false negatives (due to moderate sensitivity), but the latter are assumed to be associated with a lower viral load and thus a less contagious individual. If a false negative rapid test individual is allowed to move about his/her sphere, the chances are that his or her viral load is no longer a threat.

## Conclusion

The COVID-19 pandemic has stimulated innovation in COVID-19 IVD assays, treatments, and vaccines, and that progress has brought confusion, disappointment, rapidity, ingenuity, and elegance. There is no doubt that diagnosis, treatment, and prevention will all play key roles in managing the current and any future pandemics. Hopefully, the lessons learned from COVID-19 diagnostic product development will translate to other IVD diagnostics, infectious or otherwise. ■

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