Selecting a SARS-CoV-2/COVID molecular testing method for your laboratory

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In early March 2020 it became apparent that clinical laboratories would need to quickly develop strategies for SARS-CoV-2/COVID-19 testing. For most, the initial approach was to send out testing to a reference laboratory. As the pandemic has progressed, the food and drug administration (FDA) has allowed for several manufacturers to make testing reagents commercially available. Concurrently, the demand for rapid accessibility of results persists, leading many laboratories to evaluate options for "in house" testing. This reflection highlights some of the considerations when selecting the best method for your laboratory, with specific examples highlighted from a medium volume laboratory's experience.

1. Does your laboratory have access to a research scientist with expertise in molecular or virology testing?

    If yes, your institution may consider validating a laboratory developed test following the criteria outlined by the FDA emergency use authorization (EUA) guidance for CLIA certified high complexity laboratories. There has been one study evaluating primer/probe pairs for laboratories and manufacturers to use as a reference(1).

    Many laboratories will not have such an expert available, as was the case for our laboratory, and therefore should consider implementing one of the already FDA EUA options. Additionally, even with the expertise, a laboratory may choose to adopt one of the commercially available EUA options, either as their primary testing method or as a back-up method to increase the laboratory throughput and/or allow for a second source of reagents. A full list of the FDA EUA assays can be found t the website referenced here (2).

2. What instrumentation does your laboratory currently have available?

    At the time of writing, there were 35 different commercially available EUA assay kits manufactured to detect SARS-CoV-2 RNA in upper and lower respiratory specimens. Of these, at least 18 utilize an Applied Biosystem RT PCR instrument for amplification and detection; a subset was also authorized for the BioRad CFX RT-PCR instrument. Thus, the question becomes: is either of these instruments available in your laboratory? If yes, the differences between these assays are primarily a function of recommended extraction instrumentation, primer design, and type of internal control. Comparing the primer and probe pairs to the published article might allow for some assessment of analytical sensitivity(1), but at this point, the literature is void of publications illustrating differences in sensitivity or specificity of the various kits; all met a set of criteria defined by the FDA for EUA.

For laboratories without the aforementioned sequencing platform, assessing availability of alternative instrumentation within routine laboratory services would be most beneficial. Avoiding purchasing a new instrument can minimize capitol expenses and decrease overall implementation timeline, including technologist training and interface connectivity (when applicable). Additionally, it allows the laboratory to utilize pre-existing vendor relationships in the reagent acquisition process and dismisses the need to assess space constraints that a new instrument may impose.

In my laboratory, we had platforms available for two manufacturers producing SARS-CoV-2 detection assays, and went with our final selection because of the sampling process (continual loading) and because we had shifts where this instrument was not in use, allowing us to continue with our routine pathogen/viral testing and implement a new test.

If the lab has no existing platform to which SARS-CoV-2 can be added, the below considerations are of even greater importance.

3. What throughput and turnaround time is needed?

In general, turnaround time and throughput are a tradeoff. A subset of the available assays/instruments performs small batches of samples (1-4 samples at a time), but provide results in less than an hour, some in as little as ~30 minutes. Alternatively, higher volume platforms are available, but require up to ~3 hours until the first result (or first batch of results). The latter can have fixed batch volumes (96 well plate or cassette formats) or be loaded real-time, depending on the instrument design.

A current misconception propagated by popular news sources is that a "point-of-care" (POC) molecular assay is available. While some manufacturers specifically markets their device as POC, the FDA EUA still limits its use to CLIA certified moderate/highly complex laboratories, thereby dismissing the idea that this is a bed-side platform that can provide immediate results. There is at least one manufacturer with waived authorization, but there has been limited reagent availability for this device and the sensitivity seems to be less than several of the other testing platforms(3). This device is also impractical to provide results for more than 5 patients/hour per instrument.

In my laboratory, we have a moderate testing volume, averaging about 200 SARS-CoV-2 PCR orders per day. We selected the instrument that allowed us to meet a median TAT for <8 hour from receipt. Additionally, we tried to acquire POC reagents for emergency

high-risk situations, but were not within the Federal definition of a "hot-spot" and therefore were not rationed a reagent supply.

4. Are there space or storage constraints?

   The instrument options for testing range in size, from about the size of a small printer, to the size of a small car. Generally, the larger instruments will have higher throughput. However, there are some options that are relatively small and can process dozens of samples at a time (ex: Diasorin Liasion MDX, Cepheid GeneXpert). Many of the testing platform options require two separate pieces of instrumentation – one for RNA extraction and a second for amplification and detection, which tends to give them a slightly larger footprint. The latter platforms are generally used by laboratories with more advanced molecular services (such as molecular oncology or pharmacogenomics), but could be amenable to any laboratory that wants to increase their genetic testing menu.

   In addition to space constraints, storage conditions should also be evaluated. An example that is easily overlooked is a need for reagent refrigeration. Temperature requirements varies between manufacturers, and are often an easily overlooked, yet highly relevant, component of selecting which instrumentation would work best for the laboratory's capacity.

5. Is there other testing needs for the laboratory?

   Diagnosis of COVID-19 is clearly a primary goal for healthcare systems worldwide, but keeping the laboratory's overall needs and scope in mind with purchase of new instrumentation can benefit everyone in the long term. For example, in my laboratory we were interested in a platform that could perform high throughput flu testing in addition to SARS-CoV-2, and therefore this was included in our discussion before we selected a manufacturer. Similarly, an alternative platform was high on our short list because it had already been accounted for with our pre-pandemic budget as a means to improve our stool culture utilization.

6. If an instrument needs to be purchased, what is the current wait time for installation?

   Most, if not all, vendors who are manufacturing SARS-CoV-2 detection assays are being bombarded with requests for reagents and instrumentation. Depending on your laboratory's pre-existing relationship with the various manufacturers, it may be beneficial to

select your top three platforms and make a final selection based on instrument availability.

7. Is the company experiencing any reagent allocation?

   Estimating the probability of encountering reagent shortages is difficult, but there are a few practical steps that can be taken to build confidence in reagent availability. First, reach out to your colleagues for their experience – have they had any trouble receiving reagents? Second, ask about the manufacturing process, and what the company anticipates producing and distributing. Specifically ask them their strategies for ensuring all of their customers can meet their testing volume.

   We had a pre-exisiting relationship with the vendor we selected, and they were forthcoming with telling us they would try to meet our demands of 200-300 tests/day, but if there were any glitches in the manufacturing process there could be allocation issues. Thus, we developed a back-up plan for routing tests to our reference laboratory as a contingency plan for reagent backorder.

8. What specimen types are approved for use?

   In addition to reagent allocation, collection devices and media are limited. Further, transitioning a collection device away from the norm can cause confusion for healthcare providers performing the collection. Assessing the intended use for collection devices that are compatible with availability and familiarity will help your institution be better prepared for implementation.

   There have been recent publications evaluating alternative swabs and media, but each lab would be responsible for this validation, which can be tricky with the ongoing limited reagent supply(4, 5).

9. Cost

   Budget is one of many laboratorians least favorite topic, but nevertheless a relevant consideration. Comparing the cost of the different testing platforms and integrating the cost per test into that assessment can help in selecting the preferred manufacturer. If one of the preferred choices is more expensive it may be helpful to compare the reagent cost to the current send-out cost and calculate the time/volume needed to result before the laboratory is decreasing cost by internalizing testing.

10. Be careful of illicit tests

Buyer beware. There have been reports of illicit reagent manufacturing. Ensure your purchases are coming from known manufacturers or distributers. Complete a verification process is with the original reagent shipment and lot-to-lot or shipment-to-shipment comparisons with additional reagent deliveries.

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