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The changing respiratory testing landscape: Why the value of flexibility is key

By Ayaz Majid, PhD and Chris Gardner

In the post-pandemic era of respiratory testing, laboratories need to consolidate platforms and assays to accomplish more with less all while ensuring sufficient testing menus for meeting clinical needs.[1] At the same time, there is growing pressure to align testing procedures with a changing landscape of diagnostic stewardship protocols and ensure that each patient gets the right test at the right time to generate meaningful information that influences appropriate clinical decisions. Ultimately, the goal is to lead to both better patient outcomes and reduce unnecessary testing that increases healthcare costs without producing actionable results.[2]

Achieving these goals simultaneously will be a significant challenge for the clinical laboratory community. However, it's never too early to begin planning for seasonal respiratory testing as a year-round strategy. This is key for ensuring flexible testing algorithms. The most important factor in today's respiratory testing is flexibility in workflows. Fixed testing products such as broad syndromic panels make it far more difficult to tailor testing to each patient's needs, and their fixed costs are not conducive to lowering laboratory bills.

Given the multitude of respiratory pathogens as well as clinical, epidemiological, and economic factors, testing for respiratory infections involves a high degree of complexity and burden. Differences in seasons, patient demographics, severity of disease, specimen type, suspected pathogen type, and more can influence the testing process.[1,3]

Several key factors[4,5] that must be considered for respiratory testing workflows include the following:

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LEARNING OBJECTIVES

Upon completion of this article, the reader will be able to:

1. Identify the goal of developing appropriate diagnostic respiratory testing panels.
2. Differentiate the key factors in the development of testing workflows for diagnosing respiratory illness.
3. Identify the goals of creating a diagnostic stewardship program for respiratory illnesses.
4. Discuss the different options in choosing the right testing algorithms for the diagnosis of respiratory illness.

Seasonality: Respiratory testing algorithms are highly influenced by co-circulating respiratory pathogens that may follow a seasonal pattern, such as influenza viruses and respiratory syncytial virus (RSV), while other respiratory infections may present opportunistically in season following a flu infection, such as bacterial pneumonia caused by *Staphylococcus aureus* or *Hemophilus influenzae.* In these seasonal scenarios, typical outpatients with less severe symptoms may require standard targeted flu A/B and RSV testing; hospitalized patients with more severe symptoms could require a broader panel-based test. Conversely, a combination of targeted seasonal testing and reflex testing to a panel-based syndromic approach for patients with ongoing disease or pediatric patients may be warranted.

Out-of-season testing is largely driven by symptoms and etiological risk factors such as travel and/or exposure. As examples, targeted testing for COVID-19, group A streptococcus, and *Bordetella pertussis* might be warranted in some cases, while a syndromic panel approach might be needed based on disease risk or severity.

Patient needs: Regardless of season or the regional epidemiological landscape, patient demographics can require different levels of testing. The presence of common respiratory pathogens may be affected by age (e.g., RSV for children or the elderly), health status (e.g., immunocompromised or severe pneumonia), and vaccination status. Single-pathogen tests or targeted mini-panels might be appropriate for an otherwise healthy adult, but an immunocompromised patient, an elderly patient, or a child might require a broader approach — and typically a *different* broader approach for each of these types of patients depending on their exact clinical situation.

Pathogen type: In some situations, such as during a COVID-19 community surge, it may be safe to assume that the pathogen responsible for a patient's respiratory infection is the SARS-CoV-2 virus, so starting with a targeted test would be justified. However, for immunosuppressed individuals or patients with, or at risk for, critically ill respiratory disease, a syndromic approach makes for better clinical utility given the multitude of potential pathogens causing similar symptoms. Identifying the correct pathogen is essential for ensuring appropriate therapy and avoiding prolonged disease or mortality.

Diagnostic stewardship

Applying appropriate clinical and epidemiological factors to select the right test for the right patient at the right time allows laboratory medicine specialists to align with the principles of diagnostic and antimicrobial stewardship.[2,6]

Laboratory interventions to guide clinical testing and patient management are key, given that most healthcare decisions today are based on diagnostic tests. This is a testament to the importance of clinical laboratories in patient care, but it also puts laboratory testing front and center in efforts to reduce healthcare costs by ensuring appropriate testing and prompting the right healthcare actions.

For respiratory testing, where symptoms in many cases are very similar, diagnostic stewardship aims to deliver appropriate testing algorithms in order to fast-track clinical decisions and facilitate appropriate treatments for patients while reducing the unnecessary use of antibiotics or antivirals. Another aim, less important for patient care but just as important for the responsible management of healthcare costs on behalf of patients, is to get the right clinical information quickly at the lowest possible price point. A lab that relies on fixed syndromic panels for all suspected respiratory infections, regardless of patient demographics or seasonality, might offer a comprehensive testing approach but fail to meet the goals of diagnostic stewardship.

Choosing the right test

Going forward, post-pandemic respiratory testing algorithms are already taking shape based on clinical, epidemiological, and economic factors. Appropriate strategies will enable

Respiratory test options

With many different types of respiratory test formats available, it can prove challenging to know which test to use in which scenario. Here is a quick overview of the most common types of diagnostic tools for respiratory infections.

Rapid antigen testing: Also known as lateral flow testing, rapid antigen tests moved into physicians' offices years ago and more recently became widely used for at-home COVID-19 testing. Their benefits include rapid results (generally 15 minutes or less) and ease of use (even an untrained consumer can typically use the test properly); they also tend to be fairly inexpensive. However, rapid antigen tests are generally less sensitive than molecular options, often requiring confirmation of negative results by PCR when symptoms persist.

Targeted molecular laboratory tests: Molecular tests are known for their accuracy, with high sensitivity and specificity. Also called nucleic acid amplification tests, these targeted assays can be used to detect a single pathogen at a time (such as group A Streptococcus (GAS) or SARS-CoV-2) or a small number of pathogens that make sense to test together (such as flu A/B and RSV). Molecular tests may be performed with automated sample-to-answer platforms that require very little hands-on time, as is the case of many commercial in-vitro diagnostic assays, or they may require a more traditional, higher level of laboratory expertise with more complex workflows. These typically require sample preparation (manual or automated) prior to running on a separate thermocycler or reader. Results are produced fairly quickly, generally in about 2–3 hours depending upon the system.

Syndromic molecular tests: These test panels share all the benefits of other molecular tests — including accuracy and fairly rapid results — but provide results for a much broader group of pathogens per sample. Since these tests cover many more targets, syndromic panels can be more expensive than their targeted molecular counterparts and are frequently reserved for in-patient and critical care testing. If flexible testing options are available, syndromic molecular assays can be equally cost-effective as other solutions by only resulting and paying for the pathogens needed to drive clinical action.

optimal patient outcomes without wasteful and costly testing or treatment while facilitating laboratory profitability and alleviating hospital burdens. In addition, simplicity and flexibility in testing algorithms will help reduce the burden on ordering physicians and laboratory staff.

While many labs have adopted targeted testing for differential diagnosis of common respiratory pathogens, others have adopted flexible testing approaches based on syndromic panels. A flexible syndromic method allows for the creation of targeted custom panels as subsets of the broader syndromic panel. In this model, labs pay only for the results they select from the broader test.[7,8] Should all results of an initial grouping come back negative, staff may choose to view results for more targets on the syndromic panel without re-running the assay. This is accomplished through software manipulation rather than as part of the assay workflow. This flexible approach makes it possible for laboratory staff to use a streamlined syndromic algorithm for their unique test situations, minimizing the need for training and validation while meeting the diagnostic stewardship goal to avoid over-testing.

For example, some laboratories begin with syndromic panels of about 20 respiratory pathogens, from which they select targeted groupings that can be used for a more customized testing approach. One grouping might include viral and bacterial pathogens that cause similar symptoms. Others might represent the full range of testing needs based on patient demographics, such as a targeted panel of influenza A/B and RSV for a pediatric patient, or a broader group of viral targets for an immunocompromised patient. These groups can also be used as a reflex when singleplex testing is negative either on the same platform or a different platform.

Alternatively, a successful approach for clinical labs is to run respiratory tests on one platform, eliminating the need to bring in multiple platforms to handle all pathogens, all throughputs, and all price points.

What's next

The confluence of endemic COVID-19, diagnostic stewardship programs, and rising healthcare costs has led to more complexity than ever in the world of respiratory testing. Laboratories must decide when to test which patients for which pathogens, and then be prepared to justify the costs of those decisions — all on a patient-by-patient basis.

Regardless of which diagnostic platforms a clinical laboratory chooses to implement, the most important factors in meeting these different goals should be simplicity, flexibility, and test appropriateness. In planning for future respiratory testing, laboratory leaders will want to prioritize testing options based on clinical and epidemiological factors that align with their institutional needs and allow for the championing of the quest for diagnostic stewardship and optimized healthcare. Targeted respiratory testing or flexible syndromic panel testing can fit nicely into this approach, addressing reimbursement concerns, and managing costs without an overly complicated workflow.

Ultimately, clinical laboratories have a unique opportunity within the changing post-pandemic respiratory landscape to ensure diagnostic stewardship principles for respiratory testing practice and beyond. Collectively, these initiatives will drive appropriate clinical and economic outcomes against ongoing healthcare challenges.

Test selection by patient demographics

For respiratory infections, clinical laboratory testing algorithms can become quite complex. Broadly, a few key categories based on patient demographics can help guide selection of the most appropriate test. The information below is gleaned from typical algorithms at many clinical laboratories.

Otherwise healthy adults: The clinical utility of respiratory antigen testing was exemplified with at-home COVID-19 antigen tests to facilitate rapid and low-cost testing for patient isolation and prevent spread. Other respiratory pathogen antigen tests are performed by health care providers (e.g., GAS, flu, and RSV) in symptomatic individuals. However, those negative by antigen testing yet clearly symptomatic benefit from more sensitive targeted molecular testing based on viruses in circulation (e.g., COVID-19 and flu A/B or COVID-19, flu A/B, and RSV) or differentiated patient symptoms (e.g., GAS). Syndromic panel-based testing is beneficial especially when the predicted targeted molecular testing was negative and symptoms persist.

Outside of the typical respiratory season, clinicians may recommend targeted tests based on signs and symptoms or regional epidemiology. However, based on severity of disease, a syndromic test may be warranted to effectively treat and or track out-of-season respiratory outbreaks.

Otherwise healthy children: The youngest kids — typically below age five — are at high risk for RSV and typically require a molecular test covering COVID-19, flu A/B, and RSV.[9] Kids over the age of five might need that same test with the addition of group A strep (antigen or molecular test). In those children presenting with additional symptoms like a persistent cough, a syndromic test will enable appropriate management without delay and help rule out causative viruses and bacteria not captured in the initial screening assays.

Elderly: The elderly can be particularly vulnerable to respiratory infections due to underlying disease and/or compromised immune systems. Careful clinical evaluation can direct appropriate ordering for targeted molecular testing to rule out select viruses that may be circulating concurrently (i.e., COVID-19/, flu A/B, and RSV) or based on the severity of disease and underlying risk, then immediate syndromic testing may be warranted to initiate appropriate clinical action and patient treatment.

Immunocompromised adults or children: These vulnerable patients are susceptible to more severe respiratory infections and may become hospitalized. Patients in this group likely need a broad syndromic panel covering all pathogens typically responsible for respiratory infections.

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Ayaz Majid, PhD and **Chris Gardner** are Directors of Product Management at **Diasorin**, responsible for targeted and syndromic in vitro diagnostic molecular technologies respectively. They each have extensive experience in molecular diagnostics for a wide range of infectious disease applications.