

Expert Commentary: A Clinician's Perspective on Flexible Testing

with Bert Lopansri, M.D. (March 2016)

Clinicians, like laboratorians, are having to adapt to the changing landscape in healthcare. Included in these changes are the facts that payers and patients are demanding better care at a more affordable rate, and the emergence and spread of antimicrobial resistance is placing a magnifying glass over many antimicrobial prescription decisions. With these changes, clinicians are having to become more selective in both the ordering of diagnostic testing and the use of antimicrobials.

Laboratorians are now much better equipped to support the changing needs of the provider and patient with the emergence of rapid diagnostic testing solutions. While these tests have helped clinicians improve clinical and economic outcomes for certain disease states, the limitation of these tests has been that they don't provide the necessary flexibility to adapt to the way medicine is being practiced.

The recent introduction of flexible multiplex infectious disease testing for respiratory pathogens is allowing laboratorians the ability to better adapt the testing they can offer to the needs of their providers and patients. Bert Lopansri, M.D., is uniquely suited to speak on the impact of the changing landscape of healthcare and the value of flexible testing from both the clinician's and laboratorian's perspective, serving as the Chief of Infectious Diseases and Medical Director of the Urban Central Regional Microbiology Lab at Intermountain Health.

As a clinician, what is your thought process when evaluating a patient that presents with a possible respiratory tract infection?

Bert Lopansri, M.D.: As with everything in clinical medicine, the patient's clinical status is the most important factor. When dealing with a respiratory tract infection, localizing illness to the upper or lower respiratory tract is critical. With upper tract illnesses, localizing symptoms further to determine the likely site of infection such as sinusitis, pharyngitis or bronchitis is important. With lower respiratory tract infections, the challenge is in distinguishing between a bacterial or viral cause, which is difficult to do using

clinical criteria alone. Some cues that are helpful are the presence or absence of systemic symptoms, such as fever and respiratory red flags like tachypnea and hypoxia, but these again are not perfect.

In an outpatient setting during respiratory season, what would drive your test ordering and what results would impact actual treatment?

Lopansri: There are many different reasons to test for respiratory viruses in the outpatient setting, but generally speaking, I tend to be a bit more conservative, as the cost to patients can be significant. To me, the main question revolves around the presenting syndrome, the patient's clinical status, and if testing will change how I manage a patient beyond supportive care. If a patient presents with symptoms compatible with influenza early in the course of disease, or symptoms consistent with croup, then confirming with laboratory testing may impact how you manage the patient and/or vulnerable household contacts.

Prior to the advent of rapid molecular solutions for respiratory pathogens, what value did you see in the results provided by the more conventional diagnostic methods that had days-long turnaround times?

Lopansri: My observation is that conventional tests were used much more sparingly due to the slower turnaround times – especially for patients suspected to have a respiratory virus infection. I would imagine that these tests would have limited impact on a patient's care, as antiviral or antibiotic use would have to be initiated prior

About Dr. Lopansri:

Dr. Lopansri received his Doctor of Medicine from Loyola University of Chicago in 1997. He completed his residency at Loyola University of Chicago in Internal Medicine from 1997 - 2000 and a fellowship in infectious disease from the University of Utah Medical Center in Salt Lake City, Utah from 2000 - 2003. From 2003 through the present, Dr. Lopansri has worked at Intermountain Medical Center and is currently serving as Associate Professor of Medicine, Division of Infectious Diseases at the University of Utah. Dr. Lopansri is board certified by the American Board of Internal Medicine for infectious diseases.

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to availability of test results and driven by the patient's condition. Nowadays, the tests are rapid and readily available and have much shorter turnaround times, so they are ordered much more frequently.

The value of a test lies in how a clinician uses it. Preventing unneeded antibiotic use and other resource utilization for viral respiratory tract infections and prompt use of antivirals for treatable causes are important goals for use of molecular testing. An example of this was when I had the opportunity to volunteer in an urgent care clinic at a four-week winter sporting event. One of my mentors was in charge of the clinic and devised a process whereby clinical algorithms were developed and used to guide management of different respiratory syndromes. The predominant symptom (e.g., cough, sore throat, congestion) drove which algorithm to use. If needed, targeted testing with rapid influenza test backed up by influenza PCR, and detection of other respiratory viruses by DFA was directed by the algorithm. The turnaround time for tests used, excluding rapid influenza, was somewhere between the molecular tests and the conventional testing. At the end of the experience, we learned that approximately 20-25% of the patients presenting with upper respiratory tract symptoms received antibiotics, which was below the rate of antibiotics used (up to 75%) described by many for similar syndromes.

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Which features of these tests have you liked and which would you change?

Lopansri: I like the rapid turnaround time, simplicity and reduced hands-on time for the technician. Automated testing makes it more feasible for use in real-time, as opposed to the batching strategy. I like the ability to detect multiple pathogens in one test; however, I don't feel that this should be the standard for viral diagnostic testing given the added cost for a test that may not lead to meaningful

changes in care beyond supportive measures. The feature that is lacking in the molecular tests for respiratory pathogens is the inability to exclude a bacterial co-infection, primarily for patients with lower respiratory tract involvement. In a severely ill patient, this limits a clinician's confidence in a test result and may not impact antibiotic use or other resource utilization in patients who are ill enough to be hospitalized despite detection of a pathogen such as metapneumovirus or coronaviruses.

How conscious are you and other clinicians about out-of-pocket payments for your patients and does this influence test ordering decisions?

Lopansri: Cost is a very real concern and is an important consideration when discussing diagnostic testing, especially in the outpatient setting. I periodically receive calls from patients upset at the cost of a diagnostic test that I ordered or the copay for an antibiotic I prescribed. I've had a few patients who would negotiate what diagnostic test was needed, as they are on a high-deductible plan and have not yet met their cap and can't afford too many tests.

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If your lab allowed clinicians to order flu testing only, flu and RSV testing, a respiratory viral panel, and a pertussis test with the cost of the testing being proportionate to the number of targets ordered, would there be situations when each of these testing options would represent optimal patient management for certain patients?

Lopansri: Not all patients are the same, and not all physicians practice the same way, so our lab offers targeted testing for influenza and RSV in addition to panels that detect multiple viral and

atypical bacterial pathogens. Optimal patient management depends on clinical judgment in addition to timely and accurate lab results. If at the conclusion of a patient encounter there is a fair degree of certainty that an illness is due to a particular pathogen, then having targeted testing makes sense. However, if there is uncertainty, then it may make more sense to test for a broader array of pathogens, especially in an immunosuppressed patient.

What clinical risk is there if the clinician orders too narrow of a respiratory pathogen test?

Lopansri: This is largely dependent on the patient’s clinical presentation and underlying health status. In general, for upper respiratory tract illnesses based on the configuration of the current respiratory molecular panels, the risk to otherwise healthy adults in the ambulatory setting is fairly limited. Panels that include atypical pathogens such as pertussis have public health implications and can potentially lead to earlier intervention to prevent transmission when it is not initially considered. Another consideration for risk related to missing a respiratory pathogen is if there was a household contact with significant underlying comorbidities – such as being immunocompromised – which increases risk for severe outcome. In this case, antiviral prophylaxis may be an option (e.g., influenza A). For an inpatient, missing a diagnosis can lead to transmission to other patients or healthcare workers. With respect to lower respiratory tract infections, missing a pathogen may lead to unnecessary antibiotic use or delayed treatment for treatable causes such as influenza or, in the pediatric and immunocompromised patient population, RSV.

If the clinician knows they could order a more targeted panel for respiratory pathogens, see those results, and then be able to add on additional testing requests and get those within an hour, how do you think this would affect clinical ordering patterns?

Lopansri: This is something that is difficult to predict and is largely clinician-dependent. Many are influenced more by cost and are more pragmatic about the tests that they order while others favor the simplicity of ordering a single test and not having to worry about missing anything. I think that it is important to have flexibility to accommodate the different approaches.

How would you respond to a laboratorian who wants to provide a broad respiratory pathogen panel for all test orders for fear of missing detection of a respiratory pathogen?

Lopansri: It is my firm belief that there is a role for both the targeted and the comprehensive approach. First, as I mentioned earlier, there is a great deal of heterogeneity in the clinical approach to a patient with respiratory illness, and different doctors think differently. Just because we are capable of detecting most of the major respiratory pathogens in a single test doesn’t mean that we need to be doing so routinely. Be prepared to address the physician who only wants to look for influenza and doesn’t need to know about rhinovirus or coronavirus, since there isn’t much you can do beyond supportive

care anyway. Secondly, there is a great deal of heterogeneity in how patients respond to a respiratory pathogen and different patients manifest infections differently. The need to identify a pathogen in an otherwise healthy individual with an upper respiratory tract infection may not be as great as for a young child or a patient who is immunocompromised following a solid organ or stem cell transplant. One other important thing to consider is that a positive target may not be clinically relevant, as the current panels do not enhance our ability to determine the probability of a bacterial co-infection.

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Do you think flexible testing that has been introduced for respiratory pathogens would be applicable for other areas of infectious disease diagnosis?

Lopansri: Absolutely. One exciting advance in the syndromic approach to diagnostic testing is with gastroenteritis. But to me, the jury is still out as to what impact the shotgun diagnostic approach will have. There are many different things that can cause diarrhea and taking a detailed history with a detailed physical exam can resolve it in many patients. So for those clinicians who have a good idea what is causing diarrhea and need to confirm the clinical suspicion, there is still a role for targeted testing. For cases in which historical clues do not shed a light on the etiology, then a broader approach may be beneficial. That being said, it is estimated that there are 180 million cases of diarrhea a year in the U.S., so we need to be judicious with use of syndromic panels, especially for conditions which are self-limiting to begin with. The cost to the health system would be staggering and the cost to patients with high-deductible health care plans would be unpleasant. This is an advantage of a flexible strategy.

The one nagging fear that I have with routine use of the broad, multiplex testing approach is that the balance of a patient encounter will shift from reliance on history and clinical findings to guide therapy to increased reliance on laboratory test results – which will not always represent the true pathogen. Use of the broad panel approach guarantees that a clinician will often encounter an unexpected result, or results that are inconsistent with the clinical presentation. For example, if a patient presents with a clinical syndrome consistent with an acute bacterial gastroenteritis associated with systemic symptoms, what will one do if *Shigella* and *Clostridium difficile* are detected and the patient had not previously received antibiotics? Conversely, if a debilitated patient or a returned traveler is admitted with diarrhea and the etiology is uncertain and the differential is broad, use of a broader panel may be more time and cost effective than using many different singleplex tests.

In the landscape of declining reimbursement and a drive towards responsible test and resource stewardship, what is the downside of a flexible panel?

Lopansri: As with all diagnostic tests, it is only as good as why it's being used. Having to select what pathogens to test for may lead to missed diagnosis and treatment due to the failure to consider other viruses or atypical bacteria that may be causing an infection. Not considering a pathogen could lead to delayed or missed diagnosis and adverse consequences such as transmission events in a hospitalized patient or worsening disease from a treatable cause such as influenza or RSV in an immunocompromised patient.