Opinion on Syndromic Panel-Based Testing in Clinical Microbiology

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Molecular syndromic testing has received increased attention in the last 5 to 10 years. However, clinical microbiology laboratories have been doing syndromic testing for decades. Cultures for bacteria, viruses, fungi, and mycobacteria use methods (i.e., culture media, cell lines, temperatures, incubation conditions) that allow the recovery of a wide breadth of organisms causing infection at a particular body site; this is syndromic testing. Although parasitology largely relies on microscopic examination of special stains, these techniques encompass detection of the majority of human parasites described. Combined, these methods have allowed providers to cast a broad diagnostic net to determine etiologies of infectious diseases.

In contrast to the syndromic approach of traditional microscopic and culture-based methods, the initial molecular revolution in the clinical laboratory required providers to order each specific pathogen that they wanted to detect by molecular methods (i.e., orders for both enteroviruses and herpes simplex viruses from cerebrospinal fluid). The implementation of molecular detection for viruses by real-time PCR was a gigantic leap forward in terms of test sensitivity and time to result. However, molecular detection complicated test-ordering practices for clinical providers. Instead of ordering a viral culture for a patient with central nervous system disease, they now had to list their pathogens of priority. With this approach, a provider may not order an analyte for which the patient is positive (1).

Molecular syndromic testing combines the advantages of the approaches above: increased analytic sensitivity of molecular-based detection with the syndromic “panel”-based approach of culture and microscopy. Food and Drug Administration–cleared molecular panels now exist for upper respiratory tract infections, pneumonia, gastroenteritis, meningitis/encephalitis, sepsis and positive blood culture identification (1). The controversy lies in how best to use syndromic panels and whether the tests actually influence clinical management and improve patient outcomes. Although syndromic panels have substantially improved our ability to diagnose infectious diseases, these panels should be used cautiously and thoughtfully. When combined with antimicrobial and diagnostic stewardship efforts, syndromic tests are an important part of clinical decision-making, but their role in improving patient outcomes is more difficult to assess.

The debate around molecular syndromic panels includes varying opinions on appropriate panel targets, whether to use them as an initial test, in a testing algorithm or even whether to use them at all (2, 3). Diagnostic companies spend considerable time determining the “best” panel, yet the final marketed panel will never address every laboratory’s needs. Because of differences in patient populations, prevalence of pathogens, and provider ordering patterns, there will not be a “one size fits all” panel. In the quest to meet the clinical needs of a majority of laboratories, manufacturers have potentially extended some of the panels too far. By including rare targets, or targets that are unique to certain patient populations, the risk of medical errors increases owing to a higher probability of false-positive results (analytically or clinically). In addition, as the diagnostic limits of syndromic panels are tested, we risk false-negative results due to the limits of multiplexed analyses or specimen input volume. The inability of many panels to hide targets from reporting creates challenges for the laboratory, from creating the necessity to validate rare targets to testing and reporting unnecessary targets in some clinical circumstances. That being said, creating customizable panels for providers to order may lead to missed diagnoses. Further, if the same test is used by multiple facilities in a healthcare system, but each institution has a customized panel, it may create confusion and lead to medical errors. It is important for clinicians, laboratorians, and manufacturers alike to consider the guiding principle “first, do no harm” when applying molecular syndromic panels directly to patient care. Careful consideration is needed to determine the medical risks (false positives and false negatives) and how best to mitigate those risks (i.e., additional testing, interpretive comments, hiding targets).

Molecular syndromic panels (in particular, respiratory and gastrointestinal) have also come under scrutiny by third-party insurers and Medicare administrative contractors. Specifically, some payers have determined that large panel testing (>5 targets) is not medically necessary.
et al. implemented/discontinued antimicrobial use with the implementation of a gastrointestinal panel, whereas Hitchcock et al. described improved clinical sensitivity and targeted/discontinued antimicrobial use with the implementation of a gastrointestinal panel, whereas Hitchcock et al. (7) report the low yield of the same panel in adult inpatients, and Axelrad et al. (8) show the decrease in endoscopy, radiology, and antibiotic prescribing in a combined inpatient/outpatient setting. Perhaps more controversial is the analytical performance and potential effect (both positive and negative) of a meningitis/encephalitis panel, including false-negative Cryptococcus and false-positive herpes simplex virus and Streptococcus pneumoniae results (2, 9–11). The use of a meningitis/encephalitis panel led to a reduced length of stay in 1 study (12), but another publication reported that the meningitis/encephalitis panel’s rapid turnaround time led to overuse of the test and approximately 25% of positive results were determined to be clinically insignificant (13). These examples highlight the importance of keeping the results obtained with syndromic panels in clinical context and in the context of other laboratory results. Although the availability of molecular syndromic panels may allow testing at institutions that otherwise do not have molecular capability, careful consideration is needed to determine appropriate use of the test, including consideration of pretest probability, contamination monitoring, postanalytical interpretation, and the potential for additional laboratory testing for both positive and negative results.

Although the initial adoption of syndromic molecular panels was slow when only upper respiratory tract panels were available, the pace of adoption and the breadth of testing has markedly increased. Laboratories of all sizes are now offering one or more molecular syndromic tests. In addition, with the CLIA-waiver of syndromic panels, the opportunity of bringing testing closer to the patient is a reality. Major challenges exist when offering molecular tests in a nonlaboratory setting. For example, in addition to the usual challenges of point-of-care testing, contamination (amplicon and environment) is more likely to occur and less likely to be recognized than if the test was performed in a laboratory; test orders and results may not be documented in a patient’s electronic medical record; and the expertise of clinical micro-

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<th>Test performance</th>
<th>Patient care</th>
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<td>Detection of additional pathogens and resistance genes</td>
<td>Decrease unnecessary testing</td>
<td>Fewer healthcare-associated infections</td>
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<tr>
<td>Improved analytic sensitivity</td>
<td>Changes in antimicrobial therapy (escalation, de-escalation, or cessation)</td>
<td>Shorter hospital length of stay</td>
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<tr>
<td>Decreased time to result</td>
<td>Effect on infection control precautions (early removal or implementation)</td>
<td>Fewer unnecessary admissions and re-admissions</td>
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<td>Near-patient testing using moderate-complexity or CLIA-waived tests</td>
<td>Lower mortality</td>
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<td>Reduced cost of care</td>
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There are many documented and hypothesized benefits of molecular syndromic testing (Table 1). For most panels, improvements in test performance relative to traditional methods have been documented, namely an increase in analytical sensitivity and a decrease in time to result. In some instances, analytic and clinical specificity may be compromised. Demonstration of improvements in patient care have primarily focused on antimicrobial stewardship goals such as decreasing antimicrobial use through viral respiratory panel testing or faster time to targeted therapy for positive blood culture panel results. Although many studies have investigated the effect of rapid blood culture identification on patient care with success, data demonstrating the effect of non–blood culture syndromic panel use on patient or cost outcomes are sparse. It is challenging to design and perform studies that measure improvements in patient care and clinical outcomes; therefore, data supporting these hypothesized benefits are still greatly needed (5). The outcome data available are generally limited to a single institution or a limited patient population (i.e., respiratory panels in pediatrics). Further, reports on impact conflict in varying patient populations. For example, Cybulski and colleagues (6) describe improved clinical sensitivity and targeted/discontinued antimicrobial use with the implementation of a gastrointestinal panel, whereas Hitchcock et al. (7) report the low yield of the same panel in adult inpatients, and Axelrad et al. (8) show the decrease in endoscopy, radiology, and antibiotic prescribing in a combined inpatient/outpatient setting. Perhaps more controversial is the analytical performance and potential effect (both positive and negative) of a meningitis/encephalitis panel, including false-negative Cryptococcus and false-positive herpes simplex virus and Streptococcus pneumoniae results (2, 9–11). The use of a meningitis/encephalitis panel led to a reduced length of stay in 1 study (12), but another publication reported that the meningitis/encephalitis panel’s rapid turnaround time led to overuse of the test and approximately 25% of positive results were determined to be clinically insignificant (13). These examples highlight the importance of keeping the results obtained with syndromic panels in clinical context and in the context of other laboratory results. Although the availability of molecular syndromic panels may allow testing at institutions that otherwise do not have molecular capability, careful consideration is needed to determine appropriate use of the test, including consideration of pretest probability, contamination monitoring, postanalytical interpretation, and the potential for additional laboratory testing for both positive and negative results.
biologists and infectious disease physicians may not be readily accessible (14). However, these challenges are worth addressing, because it may only be when testing is done truly at the point of care that we will realize some of the reputed benefits of syndromic testing.

Perhaps the most exciting investigative path for syndromic testing is the combination of host expression patterns and organism detection (15). By determining whether a syndrome is likely infectious or noninfectious, providers can be reassured when not prescribing antibiotics. Although biomarkers such as procalcitonin and C-reactive protein are frequently used in the evaluation of sepsis, pneumonia, and other infections, their use is controversial and lacks clinical specificity. Some may argue that a syndromic test is not needed for some clinical presentations (including respiratory and gastrointestinal) because they are most commonly viral with no intervention. However, if patients can be reassured that antibiotics are not needed by providers who are empowered with rapid, accurate, and inexpensive syndromic tests, we can begin to reverse antibiotic overprescribing, which will aid in our war on antimicrobial resistance.

As with the implementation of any new technology, there are still more questions to be answered. Just because we can test for so many targets, should we? Which patients would benefit most from syndromic testing? As laboratorians, how do we educate clinical providers on best ordering practices and result interpretation? For institutional economics, how is the return on investment in molecular syndromic testing measured (i.e., length of stay, readmission, decreased antibiotic use, or additional testing)? How does a laboratory or healthcare system determine the best panel for their institution? Should the Food and Drug Administration require that all panels be customizable via software?

Despite the caveats and questions highlighted here, I am optimistic that the surge of syndromic panels, and the associated competitive market, will continue to push diagnostics toward excellence. Our charge is to determine and publish “real-world” performance characteristics, by target, of syndromic panels. We need to provide postmarket feedback to manufacturers on the clinical performance of tests, and these data should be publicly available. We need to collaborate with industry and clinical colleagues to ascertain the effect on patient care and outcomes. We need to work with payers to define medical necessity and reimbursement strategies. No test is perfect, but if we are armed with the knowledge of true test performance and clinical utility in specific patient populations, we can use these powerful tests in a safe and impactful manner.

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