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# Syndromic diagnostic testing: a new way to approach patient care in the treatment of infectious diseases

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Advanced microbiology technologies such as multiplex molecular assays (i.e. syndromic diagnostic tests) are a novel approach to the rapid diagnosis of common infectious diseases. As the global burden of antimicrobial resistance continues to rise, the judicious use of antimicrobials is of utmost importance. Syndromic panels are now being recognized in some clinical practice guidelines as a 'game-changer' in the diagnosis of infectious diseases. These syndromic panels, if implemented thoughtfully and interpreted carefully, have the potential to improve patient outcomes through improved clinical decision making, optimized laboratory workflow, and enhanced antimicrobial stewardship. This paper reviews the potential benefits of and considerations regarding various infectious diseases syndromic panels, and highlights how to maximize impact through collaboration between clinical microbiology laboratory and antimicrobial stewardship programmes.

## Introduction

The increasing global burden of antimicrobial resistance has highlighted the need to develop new antimicrobial therapies.[1,2] Unfortunately, the development of novel, effective antimicrobial agents continues to lag behind this demand, leaving clinicians searching for methods to preserve and optimize current therapies.[3] Often, the microbiological diagnosis of infectious diseases is tied directly to the antimicrobial regimen chosen for treatment, with quicker time to result potentially sparing days of broad-spectrum antimicrobial use.[4,5]

Traditional methods of culture and susceptibility testing rely on biochemical and phenotypic analyses, which can take days to identify the causative pathogen(s). However, significant advances in clinical microbiology practice have been made in the past two decades stemming from the development of novel molecular diagnostic platforms.

Multiplex PCR (mPCR) tests (also known as 'syndromic' panels) combine tests for numerous pathogens and resistance genes into a single test, and have changed how we diagnose infections, leading to improved patient care and clinical workflow.[4,5] These syndromic panels have the ability to impact infection control, antimicrobial stewardship, and patient outcomes by significantly reducing time to diagnosis and clinical decision making. As patients and hospitals may be charged hundreds of dollars per test, considering the optimal use of these tests is paramount prior to implementation in order to maximize clinical and economic outcomes. Syndromic diagnostic panels are now commercially available to aid in the diagnosis of common, serious infections that affect the bloodstream, respiratory, gastrointestinal, and central nervous systems.[6–8] Here, we discuss the proposed benefits and drawbacks of syndromic testing by infection type, as well as ways in which this testing can be practically implemented within clinical microbiology laboratories and infectious diseases workflows. The data discussed in each section are summarized in Table 1.

## Syndromic approaches to bloodstream infections

Bloodstream infections can be caused by a variety of pathogens and carry a high risk of mortality, which increases with every hour of delayed appropriate antimicrobial therapy.[9] Syndromic panels that can rapidly detect common causes of bloodstream infections and associated resistance genes are ideal for improving patient care and outcomes.[10] For example, several blood culture identification (BCID) assays have demonstrated reduced time to actionable results and improved patient outcomes when utilized in conjunction with antimicrobial stewardship programmes for the rapid identification of blood culture pathogens. Verroken *et al.*[11] demonstrated the impact of a BCID panel on time to optimal therapy in 110 critically ill adult patients with bloodstream infections. The implementation of this mPCR system shortened the median time to optimal therapy from 14.68 h to 4.65 h, and resulted in the adjustment of antibiotics in 31.8% of patients. Median time to pathogen identification via mPCR was 1.58 h and 96.2% of organisms were able to be identified by the multiplex panel. Walker *et al.*[12] found similar outcomes when evaluating another automated multiplex Gram-negative blood culture panel in 98 hospitalized patients with Gram-negative bacteraemia. When

**Table 1.** Summary of data comparing syndromic diagnostic testing with conventional methods

| Publication | Syndromic tool used | Syndromic specimen | Conventional method | Study design | Setting/sample size | Key findings |
|---|---|---|---|---|---|---|
| Bloodstream infections | | | | | | |
| Verroken *et al.*[11] 2019 | BioFire FilmArray | Whole blood | Gram stain, MALDI-TOF | Retrospective quasi-experimental study | • Tertiary Belgian hospital<br>• 110 critically ill patients | • Median time to optimal therapy shortened from 14.68 h to 4.65 h<br>• Antibiotics adjusted in 31.8% of patients<br>• Median time to pathogen identification: 1.58 h (96.2% of pathogens identified) |
| Walker *et al.*[12] 2016 | Verigene BC-GN® | Whole blood | Blood culture, subculture to solid medium during initial Gram stain | Retrospective quasi-experimental study | • Tertiary hospital; Los Angeles, CA<br>• 98 hospitalized patients with Gram-negative bacteraemia | • Median time to pathogen identification reduced from 30.3 h to 19.1 h<br>• ICU LOS significantly shorter: 12 versus 16.2 days, $P = 0.033$<br>• 30-day mortality significantly shorter: 8.1 verses 19.2, $P = 0.037$<br>• Estimated net cost saving for each patient in ICU: $11 661 |
| Respiratory tract infections | | | | | | |
| Rappo *et al.*[16] 2016 | BirFire FilmArray | Nasopharyngeal swabbing or BAL | Nasopharyngeal swabbing or BAL | Retrospective cohort | • Tertiary hospital; New York-Presbyterian Hospital/Weill Cornell Medical Center<br>• 337 adult patients | • Influenza result: 1.7 h versus 7.7 h, $P = 0.015$<br>• Non-influenza viruses diagnosis discharged home: 21% versus 5%, $P = 0.049$<br>• No difference in-hospital antibiotic use |
| Rogers *et al.*[17] 2015 | BioFire FilmArray | Nasopharyngeal swabbing | Nasopharyngeal swabbing | Retrospective quasi-experimental study | • Tertiary referral centre<br>• 1136 paediatric patients | • Average time to test result: 383 min versus 1119 min, $P = 0.001$<br>• Hospital LOS and antibiotic use were similar between groups |
| Srinivas *et al.*[18] 2019 | Respiratory viral PCR test | Nasopharyngeal swabbing | Nasopharyngeal swabbing | Retrospective quasi-experimental study | • Multicentre; Cleveland Clinic Health System<br>• 55 actionable antimicrobial stewardship interventions identified | • 47% of stewardship interventions accepted<br>• Time to de-escalation of antibiotics were similar between pre- and post-multiplex PCR: 2.7 versus 2.3 days, $P = 0.88$ |
| Brendish *et al.*[19] 2020 | QIAstat-Dx Respiratory SARS-CoV-2 Panel | Nasopharyngeal swabbing | Nasopharyngeal swabbing | Prospective, non-randomized, interventional study | • Secondary care facility, UK<br>• 1054 adult patients | • Median time to result of POC test: 1.7 h versus 21.3 h for control<br>• Time to arrival in definitive clinical area: 8 h versus 28.8 h, $P = 0.0001$ |
| Buchan *et al.*[21] 2020 | Biofire FilmArray Pneumonia panel (PP) | Sputum | Bacterial culture following BAL, mini-BAL, or endotracheal aspirate, | Retrospective, multicentre, | • 8 U.S. medical centres<br>• 259 adult patients | • Biofire Film Array Pneumonia panel had 96.2% positive agreement with |

*Continued*

**Table 1.** *Continued*

| Publication | Syndromic tool used | Syndromic specimen | Conventional method | Study design | Setting/sample size | Key findings |
|---|---|---|---|---|---|---|
| | | | MALDI-TOF, nucleic acid amplification | observational study | | routine cultures, and 98.1% negative agreement<br>• Estimated multiplex panel results would have allowed for earlier antibiotic adjustments in 70.7% of patients resulting in an average of 6.2 antibiotic days saved per patient |
| Lee *et al.*[22] 2019 | Biofire FilmArray Pneumonia panel (PP) | Sputum | Gram stain and bacterial culture for sputum, MALDI-TOF, nucleic acid amplification, urine antigen testing (for *Legionella* and pneumococcal detection), nasopharyngeal swab for influenza | Prospective, single centre, observational study | • Tertiary referral hospital in Taiwan<br>• 51 critically ill adult patients | • Overall agreement: 79%<br>• Qualitative agreement: 90% positive and 97.4% negative agreement<br>• Quantitative agreement: 53.6% for culture-positive specimens and 86.3% for culture-negative specimens<br>• Estimated multiplex panel may have led to de-escalation of empirical antibiotics in 27.1% of patients and escalation in 13.6% of patients |
| Infectious diarrhoea | | | | | | |
| Beal *et al.*[24] 2017 | Biofire FilmArray Gastrointestinal panel (GIP) | Stool | Stool culture antigen testing | Retrospective quasi-experimental study | • Tertiary care, academic medical centre; Florida<br>• 241 stool samples tested with GIP<br>594 tested with conventional methods | • *Clostridioides difficile* testing results were excluded<br>• Stool positivity rate increased from 6.7% to 32%, $P = 0.0002$<br>• Average LOS using GIP was 3.9 days versus 3.4 days for conventional methods, $P = 0.04$<br>Multiplex estimated to decrease cost of care by $293.61 per patient |
| Axelrad *et al.*[25] 2019 | Biofire FilmArray Gastrointestinal panel (GIP) | Stool | Stool culture, antigen testing, modified acid-fast staining | Retrospective cross-sectional study | • Quaternary care centre; New York<br>• 9402 stool samples tested with GIP<br>• 5986 stool samples tested with conventional methods | • Percent positivity increased from 4.1% to 29.2%, $P = 0.001$<br>• Patients assessed via multiplex PCR were less likely to undergo endoscopy: 9.6% versus 8.4%, $P = 0.008$<br>• Patients assessed via multiplex PCR were less likely to be prescribed antibiotics: 40.9% versus 36.2%, $P = 0.001$ |
| CNS infections | | | | | | |
| Leber *et al.*[27] 2016 | The FilmArray Meningitis/ | CSF | Bacterial culture and Gram stain of CSF sample, MALDI-TOF, | Prospective, multicentre, cohort study | • 11 sites in the U.S.<br>• 1560 CSF samples | • ME panel was able to detect 141 of the most common pathogens associated with meningitis versus 104 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Encephalitis (ME) | | nucleic acid amplification | | | pathogens with using traditional methods<br>• Negative predictive value was >99% |
| Tarai and Das[28] 2019 | The FilmArray Meningitis/ Encephalitis (ME) | CSF | Bacterial culture and Gram stain of CSF sample, nucleic acid amplification | Retrospective cohort study | • Tertiary care hospital; north India<br>• 969 CSF samples | • ME panel identified 101 organisms (10.4% of cases)<br>• Breakdown of cases identified: 55 viral, 38 bacterial, 7 fungal and 1 polymicrobial<br>• ME detected more cases that are difficult to diagnose by conventional methods |
| Pfefferle *et al.*[29] 2020 | The FilmArray Meningitis/ Encephalitis (ME) | CSF | Bacterial culture and Gram stain of CSF sample, nucleic acid amplification | Prospective observational study | • Tertiary care, university hospital; Germany<br>• 4623 CSF samples with 171 matching criteria for multiplex analysis | • ME panel identified 56 pathogens (32.7%)<br>• 96.3% sensitivity<br>• 96.58 specificity |

LOS, length of stay; BAL, bronchoalveolar lavage; POC, point-of-care.

compared with traditional blood culture workup, mPCR reduced the median time to organism identification from 30.3 to 19.1 h. In the mPCR group, ICU length of stay was significantly shorter (12.0 versus 16.2 days, $P = 0.033$) and 30 day mortality was significantly lower (8.1% versus 19.2%, $P = 0.037$). Additionally, a net cost saving to the health system of US$11 661 was estimated for each patient who had an ICU admission and diagnostic workup completed using mPCR testing. These findings demonstrate that improved time to bloodstream pathogen identification and diagnosis with syndromic testing may lead to significant positive downstream effects, including improved time to optimal therapy, improved clinical outcomes, and decreased cost of care.

Clinical microbiology laboratories will likely find the most benefit when incorporating molecular testing for bloodstream infections as part of their routine workflow.[11] Once blood cultures flag as positive, these tests can be set up immediately to identify the causative pathogen and a selection of resistance gene targets such as *mecA, vanA/B*, or *Klebsiella pneumoniae* carbapenemase (KPC). Despite this rapid time to organism genotypic identification, these tests do not provide phenotype and are not cleared by the US FDA to replace automated identification (ID) or antibiotic susceptibility testing (AST). Therefore, confirmatory testing for ID and AST must still be performed by automated methods, which can take 24–72 h. Another important limitation of these tests is that while the majority of common organisms can be identified using molecular methods, cartridge and probe limitations do exist for less-common organisms, as well as in cases of polymicrobial bacteraemia.[6] Finally, hospitals must assess their current antibiogram trends for pathogens isolated and susceptibilities to determine if the earlier time to organism identification will result in actionable changes to benefit patient care, as well as whether they have staffing resources in place to act on the results.

## Syndromic approaches to respiratory tract infections

Given the substantial burden of viral respiratory illnesses and pneumonia, syndromic diagnostic testing that allows for rapid pathogen identification to distinguish between viral and bacterial pathogens would be ideal for health systems aiming to optimize antimicrobial use.[12] Syndromic diagnostic respiratory panels (RP) are available for both upper respiratory tract infections via nasopharyngeal swab or secretion samples and lower respiratory tract infections via sputum or protected specimen collection.[13] While outpatient primary care sites or urgent care sites may seem ideal locations to implement upper respiratory testing, considerations for rapid access to testing and trained personnel are needed. In the United States, the majority of syndromic diagnostic platforms are not Clinical Laboratory Improvement Amendment (CLIA)-waived for point-of-care (POC) use, making it difficult to perform testing outside of facilities adjoining the central laboratory. Although CLIA-waived respiratory panels are considered low-complexity, allowing non-laboratory personnel to conduct the test at the site of care, the additional cost of the diagnostic platform and the need to train personnel must be considered. In addition, sites must take into account whether the results of these panels will improve practice and therapeutic decision making enough to justify the extra cost.[14] In Europe and other countries that allow

for CE-marked devices to be utilized in nearer-patient settings, there have been many studies demonstrating benefits across a range of clinical outcomes, including infection control measures.

The emergency department may represent a better location for syndromic diagnostic testing of respiratory illnesses. At the juxtaposition between inpatient and outpatient care, there is the potential to impact both antibiotic prescribing and the use of additional healthcare resources.[15] A retrospective cohort study by Rappo *et al.*[16] compared test turnaround time and treatment outcomes of 337 adult patients evaluated in the emergency department with a multiplex upper respiratory PCR panel or conventional diagnostic methods. Median turnaround time to test results was significantly reduced in the mPCR testing group of patients who had influenza (1.7 versus 7.7 h, $P = 0.015$) and non-influenza viruses (1.5 versus 13.5 h, $P = 0.001$). Patients diagnosed with non-influenza viruses via mPCR were also more likely to be discharged home from the emergency department before arrival to the ward, despite being initially identified for hospital admission (21% versus 5%, $P = 0.049$). Unfortunately, the authors found no difference between groups with respect to in-hospital antibiotic use among patients testing positive for any virus. In multivariate logistic regression adjusting for age, comorbidities and ICU status, the authors found that patients who were diagnosed with influenza via mPCR had a significantly shorter length of stay ($P = 0.040$), antimicrobial duration ($P = 0.032$) and use of chest radiography ($P = 0.005$) when compared with conventional diagnostic methods. Rogers *et al.*[17] demonstrated similar findings in a quasi-experimental study of 1136 paediatric patients diagnosed with upper respiratory viral illnesses via mPCR compared with conventional PCR testing. A significant reduction in average time to test result was observed with mPCR [383 min (range 72–3143) versus 1119 min (range 250–3705), $P = 0.001$]. Patients were more likely to receive their results while in the emergency department (51.6% versus 13.4%, $P = 0.001$); however, hospital length of stay and antibiotic use were similar between groups. These findings demonstrate the difficulties that stewardship programmes may encounter, even with rapid results, in implementing syndromic testing for viral respiratory pathogens and in reducing unnecessary antibiotic use. Those patients clinically-ill enough to warrant hospital admission from the emergency department for observation of respiratory status are often started on empirical antibiotics based on continued clinical suspicion of bacterial infection and positive chest radiography. Importantly, Srinivas *et al.*[18] evaluated the inpatient use of molecular viral respiratory testing combined with antimicrobial stewardship team alerting and intervention within a large health system. They similarly found that a large number of patients with positive rapid viral test results received antibiotics; only 47% of stewardship interventions for de-escalation were accepted and time to de-escalation of antibiotics was similar between the pre- and post-mPCR testing (2.7 versus 2.3 days, $P = 0.88$). Health systems and stewardship teams implementing syndromic testing with upper RPs as standard of care should be cautious of the limitations regarding actionable results and consider performing test audits after implementation to evaluate opportunities to minimize waste.

In the midst of the coronavirus disease 2019 (COVID-19) pandemic, it would be remiss not to discuss the potential impacts of using a syndromic RP from the perspectives of differential diagnosis, co-infection and public health. Recently, Brendish *et al.*[19] prospectively evaluated the utility of a SARS-CoV-2 RP in a POC setting. Median time to result with the RP at POC was 1.7 h versus 21.3 h in the control group. Importantly, time to arrival in the definitive clinical area (i.e. COVID-19-positive or -negative ward) was 8.0 h in the RP group versus 28.8 h in the control group ($P < 0.0001$). Isolation and containment are paramount to controlling this deadly disease. Brendish *et al.*[19] demonstrated that usage of an RP in a nearer-patient setting led to improvement in infection control measures and patient flow, with patients spending 1 day fewer in assessment areas and having fewer bed moves prior to their definitive care area.

Syndromic diagnostic panels for identification of lower respiratory tract pathogens have additional sample types, an expanded pathogen catalogue, and often include resistance genes.[20] In a multicentre study, Buchan *et al.*[21] evaluated the impact of a pneumonia panel compared with routine bacterial culture in 259 adult patients with bronchoalveolar lavage samples. For organisms included within the mPCR panel, they found 96.2% positive agreement and 98.1% negative agreement when compared with routine culture. Semi-quantitative values were also reported, with an agreement of 43.6%. The authors further evaluated the potential impact of mPCR technology on patient care. They estimated that the multiplex panel results would have allowed for earlier antibiotic adjustment in 70.7% of patients, including de-escalation or discontinuation in 48.2%; this would have resulted in an average of 6.2 antibiotic days saved per patient. Lee *et al.*[22] evaluated the same syndromic panel in a prospective, single-centre study of 51 critically ill adult patients with tracheal aspirate or bronchoalveolar specimens. Overall agreement between methods was 79%, with 90% positive agreement and 97.4% negative agreement when considering qualitative agreement alone. Quantitative agreement was much lower: 53.6% for culture-positive specimens and 86.3% for culture-negative specimens. The authors cautioned that overestimation of quantification was observed, possibly attributable to non-viable organisms. The syndromic panel detected significantly more viruses, and co-infections in 42.3% of patients. Of the patients with bacteria detected via either diagnostic method, mPCR testing was able to detect 7 (24.1%) bacterial pathogens that were not identified via routine culture; however, specimens from 18 (30.5%) patients grew bacteria on culture that were not included in the syndromic panel. Substantial discrepancies were observed in the identification of antimicrobial resistance genes by mPCR and automated susceptibility testing. The authors estimated that syndromic testing for pneumonia pathogens may have led to de-escalation of empirical antibiotics in 27.1% of patients, escalation in 13.6% of patients and no change in 55.9% of patients. They concluded that the patients most likely to benefit from testing were early in their disease course, when results would impact empirical therapy decisions.

These findings bring to light important considerations and limitations of syndromic testing for lower respiratory tract infections. For instance, quantitative values are reported in addition to qualitative values, warranting caution in interpreting results to avoid overestimating their significance. Clinicians must interpret both the mPCR result and final culture results together when making definitive antimicrobial therapy plans. Furthermore, it is important to consider inconsistencies with resistance gene detection, especially in the case of co-infections or in sites with low prevalence of resistant pathogens. Optimal test implementation will likely

benefit from clinical expertise in ordering and interpretation of the platform results. As specimen type is limited to sputum, tracheal aspirate, or bronchoalveolar lavage, it may be reasonable for hospitals to limit this technology to pulmonology, critical care, or infectious diseases teams caring for critically ill patients.

## Syndromic approaches to infectious diarrhoea

Multiplex PCR testing for viral, bacterial and parasitic causes of gastrointestinal illnesses and infectious diarrhoea is one of the newer uses of syndromic diagnostic testing. As infectious diarrhoea is estimated to cause more than 48 million illnesses and 3000 deaths per year in the United States alone, syndromic diagnostic methods are important to consider in improving time to pathogen identification.[23] Beal *et al.*[24] noted improvement in time to test results as well as improved pathogen identification when comparing 241 patient stool samples tested via a gastrointestinal panel (GIP) with 594 patients tested via conventional methods for infectious diarrhoea. Of note, *Clostridioides difficile* testing results were excluded from the study. Stool positivity rate increased from 6.7% to 32% and average time to test result was significantly shorter with mPCR (8.94 h versus 54.75 h, $P < 0.0001$). Additionally, patients tested with a GIP were less likely to have additional stool testing ($P = 0.0001$) or abdominal imaging studies ($P = 0.0002$) and the average length of stay following stool sample collection that was 0.5 days shorter than those tested with conventional methods (3.9 versus 3.4 days, $P = 0.04$). When considering length of stay, imaging, antimicrobial and test costs, the authors concluded that the use of mPCR decreased cost of care by $293.61 per patient. As syndromic testing was driven by study protocol, they also noted that a significant number of clinically relevant pathogens—including 4 bacterial pathogens, 6 parasites and 21 cases of norovirus—were identified that may not have been identified otherwise, considering the conventional test orders placed by the primary care provider. Axelrad *et al.*[25] corroborated these results when testing 15 388 patients for infectious diarrhoea by either conventional methods or GIP. Percentage positivity increased from 4.1% to 29.2% and patients assessed via mPCR were less likely to undergo endoscopy (9.6% versus 8.4%, $P = 0.008$), have abdominal radiology performed (31.7% versus 29.4%, $P = 0.0002$), or be prescribed antibiotics (40.9% versus 36.2%, $P = 0.001$).

Hospitals implementing syndromic diagnostic testing for gastrointestinal infections should be cautious, however, due to the significant cost, potential for waste and limitations of these tests. Some of the main difficulties noted with syndromic GIPs are the ability to distinguish clinically relevant pathogens from non-pathogenic bystanders, yielding potential false-positive results. Patients with community-onset, non-severe disease are unlikely to benefit from syndromic testing; they tend to require only supportive care, with limited need for additional radiology or diagnostic workup. As demonstrated by Beal *et al.*,[24] 31 patients who may have otherwise not had a definitive diagnosis were able to have a causative pathogen identified due to the broad syndromic panel. It is important to note, however, that most of these cases were caused by pathogens that would require no pharmacological treatment outside of supportive care. Additionally, patients who have an onset of diarrhoea at >72 h of hospitalization are unlikely to benefit from more than *C. difficile* testing alone, which can be done more cost effectively outside of the full syndromic panel.

An additional limitation of syndromic diagnostic testing for infectious diarrhoea relates to *C. difficile*. In the study by Beal *et al.*,[24] reporting of *C. difficile* results obtained via the syndromic panel were hidden from the electronic health record. This may be an important strategy for other sites to use when implementing syndromic GI testing, because stool samples for *C. difficile* are recommended to be unformed, which may not be the case with other causes of infectious diarrhoea. Furthermore, testing via mPCR may over-call *C. difficile* in hospitals that are currently using antigen testing. Laboratories should consider limiting the use of the syndromic GIP to the first 72 h of hospitalization to avoid potential wasteful testing in patients with a high likelihood of *C. difficile* or non-infectious diarrhoea. For these reasons, algorithmic approaches that incorporate disease severity, travel and dietary history, and length of hospitalization may work best to optimize implementation while limiting cost. Sites may also consider prior authorization by specialists in infectious diseases or gastroenterology.

## Syndromic approaches to CNS infections

Of the four infection types discussed in this review, the diagnosis of CNS infections using syndromic testing may pose the most challenges for health systems to implement. Limited data exist evaluating the implementation of mPCR testing for meningitis or encephalitis. A meningitis/encephalitis (ME) panel is able to detect the most common bacterial, viral and fungal causes of community-acquired CNS infections concurrently with a single CSF sample.[26] Leber *et al.*[27] performed a prospective, multicentre evaluation of 1560 CSF samples to demonstrate the sensitivity and specificity of an ME panel compared with traditional culture and PCR testing methods. The ME panel was able to detect 141 of the most common pathogens associated with meningitis; the traditional methods detected only 104 pathogens. The negative predictive value was greater than 99% for all analyses. Tarai and Das[28] demonstrated benefit in implementing syndromic ME testing in a tertiary care hospital in patients with suspected meningitis, which resulted in rapid diagnosis of meningitis and identification of common causative organisms. Out of 969 CSF samples taken from patients with symptoms consistent with CNS infections, organisms were identified in only 101 (10.4%) cases (55 viral, 38 bacterial, 7 fungal and 1 polymicrobial).

Syndromic testing for meningitis can add a high diagnostic cost burden that may not be offset if suspicion of infection is low, so careful planning should be considered before implementation. Pfefferle *et al.*[29] also evaluated the use of a ME panel for routine diagnosis of CNS infections in a university hospital setting. The authors assessed clinical performance, utility and cost. A total of 4623 CSF samples were evaluated; however, to minimize unnecessary cost, mPCR technology was used to evaluate only those samples with findings indicative of infectious meningitis (e.g. positive Gram stain, leucocytes, or cases where clinicians maintained a high suspicion of infection). Of the 4623 CSF samples, 171 (3.7%) matched these criteria and were analysed. Fifty-six pathogens (32.7%) were detected with 96.3% and 96.58% sensitivity and specificity, respectively. Pfefferle *et al.*[29] were able to demonstrate a higher sample positivity rate compared with other studies, which is likely due to implementing the criteria that limited laboratory use of the ME panel to samples with findings suggestive of

infectious meningitis. Patients with lumbar puncture findings not suspicious for infection are unlikely to benefit from this technology.

An additional important consideration is that the meningitis panel currently available contains probes only for pathogens associated with community-onset infections. Therefore, patients with a diagnosis of post-procedural or healthcare-associated meningitis are not likely to benefit from this testing, nor would patients who are being worked up for atypical pathogens (such as syphilis or West Nile virus). With these considerations in mind, is not ideal for laboratories to automatically perform syndromic testing of CSF samples following lumbar puncture. Optimal implementation of syndromic testing for CNS infections should involve clinician review following lumbar puncture and prior to initiating mPCR testing. To optimize testing while limiting cost and waste, hospitals may consider restricting this technology to use or approval by infectious diseases or antimicrobial stewardship teams.

## Considerations for implementation of syndromic tests into stewardship programmes to combat antimicrobial resistance

Antimicrobial resistance trends continue to be a major threat and concerns related to drug-resistant pathogens are often a driving factor behind the selection of empirical broad-spectrum antimicrobials.[30] The potential benefits of syndromic diagnostic testing can be far-reaching—both to individual patient outcomes and at the health system level—because appropriate antibiotic use can directly impact patient outcomes, length of hospital stay, and cost of care.[5] Syndromic approaches to diagnosis are not without their drawbacks however, so these tests must be implemented practically and interpreted carefully to prevent waste. Multidisciplinary input from clinical microbiology, infectious diseases, and antimicrobial stewardship teams is needed to optimize workflow and processes for test result notification, as well as to promote action on results.

From the laboratory perspective, these tests reduce the hands-on time required of technicians for both specimen set-up and analysis compared with conventional diagnostic methods, potentially aiding in streamlining processes and freeing up technician time for other tasks that are more labour-intensive. The laboratory space required for most platforms is also minimal and the majority will interface with most common electronic health records. Unfortunately, automated susceptibility testing following the use of syndromic panels is still required; this must be considered when deciding whether panels will be run on demand or as batched specimens.

It is also important for teams to consider when the test will be used (i.e. instead of, or in addition to, routine workup) and if the test results will impact patient management. Collaboration with the antimicrobial stewardship team may also further augment the use of syndromic diagnostic testing. Studies evaluating the impact of implementing syndromic diagnostic panels for bloodstream infections along with antimicrobial stewardship programme intervention have consistently shown improvement in organism identification due to faster turnaround time, which leads to de-escalated and targeted antibiotic use, decreased hospital length of stay, and decreased cost of care.[31–35] Additionally, as more genetic determinants of resistance are included in syndromic panels, non-infectious-diseases personnel will need to be appropriately educated on their clinical interpretation in order to understand and act upon the results.

## Conclusions

Syndromic diagnostic testing is a novel approach to the rapid diagnosis of common infectious diseases, including bloodstream, respiratory, gastrointestinal, and CNS infections. As the global burden of antimicrobial resistance continues to rise, the judicious use of antimicrobials is of utmost importance. Syndromic panels, if implemented thoughtfully and interpreted carefully, have the potential to improve antimicrobial use and patient outcomes through improved clinical decision making, optimized laboratory workflow, and enhanced antimicrobial and laboratory stewardship. As clinical experience with new syndromic diagnostic platforms continues to grow, it will be important for clinicians to share their experiences regarding implementation and optimization strategies.

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L.D and L.W. have none to declare. S.R. is an employee of QIAGEN. This article forms part of a Supplement sponsored by QIAGEN.

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