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Panels and Syndromic Testing in Clinical Microbiology



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KEYWORDS

- Syndromic panel • Respiratory panel • Bloodstream infection panel
- Gastroenteritis panel • Meningitis panel • Encephalitis panel
- Diagnostic stewardship • Laboratory stewardship

KEY POINTS

- Syndromic testing allows clinicians to rapidly test for a broad number of pathogens, generally with greater sensitivity and specificity than traditional methods.
- With the ease of testing has come the overuse of testing.
- Diagnostic stewardship is necessary to ensure proper use of syndromic testing and correct interpretation of the results in the context of the patient.

INTRODUCTION

In 2011, the first respiratory syndromic panel was cleared by the US Food and Drug Administration (FDA). In less than 10 years' time, syndromic panel testing has expanded to multiple commercial assays for detection of respiratory, blood, gastrointestinal (GI), acute meningitis and encephalitis (ME), and lower respiratory tract infections (LRTIs) and in doing so it has revolutionized the clinical microbiology laboratory. Syndromic panels have been embraced by clinical microbiology laboratories who appreciate the low hands-on time and integrated work flow these assays provide. They have also been embraced by clinicians who love the rapid turnaround time and broad number of targets, many of which they had not been able to routinely

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test for before syndromic panels. However, with these advances have come complications—the high cost of testing, overtesting, and confusing results that do not have a clear link to patient care, such as multiple positive results or targets of unknown significance. In this article, we discuss the commercially available syndromic panels, the benefits and limitations of testing, and how diagnostic and laboratory stewardship can be used to optimize testing and improve patient care while keeping costs under control.

DETECTION OF BLOODSTREAM PATHOGENS

Detection of bloodstream infections (BSI) is one of the most important functions of the microbiology laboratory. Because these infections cause great morbidity and mortality, placing patients on optimal treatment as quickly as possible is a high priority.¹ Syndromic testing of positive blood culture broth provides rapid pathogen identification for the majority of bacteria that cause BSIs as well as common contaminants that do not require treatment.² In addition, several syndromic blood panels detect antimicrobial resistance genes and 1 assay provides rapid phenotypic susceptibility results. **Table 1** provides a list of FDA-cleared syndromic panels for diagnosis of BSIs. These assays provide bacterial identification 18 to 24 hours earlier than conventional culture and identification methods. The limited susceptibility information is available 48 hours earlier than traditional phenotypic susceptibility results. Syndromic panels for BSIs represent an adjunct test and do not replace culture or complete antimicrobial susceptibility testing. The exception is the Accelerate PhenoTest BC (Accelerate Diagnostics, Tucson, AZ), which provides identification and complete phenotypic susceptibility results in 9 hours.³

Limitations of these assays include no detection of off-target pathogens, a lack of full susceptibility information, cost, and false-positive results. Not every bloodstream pathogen is represented as a target organism on syndromic panels and for these off-target organisms no identification is provided. The scope of antimicrobial resistance information provided depends on the targets present on the syndromic panel. Resistance markers provided for gram-positive organisms are largely sufficient for optimal antimicrobial treatment. For gram-negative organisms, most panels provide only partial information. For the PhenoTest BC, the antibiotics tested are set by the manufacturer and may or may not meet the needs of your patient population or hospital drug formulary. In many cases, traditional identification and susceptibility testing, and the associated delay, is still required to provide all of the information needed for patient care. Syndromic panels are expensive, especially compared with other testing performed in the microbiology laboratory and the cost may be a challenge to implement these assays into your institution. This issue is somewhat less important with syndromic tests for BSIs because only positive blood culture broth is tested and the infections being treated are of critical importance. Recently there have been reports of false-positive *Proteus* and *Escherichia coli* results caused by nonviable DNA in the blood culture broth of some blood culture bottles.² These false-positive results cause patients to be treated for bacterial infections they do not have and potentially mistreated for bacteria that is present in their blood.

Although all laboratories have reported decreased turnaround time to results using syndromic blood culture panels, the results of outcome studies measuring their effect on patient care and hospital finances has been mixed. The biggest benefits are seen with the detection of highly resistant organisms such as multidrug-resistant gram-negative bacteria or vancomycin-resistant enterococci.^{4–7} Empiric therapy is often ineffective against these organisms, so rapid identification and antibiotic escalation

Table 1
Multiplex blood culture panels, FDA-cleared

Assay	Turnaround Time	Throughput	Targets	Antimicrobial Resistance
BioFire FilmArray BCID Panel	1 h	1 test module per instrument (v2.0) 2–12 test modules per instrument (Torch)	Bacterial targets <i>Enterococcus</i> spp. <i>Listeria monocytogenes</i> <i>Staphylococcus</i> spp. <i>Staphylococcus aureus</i> <i>Streptococcus</i> spp. <i>Streptococcus agalactiae</i> <i>Streptococcus pyogenes</i> <i>Streptococcus pneumoniae</i> <i>Acinetobacter baumannii</i> <i>Haemophilus influenzae</i> <i>Neisseria meningitidis</i> <i>Pseudomonas aeruginosa</i> Enterobacteriaceae <i>Enterobacter cloacae</i> complex <i>Escherichia coli</i> <i>Klebsiella oxytoca</i> <i>Klebsiella pneumoniae</i> <i>Proteus</i> spp. <i>Serratia marcescens</i> Fungal Targets <i>Candida albicans</i> <i>Candida glabrata</i> <i>Candida krusei</i> <i>Candida parapsilosis</i> <i>Candida tropicalis</i>	Methicillin resistance detection <i>mecA</i> Vancomycin resistance detection <i>vanA</i> <i>vanB</i> Carbapenemase detection KPC

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Table 1
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Assay	Turnaround Time	Throughput	Targets	Antimicrobial Resistance
GenMark ePlex BCID-GP Panel	1.5 h	3–24 test modules per instrument	Bacterial targets <i>Bacillus cereus</i> group <i>Bacillus subtilis</i> group <i>Corynebacterium</i> <i>Cutibacterium acnes</i> <i>(Propionibacterium acnes)</i> <i>Enterococcus</i> spp. <i>Enterococcus faecalis</i> <i>Enterococcus faecium</i> <i>Lactobacillus</i> spp. <i>Listeria</i> spp. <i>L. monocytogenes</i> <i>Micrococcus</i> <i>Staphylococcus</i> spp. <i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i> <i>Staphylococcus lugdunensis</i> <i>Streptococcus</i> spp. <i>Streptococcus agalactiae</i> <i>Streptococcus anginosus</i> group <i>Streptococcus pneumoniae</i> <i>Streptococcus pyogenes</i> Other targets Pan gram-negative Pan <i>Candida</i>	Methicillin resistance detection <i>mecA</i> Vancomycin resistance detection <i>vanA</i> <i>vanB</i>

GenMark ePlex BCID-GN
Panel

1.5 h

3–24 test modules per
instrument

Bacterial targets

A baumannii
Bacteroides fragilis
Citrobacter spp.
Cronobacter sakazakii
Enterobacter spp. (non-
cloacae complex)
Enterobacter cloacae
complex
E coli
Fusobacterium
nucleatum
Fusobacterium
necrophorum
H influenzae
K oxytoca
K pneumoniae group
Morganella morganii
N meningitidis
Proteus spp.
Proteus mirabilis
P aeruginosa
Salmonella spp.
Serratias spp.
S marcescens
Stenotrophomonas
maltophilia

Other targets

Pan gram positive
Pan *Candida*

ESBL detection

CTX-M

Carbapenemase detection

IMP

KPC

NDM

OXA (OXA-23 and OXA-
48)

VIM

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Table 1
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Assay	Turnaround Time	Throughput	Targets	Antimicrobial Resistance
GenMark ePlex BCID-FP Panel	1.5 h	3–24 test modules per instrument	Fungal targets <i>Candida albicans</i> <i>Candida auris</i> <i>Candida dubliniensis</i> <i>Candida famata</i> <i>Candida glabrata</i> <i>Candida guilliermondii</i> <i>Candida kefyr</i> <i>Candida krusei</i> <i>Candida lusitaniae</i> <i>Candida parapsilosis</i> <i>Candida tropicalis</i> <i>Cryptococcus gattii</i> <i>Cryptococcus neoformans</i> <i>Fusarium</i> <i>Rhodotorula</i>	—
Luminex Verigene Gram-Positive Blood Culture Test (BC-GP)	2 h	1 test module per instrument (v1.0) 6 test modules per instrument (v2.0)	Bacterial targets <i>S aureus</i> <i>Staphylococcus epidermidis</i> <i>Staphylococcus lugdunensis</i> <i>S agalactiae</i> <i>S pneumoniae</i> <i>S pyogenes</i>	Methicillin resistance detection mecA Vancomycin resistance detection vanA vanB

Enterococcus faecalis E
faecium
Streptococcus
anginosus
Staphylococcus spp.
Streptococcus spp.
Listeria spp.

Luminex Verigene Gram-Negative Blood Culture Test (BC-GN)	2 h	1 test module per instrument (v1.0) 6 test modules per instrument (v2.0)	Bacterial targets <i>E coli</i> <i>K pneumoniae</i> <i>K oxytoca</i> <i>P aeruginosa</i> <i>Acinetobacter</i> spp. <i>Citrobacter</i> spp. <i>Enterobacter</i> spp. <i>Proteus</i> spp.	ESBL detection CTX-M Carbapenemase detection IMP KPC NDM OXA VIM
T2 Biosystems T2Candida Panel	3–5 h	1 test per instrument	Fungal targets <i>C albicans</i> <i>C tropicalis</i> <i>C krusei</i> <i>C glabrata</i> <i>C parapsilosis</i>	
T2Biosystems T2Bacteria Panel	5 h	1 test per instrument	Bacterial targets <i>E faecium</i> <i>S aureus</i> <i>K pneumoniae</i> <i>P aeruginosa</i> <i>E coli</i>	

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Table 1
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Assay	Turnaround Time	Throughput	Targets	Antimicrobial Resistance
Accelerate Pheno	2 h for identification 7 h for phenotypic antimicrobial susceptibility testing	1 test per instrument	Bacterial targets <i>E faecium</i> <i>E faecalis</i> Coagulase-negative <i>Staphylococcus</i> spp. <i>S aureus</i> <i>S lugdunensis</i> <i>Streptococcus</i> spp. <i>E coli</i> <i>Klebsiella</i> spp. <i>Enterobacter</i> spp. <i>Proteus</i> spp. <i>Citrobacter</i> spp. <i>S marcescens</i> <i>P aeruginosa</i> <i>A baumannii</i> Fungal Targets <i>C albicans</i> <i>C glabrata</i>	Phenotypic susceptibility results

Abbreviation: ESBL, extended spectrum beta-lactamase.

can decrease mortality, hospital length of stay, and hospital costs. For routine bacteria causing BSI, which constitutes the majority of positive blood cultures, patients are receiving effective empiric therapy and syndromic panel results do not affect antimicrobial selection, patient mortality, hospital length of stay, or hospital costs.^{4,6,8,9} Passive reporting of syndromic blood culture panel information results in rapid antibiotic escalation, but deescalation and discontinuation of unnecessary antimicrobials is much slower if it happens at all.^{10,11} The biggest lesson these outcome studies have taught us is the critical value of antimicrobial stewardship programs in the timely optimization or discontinuation of antibiotics.¹²

Most syndromic blood culture assays use positive blood culture broth as their test medium. That means that a blood culture must incubate for 12 to 48 before becoming positive and testing commences. To identify bloodstream pathogens more rapidly, it would be ideal to eliminate the incubation period and test for pathogens directly from whole blood. T2 Biosystems (Lexington, MA) T2Candida and T2Bacteria panels are 2 FDA-cleared culture-independent assays for detection of BSIs. Although more rapid than culture-based syndromic panels, these assays have limited targets and do not provide susceptibility information, so traditional blood culture is still required. Although not yet FDA cleared, metagenomic next-generation sequencing of microbial cell free DNA is gaining traction as an unbiased method of bacterial, viral, fungal, and parasitic pathogen detection (Karius, Redwood City, CA).¹³ Results can be difficult to interpret because this test is often positive for multiple organisms. Although testing is performed directly from plasma, it must be sent to a reference laboratory, which dramatically impacts the turnaround time of results. In the largest outcome study to date, microbial cell-free DNA testing led to minimal impact on patient management.¹⁴ Culture-independent bloodstream pathogen assays are very expensive, even more so than those that use positive blood culture broth as their testing medium. Issues such as who should be tested, for what indications, and how frequently are not settled. Diagnostic stewardship is necessary to optimize the benefits of these tests while keeping the costs under control and clinical microbiology laboratory directors should be involved in testing approval and results interpretation in close collaboration with our infectious disease colleagues.

MENINGITIS/ENCEPHALITIS SYNDROMIC PANEL

Infections of the central nervous system, including ME, cause potentially life-threatening diseases with a myriad of infectious causes in both the pediatric and adult population. There is a dire need for improved diagnostic for ME to address the shortcomings of conventional microbiological approaches such as Gram stain and culture.

The FilmArray Meningitis/Encephalitis panel (FA-ME, BioFire Diagnostics, Salt Lake City, UT) (**Table 2**) remains the only syndromic ME panel despite being cleared by the FDA in 2015 for in vitro diagnostic use. There is a paucity of outcome studies evaluating the clinical utility of a multiplexed panel for ME compared with current standard of care testing. One clear-cut benefit of FA-ME is the significant improvement in herpes simplex virus (HSV) turnaround time, which can lead to decreased acyclovir exposure.^{15,16} Early diagnosis of aseptic meningitis through detection of enterovirus or parechovirus can allow providers to avoid antibiotics and possibly negate the need for hospital admissions.¹⁷ Limited data have been published on the economic benefits and patient outcomes associated with the FA-ME, but the data we have report hospital cost savings and decreased length of stay.^{18,19} Prospective studies investigating the impact of the FA-ME panel on antimicrobial selection, patient outcomes, and

Table 2
Multiplex meningitis encephalitis panel, FDA cleared

Assay	Turnaround Time	Throughput	Bacterial Targets	Viral Targets	Fungal Targets
BioFire FilmArray Meningitis/Encephalitis Panel	1 h	1 test module per instrument (v2.0) 2–12 test modules per instrument (Torch)	<i>Escherichia coli</i> K1 <i>Haemophilus influenzae</i> <i>Listeria monocytogenes</i> <i>Neisseria meningitidis</i> <i>Streptococcus agalactiae</i> <i>Streptococcus pneumoniae</i>	Cytomegalovirus Enterovirus HSV 1 HSV 2 HHV-6 Human parechovirus Varicella zoster virus	<i>Cryptococcus neoformans/gattii</i>

hospital economics is necessary to determine the true benefits of the syndromic panel. In this study, the potential negative impact of a large panel test should also be assessed.

Despite some clear benefits of the FA-ME panel, there are also concerns.²⁰ Primary among them is the risk of false-positive and false-negative results with the HSV-1 target.^{21,22} Yet the performance was noted to be comparable with or superior to alternate HSV polymerase chain reaction (PCR) tests in other studies.^{23,24} A recent meta-analysis on the performance of the FA-ME panel reported a negative predictive value of 99.7% after adjudication of the false-negative results.²⁵ It is important to assess the clinical sensitivity of FA-ME panel to determine the significance of these potentially weak positives detected by alternate PCR and the majority of studies reporting HSV-1 false-negative results have not pursued this point. Nevertheless, in patients with a high suspicion for HSV infection such as neonates, HSV PCR from blood and lesions is indicated before discontinuation of acyclovir. Additional testing recommendations through interpretative comments and/or direct communications with providers in these situations may assist with correct interpretation of test results.

Providers must also be aware that the FA-ME panel is not a standalone test. For instance, the diagnosis of cryptococcal meningitis in patients at high risk for cryptococcosis should consist of culture and cryptococcal antigen testing (both cerebrospinal fluid [CSF] and serum) in conjunction with the FA-ME. A multifactorial approach that include all 3 tests increases the diagnostic yield because false-negative CSF cryptococcal antigen testing results have also been reported.²⁶ A recent multicenter study of 1384 patients confirmed that the performance of the FA-ME panel for *Cryptococcus* highly correlated with culture at a sensitivity of 96.4%.²⁷ The sensitivity was lower compared with cryptococcal antigen testing, but the majority of FA-ME false negatives were from patients with chronic cryptococcal meningitis on antifungal therapy, indicating a dependence on organism burden.

The clinical specificity of human herpesvirus (HHV)-6 detection by the FA-ME panel is an ongoing conundrum that requires further investigation to differentiate between self-limiting primary infection, HHV-6 reactivation, chromosomal integrated HHV-6, or true HHV-6 central nervous system infections. The primary concern is the misdiagnosis of HHV-6 infections and unnecessary exposure to ganciclovir or foscarnet as reported in an adult-only study.²⁸ Contrary to the 40% rate of unnecessary therapy reported, a recent study of 25 HHV-6 positive pediatric patients reported only 8% of patients (2/25) were unnecessarily treated with intravenous ganciclovir for approximately 24 hours.²⁹ A 20% rate of central nervous system infections was also reported, of which all had abnormal radiographic findings and the majority were immunocompetent.²⁹ Key tips to the interpretation of positive HHV-6 result include but are not limited to the presence of central nervous system symptoms, abnormal radiographic findings, and additional HHV-6 detection from alternate sources. A quantitative HHV-6 viral load of greater than 300,000 copies/mL in peripheral blood may point to chromosomal integrated HHV-6 rather than true infection, as well as consistently high HHV-6 viral load despite antiviral therapy.²⁹ Testing for chromosomal integrated HHV-6 by droplet digital PCR is available at the University of Washington.

As with any laboratory tests, there are advantages and disadvantages to the FA-ME panel and optimal use is best achieved through collaboration between the laboratory and providers to maximize the benefits of the test while recognizing the potential challenges that may be specific to each individual patient case. An important question that warrants further investigation is which patient population would FA-ME panel have the highest diagnostic yield? A recent study of 705 inpatients with FA-ME testing reported that 31.9% of patients tested had little or no suspicion for central nervous system

infection supporting the need for potential test restrictions in patients with clear index of suspicion for central nervous system infections.²⁸ CSF testing restriction using parameters such as CSF pleocytosis have been proposed in the past.³⁰ However, a recent pediatric study on 1025 CSF samples tested by FA-ME determined that restricting based on immune status and abnormal CSF parameters (glucose, protein, and pleocytosis) would have resulted in missed diagnostic opportunities, particularly in the cases of viral central nervous system infections.³¹ Nonetheless, further work to identify more appropriate parameters is warranted because the positivity rate was only 11.8% in the patient cohort, indicating a high potential for test restrictions to identify the most pertinent patients to test. Last, the FA-ME panel does not detect the most common pathogens attributed to ventriculoperitoneal shunt infections and thus should not be performed on ventriculoperitoneal shunt samples. The panel is also only FDA-cleared for CSF specimens obtained by lumbar puncture.

DETECTION OF UPPER RESPIRATORY INFECTION

Before the advent of syndromic panels, routine respiratory viral testing was limited to influenza and respiratory syncytial virus (RSV). Syndromic multiplex PCR panels allowed laboratories to rapidly provide highly sensitive and specific test results for a broad range of viruses and bacteria causing upper respiratory illness. **Table 3** provides a list of FDA-cleared syndromic panels for the diagnosis of upper respiratory illnesses. Owing to the ease of testing, these panels have been widely adopted in clinical microbiology laboratories. Testing a broad range of targets has taught us about the prevalence and clinical significance of many viruses. We are now aware that human metapneumovirus often causes severe disease and that rhinoviruses are ubiquitous, but we are still learning about the clinical significance of some of the targets and their infectious potential in otherwise healthy patients.

Coupled with the benefits of multiplex panels are several limitations of cost, over-testing, and difficulty with results interpretation. Syndromic respiratory panels are very expensive compared with traditional methods of respiratory viral testing. The ease of testing has resulted in massive overtesting, passing on the high costs to the patient, insurance company, or hospital with little benefit to patient care. PCR detection of nucleic acids does not rely on viable organism for detection, which increases the sensitivity over traditional methods. Conversely, patients shed virus long after symptoms of upper respiratory illness have resolved and will remain PCR positive if tested. For this reason, repeat testing and test of cure should not be performed. The widespread use of syndromic panel testing has demonstrated that many patients are positive for multiple targets, and because results are qualitative it is not always obvious which pathogen is responsible for a patient's symptoms. Panels that include targets for coronaviruses HKU1, NL63, 229E, and OC43 have recently resulted in confusion with clinicians and patients mistakenly believing they are positive for severe acute respiratory syndrome coronavirus-2.

Outcome studies have been performed in an effort to quantify the benefit (or limitations) of syndromic respiratory panels. For viral targets on respiratory syndromic panels, only influenza, RSV and adenovirus have an associated antiviral therapy. Theoretically, the detection of other viral targets could benefit patients by decreasing the clinician's suspicion of bacterial infection and either preventing initiation or promoting discontinuation of antibiotic therapy. So how are upper respiratory syndromic panels affecting patient care? Results are mixed, with some studies showing a decrease in antibiotic therapy, decreased length of hospital stay, or decreased additional tests and imaging studies,³² whereas other studies showed no benefit.³³ Many

Table 3
Multiplex upper respiratory panels, FDA cleared

Assay	Turnaround Time	Throughput	Set up	Bacterial Targets	Viral Targets
Applied BioCode Respiratory Pathogen Panel (RPP)	4 h	96-well plate format	Batched	<i>Bordetella pertussis</i> <i>Chlamydia pneumoniae</i> <i>Mycoplasma pneumoniae</i>	Influenza A, A/H1, A/H3, A/H1-2009 Influenza B RSV A/B Parainfluenza virus 1, 2, 3, and 4 Human metapneumovirus Human rhinovirus/enterovirus Parainfluenza virus 1, 2, 3, and 4
BioFire FilmArray Respiratory Panel 2 (RP2)	45 min	1 test module per instrument (v2.0) 2–12 test modules per instrument (Torch)	On demand	<i>B pertussis</i> <i>Bordetella parapertussis</i> <i>C pneumoniae</i> <i>M pneumoniae</i>	Influenza A, A/H1, A/H3, A/H1-2009 Influenza B RSV Parainfluenza virus 1, 2, 3, and 4 Human metapneumovirus Human rhinovirus Adenovirus Coronavirus HKU1, NL63, 229E, and OC43 MERS coronavirus ^a

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Table 3
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Assay	Turnaround Time	Throughput	Set up	Bacterial Targets	Viral Targets
BioFire FilmArray Respiratory Panel EZ (CLIA-waived)	1 h	1 test module per instrument	On demand	<i>B pertussis</i> <i>C pneumoniae</i> <i>M pneumoniae</i>	Influenza A, A/H1, A/H3, A/H1-2009 Influenza B RSV Parainfluenza virus Human metapneumovirus Human rhinovirus/ enterovirus ^a Adenovirus Coronavirus
GenMark ePlex Respiratory Pathogen Panel (RP)	1.5 h	3–24 test modules per instrument	On demand	<i>C pneumoniae</i> <i>M pneumoniae</i>	Influenza A, A/H1, A/H3, A/H1-2009 Influenza B RSV A and B Parainfluenza virus 1, 2, 3, and 4 Human metapneumovirus Human rhinovirus/ enterovirus Adenovirus Coronavirus
Genmark eSensor XT-8 Respiratory Viral Panel	5 h	8–24 test modules per instrument	Batched		Influenza A, A/H1, A/H3, A/H1-2009 Influenza B RSV A and B Parainfluenza virus 1–3 Human metapneumovirus Human rhinovirus/ enterovirus Adenovirus B/E and C

Luminex Verigene Respiratory Pathogens Flex Test (RP Flex)	2 h	1 test module per instrument (v1.0) 6 test modules per instrument (v2.0)	On demand	<i>B pertussis</i> <i>Bordetella parapertussis</i> / <i>B bronchiseptica</i> <i>Bordetella holmesii</i>	Influenza A, and subtypes A/H1, A/H3 Influenza B RSV A and B Human rhinovirus Parainfluenza virus 1, 2, and 3 Human metapneumovirus Adenovirus
Luminex NxTAG Respiratory Pathogen Panel	5 h	96-well plate format	Batched	<i>C pneumoniae</i> <i>M pneumoniae</i>	Influenza A, A/H1, A/H3 Influenza B RSV A and B Human rhinovirus/ enterovirus Parainfluenza virus 1, 2, 3, and 4 Human metapneumovirus Adenovirus Coronavirus HKU1, NL63, 229E, and OC43 Human bocavirus
Luminex NxTAG RVP FAST v2	3.5 h	96-well plate format	Batched		Influenza A, A/H1, A/H3 Influenza B RSV Human rhinovirus/ enterovirus Parainfluenza virus 1, 2, 3, and 4 Human metapneumovirus Adenovirus Coronavirus HKU1, NL63, 229E, and OC43

Abbreviation: MERS, Middle East respiratory syndrome.

^a Available on RP2 PLUS (not an FDA-approved target).

of the studies found benefits only for patients with positive influenza results,^{34,35} showing that limited testing may be sufficient for most patients. Diagnostic stewardship is needed to identify patients who would benefit from broad syndromic panels to maximize their impact on patient care.

LOWER RESPIRATORY TRACT INFECTION SYNDROMIC PANEL

LRTIs encompass a broad spectrum of syndromes including community-acquired pneumonia, hospital-acquired pneumonia, and ventilator-acquired pneumonia and are associated with significant morbidity and mortality, especially in hospitalized patients. Infectious agents, including bacteria, fungi, and viruses associated with LRTIs, may vary depending on patient's immune status and exposure history. An etiologic diagnosis through laboratory workup followed by appropriate therapeutic management in patients with LRTIs have been associated with a significant decrease in mortality.³⁶

The status of culture as a gold standard for LRTI diagnosis is in question. Traditional quantitative or semiquantitative culture methods aim at differentiating between true pathogens and normal respiratory flora. At best, a culture is considered adequate and there are a number of factors that are contributory to its demise as the gold standard, including prior antibiotic exposure, poor growth of fastidious bacteria, and subjective interpretation of significant versus insignificant growth.³⁷ Hence, new and improved approaches to LRTI diagnosis in the clinical laboratory are needed and welcomed.

The shift in diagnostic paradigm first occurred with the development of molecular assays to detect viral pathogens and agents of atypical pneumonia years ago and have since been well-accepted as a superior approach compared with culture for these groups of organisms. There are currently 2 FDA-cleared syndromic panel for the diagnosis of LRTIs: the Unyvero LRT test (Curetis, Holzgerlingen, Germany) was the first to receive FDA clearance followed by FilmArray Pneumonia (PN)/Pneumonia plus (PNplus) panel (BioFire Diagnostics) (Table 4). A major difference between the 2 FDA-cleared panels is the semiquantitative capability offered only by the FilmArray PN panel for bacteria (excluding atypical pathogens).

To date, there are no prospective studies evaluating the clinical impact of either FDA-cleared syndromic molecular panel testing in patients with LRTIs. A nonrandomized interventional study on 49 patients with nosocomial pneumonia was published using the CE-marked version of the Unyvero assay. The difference in time to result was significant at 4 hours versus up to 96 hours for controls, and antimicrobial therapy was modified within 5 to 6 hours in 67% of patients. The cohort was not compared against a standard of care only control group.³⁸ Further studies are necessary to determine the potential positive and negative effects of such panels on the diagnosis and management of both adult and pediatric patients with LRTIs. The impact on antimicrobial stewardship and infection prevention would be important metrics to capture.

There are certainly challenges associated with the LRTI syndromic panels that require careful consideration before implementation in clinical laboratories. First, these panels function as an adjunct to traditional respiratory culture and susceptibility testing, and laboratories must determine the best reporting approach that would be complementary to culture results. As mentioned elsewhere in this article, the FilmArray PN panel best mimics the current standard of care reporting structure by providing semiquantitative values in 10-log increments. Laboratories must determine what would be classified as quantitatively significant compared with semiquantitative

Table 4
Multiplex lower respiratory panels, FDA cleared

Assay	Turnaround Time	Throughput	Set UP	Bacterial Targets	Viral/Fungal Targets	Antibiotic Resistance Genes
BioFire FilmArray Pneumonia <i>plus</i> Panel	1 h	1 test module per instrument (v2.0) 2–12 test modules per instrument (Torch)	On Demand	<i>Acinetobacter calcoaceticus-baumannii complex</i> <i>Enterobacter cloacae</i> <i>Escherichia coli</i> <i>Haemophilus influenzae</i> <i>Klebsiella aerogenes</i> <i>Klebsiella oxytoca</i> <i>Klebsiella pneumoniae</i> group <i>Moraxella catarrhalis</i> <i>Proteus</i> spp. <i>Pseudomonas aeruginosa</i> <i>Serratia marcescens</i> <i>Staphylococcus aureus</i> <i>Streptococcus agalactiae</i> <i>Streptococcus pneumoniae</i> <i>Streptococcus pyogenes</i> <i>Legionella pneumophila</i> <i>Mycoplasma pneumoniae</i> <i>Chlamydia pneumoniae</i>	Influenza A Influenza B Adenovirus Coronavirus Parainfluenza virus RSV Human rhinovirus/enterovirus Human metapneumovirus Middle East respiratory syndrome coronavirus ^a	Methicillin resistance mecA/mecC and MREJ ESBL CTX-M Carbapenemases KPC NDM Oxa-48-like VIM IMP

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Table 4
(continued)

Assay	Turnaround Time	Throughput	Set UP	Bacterial Targets	Viral/Fungal Targets	Antibiotic Resistance Genes
Curetis Unyvero Lower Respiratory Tract Panel	4–5 h	2 test modules per instrument	On Demand	<i>Acinetobacter</i> spp. <i>C pneumoniae</i> <i>Citrobacter freundii</i> <i>Enterobacter cloacae</i> complex <i>E coli</i> <i>H influenzae</i> <i>K oxytoca</i> <i>K pneumoniae</i> <i>Klebsiella variicola</i> <i>L pneumophila</i> <i>M catarrhalis</i> <i>Morganella morganii</i> <i>M pneumoniae</i> <i>P</i> spp. <i>P aeruginosa</i> <i>S marcescens</i> <i>S aureus</i> <i>Stenotrophomonas maltophilia</i> <i>S pneumoniae</i>	<i>Pneumocystis jirovecii</i>	Penicillin resistance TEM Methicillin resistance mecA, mecC, and MREJ ESBL CTX-M Carbapenemases KPC NDM Oxa-23, 24, 48, 58 VIM

Abbreviation: MREJ, mec right extremity junction.

^a Middle East Respiratory Syndrome coronavirus will only be available on the Pneumonia Panel *plus*.

culture, particularly at low abundance. Because the Unyvero LRT panel offers no quantitative values, interpretation of significance would be more difficult.

Although comprehensive, the current panels are by no means representative of all potential pathogens, particularly the bacterial targets, and a negative result may not necessarily prompt deescalation of antibiotic therapy. On the other hand, increased detection of on-target bacteria owing to increased sensitivity of molecular testing may result in excessive misinterpretation of bacterial colonization as true infection, leading to unnecessary antibiotic therapy. Studies conducted on both FDA-cleared panels reported more than 70% increases in bacterial target detected^{39,40} and the clinical significance of this warrant careful evaluation that must be interpreted in the context of clinical symptoms and other laboratory findings. Concurrently, the inability to compare and determine the significance of organisms detected against the presence of other off-target oropharyngeal flora makes interpretation of panel result all the more difficult. Laboratories should continue to be diligent stewards by screening respiratory samples microscopically to determine whether the sample has been significantly contaminated with pharyngeal flora and, if so, neither molecular testing nor culture should be pursued. Other challenges include associating the correct pathogen with the correct resistance marker, particularly for the gram-negative bacteria, because the detection of a resistance marker is not linked to a specific pathogen. However, the FilmArray PN panel does prevent the nonspecific detection of *mecA* in *Staphylococcus* spp. other than *Staphylococcus aureus* through inclusion of the staphylococcal cassette chromosome *mec* right extremity junction that links the staphylococcal cassette chromosome *mec* cassette with the *S aureus* genome. Nonetheless, selection of targeted antimicrobial therapy in many of the cases still requires follow-up culture and susceptibility testing.

Based on these challenges, laboratories that wish to implement a syndromic molecular panel to aid in the diagnosis of LRTIs must be thoughtful when considering the reporting and interpretation of the results. Both panel and culture results must be reported in a cohesive manner to avoid confusion and misinterpretation. An integrative reporting approach with inclusion of personalized expert comments by the laboratory director to aid in the interpretation of the result may be helpful, as would consultation with an infectious disease specialist. A pragmatic approach may be to offer testing on bronchoalveolar lavage fluid first, because the sample types are considered a higher quality specimen and less prone to contamination with normal oropharyngeal flora.

DETECTION OF GASTROINTESTINAL INFECTIONS

Syndromic panels for GI infections have the same benefits seen with respiratory syndromic panels. They rapidly provide highly sensitive and specific detection of a broad range of GI^{41–44} pathogens. **Table 5** provides a list of FDA-cleared syndromic panels for diagnosis of GI infections. GI syndromic panels are particularly helpful because there is significant clinical overlap between pathogens causing GI disease. The broad range of targets has highlighted the high prevalence of pathogens such as norovirus, which was not routinely tested for before syndromic panels, despite being one of the most common causes of acute gastroenteritis. Owing to the increased sensitivity and rapid turnaround time, outbreaks of *Cyclospora* have been identified more rapidly, allowing for timely investigation and source identification by public health officials.⁴⁵

The limitations of syndromic GI panels are the inclusion of several targets of questionable clinical significance, including enteropathogenic *E coli*, which is among the most frequent positive targets when present.^{41,46} Owing to the large number of targets present on some syndromic GI panels, specimens are frequently positive for

Table 5
Multiplex GI panels, FDA-cleared

Assay	Turnaround Time	Throughput	Set up	Bacterial Targets	Viral Targets	Parasitic Targets
Applied BioCode GI Pathogen Panel (GPP)	4 h	96-well plate format	Batched	<i>Campylobacter</i> spp. <i>Clostridium difficile</i> toxin A and B <i>Salmonella</i> spp. <i>Shigella</i> /enteroinvasive <i>E coli</i> Shiga-like toxin producing <i>E coli</i> <i>E coli</i> O157 Enterotoxigenic <i>E coli</i> Enteroaggregative <i>E coli</i> <i>Vibrio vulnificus</i> , <i>V. parahaemolyticus</i> , and <i>V. cholerae</i> <i>Yersinia enterocolitica</i>	Norovirus GI and GII Rotavirus A Adenovirus F40/41	<i>Giardia lamblia</i> <i>Cryptosporidium</i> spp. <i>Entamoeba histolytica</i>
BDMax Enteric Bacterial Panel	3 h	24 tests per instrument	Batched	<i>Salmonella</i> spp. <i>Campylobacter</i> spp. <i>Shigella</i> spp./enteroinvasive <i>E coli</i> Shiga toxin 1 and 2		
BDMax Extended Enteric Bacterial Panel	3.5 h	24 tests per instrument	Batched	<i>Plesiomonas shigelloides</i> <i>Vibrio vulnificus</i> , <i>V. parahaemolyticus</i> , and <i>V. cholerae</i> Enterotoxigenic <i>E coli</i> <i>Y enterocolitica</i>		

BDMax Enteric Viral Panel	3 h	24 tests per instrument	Batched		Norovirus GI and GII Rotavirus A Adenovirus F40/41 Sapovirus Human astrovirus
BDMax Enteric Parasite Panel	4.5 h	24 tests per instrument	Batched		<i>G lamblia</i> <i>Cryptosporidium</i> spp. <i>E histolytica</i>
BioFire bioMérieux FilmArray GI Panel	1 h	1 test module per instrument (v2.0) 2–12 test modules per instrument (Torch)	On demand	<i>Campylobacter</i> spp. <i>C difficile</i> <i>P shigelloides</i> <i>Salmonella</i> spp. <i>Vibrio</i> spp. Enteroaggregative <i>E coli</i> Enteropathogenic <i>E coli</i> Enterotoxigenic <i>E coli</i> Shiga-toxin like producing <i>E coli</i> <i>E coli</i> O157 <i>Shigella</i> spp./ enteroinvasive <i>E coli</i>	Adenovirus 40/41 Astrovirus Norovirus GI and GII Rotavirus Sapovirus <i>Cryptosporidium</i> <i>Cyclospora cayetanensis</i> <i>E histolytica</i> <i>Giardia</i>
Hologic Prodesse ProGastro SSCS Assay	4 h	96 tests per plate	Batched	<i>Campylobacter</i> spp. <i>Salmonella</i> spp. Shiga toxin 1 and 2 <i>Shigella</i> spp.	
Luminex Verigene Enteric Pathogens Test	2 h	1 test module per instrument (v1.0) 6 test modules per instrument (v2.0)	On demand	<i>Campylobacter</i> spp. <i>Salmonella</i> spp. <i>Shigella</i> spp. <i>Vibrio</i> spp. <i>Y enterocolitica</i> Shiga toxin 1 and 2	Norovirus GI and GII Rotavirus

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Table 5
(continued)

Assay	Turnaround Time	Throughput	Set up	Bacterial Targets	Viral Targets	Parasitic Targets
Luminex xTAG GI Pathogen Panel	5 h	96 tests per plate	Batched	<i>Campylobacter</i> spp. <i>C difficile</i> <i>E coli</i> O157 Enterotoxigenic <i>E coli</i> Shiga-toxin like producing <i>E coli</i> <i>Salmonella</i> spp. <i>Shigella</i> spp. <i>Vibrio cholera</i>	Adenovirus 40/41 Norovirus Rotavirus	<i>Cryptosporidium</i> <i>Entamoeba histolytica</i> <i>Giardia</i>

multiple target.⁴¹ Although a patient may have multiple GI illnesses concurrently, more likely scenarios are asymptomatic colonization or viral shedding owing to past exposure. False-positive results have been reported for low incidence targets *Vibrio cholera* and *Entamoeba histolytica*.⁴⁷ Another major downside is the inclusion of *Clostridioides difficile* in some panels. *C difficile* colonizes the GI tract of 5% to 10% of asymptomatic adults,⁴⁸ and more than one-half of children under 1 year of age. Detection of *C difficile* toxin does not differentiate between infection and colonization, so it is essential that testing only be performed in the appropriate clinical context. There are many instances of testing for other GI pathogens that have led to incidental detection and subsequent treatment of patients colonized with *C difficile*. In hospitalized patients, the identification of *C difficile* in any context risks being classified as a hospital-acquired infection, which affects Centers for Medicare and Medicaid Services reimbursement. For this reason, many laboratories have elected not to report syndromic panel *C difficile* results at all or have selected panels that do not include a *C difficile* target.

There are few outcome data surrounding GI syndromic panel testing. The majority of the targets do not have an associated antimicrobial treatment. Even for those targets with treatments, most GI infections are self-limited and treatment is not recommended. A retrospective study by Beal and colleagues⁴⁶ showed that the number of days on antibiotics, imaging studies, hospital length of stay, and cost of hospitalization were modestly decreased with GI syndromic panel testing compared with traditional testing methods. Another study of nearly 10,000 patients found that GI syndromic panel testing resulted in fewer endoscopies, fewer abdominal radiographs, and a decrease in antibiotic prescriptions.⁴⁹ Although these studies are promising, more studies are needed to capture the full impact of syndromic GI testing on patient care and hospital finances.

DIAGNOSTIC AND LABORATORY STEWARDSHIP

Every single in vitro diagnostic test offered in the clinical laboratories requires clinical correlation. This caveat has become more evident in the era of syndromic testing where the simplicity and ease of ordering and testing have led to an urgency and a “need to know” mindset that can be detrimental to patient care. For example, in the absence of respiratory symptoms, it would be inconceivable for viral cultures to be ordered; yet the same asymptomatic patients are tested for multiple respiratory viral and atypical bacterial targets by syndromic panel. Thus, the exhaustive overuse overshadows and hinders the true benefits of syndromic testing.

Messacar and colleagues⁵⁰ eloquently defined the goal of diagnostic stewardship as “to select the right test for the right patient, generating accurate, clinically relevant results at the right time to optimally influence clinical care and to conserve health care resources.” The laboratory is at the forefront of this mission, functioning as stewards to maximize clinical excellence. Independent of the actual performance of the syndromic panels, clinical microbiology laboratory directors must determine the added value of the panel compared with existing standard of care tests. Will the test provide highly accurate, actionable results that can improve patient outcomes? Does the test potentially improve the workload in the clinical laboratory by replacing a laborious test? Suffice to say, this decision is often made in collaboration with our infectious disease colleagues and/or antimicrobial stewardship team. Further, costs and reimbursement concerns play a significant role in the equation. It is imperative that a thorough assessment is pursued for every new diagnostic test to ensure that we are not viewing the tests with rose-colored glasses.

Once implemented, strict scrutiny must be applied to establish the most clinically relevant population to test and to optimize how the results are being communicated to the provider. Applications of laboratory stewardship include defining who to test, how often the same patient should be tested, and what targets should be reported is paramount. For instance, stewardship surrounding multiplex upper respiratory panels is a topic of discussion in most clinical microbiology laboratories. How can we identify patients that would benefit clinically from large multiplex syndromic panels to justify the increased cost? How can we identify patients for whom limited testing such as influenza and/or RSV is sufficient? Some laboratories have adopted a practice of testing all specimens for influenza with or without RSV first, and reflexing to the broad respiratory panel only if initial targets are not detected. Other stewardship measures include limiting certain syndromic upper respiratory panels to hospitalized, critically ill, or specialty clinics such as pulmonary and prohibiting repeat testing within a set period of time as retesting within a 20-day window have demonstrated minimal changes in test results.⁵¹ Clinicians should also refrain from testing asymptomatic patients, performing repeat testing owing to low assurance of the initial result, or for test of cure because it can significantly contribute to overuse without any benefit to patient care. Last, for some testing, preauthorization by the clinical microbiology laboratory director or infectious disease team may be a potential solution. Expensive and complex testing, such as metagenomic next-generation sequencing, should only be done in conjunction with an infectious disease consultation and with clinical microbiology laboratory director oversight for clinical review, testing approval, and results interpretation.

Communication between clinical microbiologists and health care providers is absolutely essential to maximize the benefit of test results in the context of the patient. This point is particularly important as tests become increasingly complex and often detect multiple organisms, some of which may not be the cause of the patient's infection. Inclusion of consult notes and recommendations to help guide the provider appropriately interpret these molecular results can be extremely valuable and may help mitigate potential harms that arise owing to limitations associated with a test such as low clinical sensitivity or specificity.

It is near impossible nor sustainable for microbiologists to advocate for appropriate use of syndromic panels at the preanalytical level in the absence of automated gatekeeping through the electronic medical record. The development of support tools range from soft stops, which function as a warning for providers to reconsider whether or not the test should be ordered, to hard stops, which require providers to actively seek approval from the laboratory director.⁵² A prime example is restricting orders on patients previously positive or negative for *C difficile* toxin within a 7- to 14-day period. However, sufficient information technology resources, information technology personnel with a clear understanding of microbiology, and the support of hospital and medical group administration is compulsory in the development of these tools. Nonetheless, these tools must be paired with continued provider education and establishment of key indicators of quality metrics to maximize their success.

SUMMARY

Syndromic panels have allowed clinical microbiology laboratories to rapidly identify bacteria, viruses, fungi, and parasites with high sensitivity and specificity to aid physicians in the diagnosis of many infectious clinical syndromes. These panels are now fully integrated into many clinical laboratories' standard testing practices. Thus, laboratories must implement strict measures to ensure that syndromic panels are

being used responsibly through optimal clinician ordering practices, prohibiting repeat testing, and continuous education of clinicians on assay usefulness and limitations. Thoughtful reporting of results with interpretative comments and/or consultation with the clinical microbiology laboratory director is needed to aid provider interpretation. Diagnostic stewardship is our best hope to maximize the benefits of syndromic panels.

DISCLOSURE

J.D. Bard is a consultant for BioFire Diagnostics and Accelerate Diagnostics and is involved in clinical trials activities with BioFire Diagnostics, Luminex Corporation, DiaSorin Molecular, Applied BioCode. E. McElvania receives speaking fees, consulting fees, and research support from BD.

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