# Rapid Diagnostic Tests for Meningitis and Encephalitis—BioFire

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**Abstract:** Meningitis and encephalitis (ME) are important causes of morbidity and mortality worldwide. Patients suspected of having ME are often hospitalized and started on empiric antimicrobial treatment, because of the potential adverse consequences of delaying the diagnosis or treatment. Multiplexed polymerase chain reaction panels are one of several rapid diagnostic technologies that have the potential to overcome some of the limitations of conventional diagnostic methods for ME. The BioFire FilmArray Meningitis/Encephalitis Panel was the first Food and Drug Administration–cleared multiplex polymerase chain reaction for the evaluation of cerebrospinal fluid samples, able to identify 14 organisms in a single test reaction. This newer rapid diagnostic tool has an overall high sensitivity and specificity for the diagnosis of ME with a fast turnaround time and has the potential to improve resource utilization for patients presenting with suspicion of ME. However, further research is needed to determine its optimal use in the evaluation of patients with suspected ME.

**Key Words:** BioFire, encephalitis, FilmArray, meningitis

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## TARGET AUDIENCE

This continuing medical education material is designed for physicians, physician assistants, and nurse practitioners who care for adult and/or pediatric patients in the outpatient, emergency department, or inpatient setting.

## LEARNING OBJECTIVES

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

1. Describe the strengths and limitations of conventional methods used to diagnose meningitis/encephalitis.
2. Examine the evidence for the use of the BioFire FilmArray Meningitis/Encephalitis Panel for the identification of organisms in cerebrospinal fluid samples of patients evaluated for meningitis and/or encephalitis.
3. Analyze the potential benefits and limitations of multiplexed molecular assays in the evaluation of patients for meningitis and/or encephalitis.

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## BACKGROUND

Meningitis and encephalitis (ME) are important causes of morbidity and mortality worldwide,[1–4] and tens of thousands of adults and children are diagnosed with meningitis or encephalitis each year in the United States.[5,6] Although viral central nervous system (CNS) infections are more common in the United States,[5,6] acute bacterial meningitis is the most rapidly fatal.[7] In other parts of the world, especially in developing countries, bacterial meningitis represents an even larger cause of morbidity and mortality.[3,8] Therefore, rapid diagnosis and treatment are essential. For diagnosis, cerebrospinal fluid (CSF) culture, Gram stain, and other molecular and cellular analyses of the CSF are frequently used.[3,7] However, some of these conventional methods can have limitations in sensitivity and specificity, whereas the culture can take several days to result.[7] Because of the potential adverse consequences of delaying the diagnosis or treatment, patients suspected of having ME are often hospitalized and started on empiric antimicrobial treatment while awaiting CSF cultures.[5,6,9–11] Polymerase chain reaction (PCR)–based methods can improve the process of identifying viral or bacterial pathogens in the CSF by increasing the diagnostic yield and providing faster turnaround times.[7] For example, viral PCR for enterovirus (EV) and herpes simplex virus (HSV) have become standard of care for diagnosis.[12] Rapid diagnostics have significant potential to improve care, optimize antibiotic utilization, decrease hospitalizations, and lower costs for patients presenting with suspicion of ME.[13,14] These make multiplex molecular assays an attractive option to screen and detect potential pathogens. The FilmArray Meningitis/Encephalitis Panel (ME) (BioFire, Salt Lake City, Utah) is the only multiplexed PCR assay currently cleared by the Food and Drug Administration (FDA) and is capable of detecting 14 organisms in the CSF.[15] To understand the potential benefits and limitations and to inform the proper implementation in clinical practice, it is essential to review the scientific literature on the FilmArray Panel.

## CURRENT APPROACH AND DIAGNOSTIC CHALLENGES

A wide array of infectious and noninfectious etiologies can cause ME, which contributes to the challenge in diagnosing these conditions.[5] Cerebrospinal fluid culture is considered the criterion standard for diagnosis of bacterial meningitis and is essential to determine the antimicrobial susceptibilities of the causative organism.[3] The sensitivity of CSF culture has been reported to range from 67% to 88%, although the sensitivity varies depending on the organism and is lower in patients pretreated with antimicrobial agents.[3] While viruses are the most common cause of ME in the United States in both children and adults, patients are often hospitalized and treated with antimicrobial and sometimes antiviral

therapy pending identification of the pathogen, which can take up to 72 hours.[5,6] The short turnaround time of CSF Gram stain can facilitate more rapid identification of the pathogen in cases of bacterial meningitis. It is also inexpensive and well-validated.[3] The sensitivity of Gram stain for bacterial meningitis has been estimated to be in the range of 35% to 90%[3,7,16–19]; however, it also varies widely, depending on the causative organism,[3,7] and is lower in patients pretreated with antimicrobial agents.[3,7] Although CSF cell count, glucose, and protein analysis can also be helpful when trying to differentiate between bacterial and viral meningitis, these tests can also be normal or not characteristic of the causative pathogen.[3] Latex agglutination test has been used to aid in a more rapid diagnosis of bacterial meningitis; however, its sensitivity also varies, depending on the organism, and is lower in samples pretreated with antimicrobial agents and ultimately may provide limited additional value compared with CSF culture.[3]

## BIOFIRE DIAGNOSTICS FilmArray MENINGITIS/ENCEPHALITIS PANEL

### Description

Multiplexed PCR technologies allow for the simultaneous detection and identification of microorganisms in a single test reaction. Currently, there are multiple FDA-cleared/approved multiplex PCR respiratory, gastrointestinal, and blood panels.[20,21] Although for years there have been FDA-approved PCR technologies to test for either EVs or HSV-1/2, in October 2015, the ME Panel was the first FDA-cleared multiplex PCR panel for the evaluation of viral, bacterial, and a fungal target in CSF samples.[20,21] The ME Panel is a multiplexed PCR able to identify 14 organisms, which include 7 viruses, 6 bacteria, and 1 fungus (Table 1).[22] The ME Panel consists of automated nucleic acid extraction, purification, reverse transcription, PCR, DNA melting analysis, and automatic results analysis.[21,22] A minimum of 0.2 mL of CSF volume is needed; the ME Panel is capable of analyzing 12 samples at a time, and less than 2 minutes of hands-on technician time is required. Most important for clinicians is that the results are obtained in approximately 1 hour.[21] Notably, the ME Panel is intended to be used jointly with additional clinical, epidemiological, and laboratory data, including CSF culture.[22] Additionally, the panel is not intended for CSF specimens collected from indwelling CNS medical devices[22,23] or from patients in whom there is concern for a nosocomial infection, as pathogens that often cause these infections are not included in the ME Panel.[24]

### Evidence

There have been multiple investigations that have evaluated the ME Panel for the detection and identification of pathogens in pediatric and adult patients assessed for meningitis/encephalitis. The largest prospective study to date by Leber et al[25] evaluated 1560 CSF samples, and the sensitivity of the ME Panel ranged from 85.7% for human herpesvirus 6 (HHV-6) to 100% for 9 of the 14 organisms. However, there were limited numbers of samples for many of the organisms, and two (*Listeria monocytogenes* and *Neisseria meningitidis*) were not detected in the study. The specificity of the ME Panel was reported to be 99.2% or greater for all 14 organisms.[25]

A recent meta-analysis by Tansarli and Chapin[12] identified 8 studies that provide data required to estimate the performance of the ME Panel through the evaluation of discordant results between the ME Panel and reference methods. Using the data from the meta-analysis, we calculated the overall performance characteristics of the ME Panel from the 8 studies (Table 2). Additionally, we calculated the combined performance characteristics for the ME Panel: pooled sensitivity, 90.2% (95% confidence interval [CI], 86.2–93.1); specificity, 97.7% (95% CI, 94.6–99.0); positive predictive value (PPV), 85.1% (95% CI, 81.6–88.2); negative predictive value (NPV), 98.5% (95% CI, 97.9–98.9); positive likelihood ratio, 38.8 (95% CI, 16.6–90.8); and negative likelihood ratio, 0.10 (95% CI, 0.07–0.14). Because of the limited number of studies and sample sizes, the authors of the meta-analysis were not able to calculate sensitivities and specificities of the ME Panel for individual organisms in the panel.[12]

From the data gathered by Tansarli and Chapin[12] from these 8 studies, we also calculated that the overall sensitivity for 5 of the 6 bacterial organisms in the ME Panel was 96.8% (95% CI, 92.7–99.0). As the 1 positive case of *L. monocytogenes* was not able to be corroborated, we were not able to include this organism in the calculation of overall sensitivity for the bacterial pathogens in the panel.[12]

Infants younger than 3 months are particularly susceptible to ME.[6,8,32] Although many studies evaluating the ME Panel have included infants in the first 3 months of life,[24–27,29,30,33–42] 2 of the investigations specifically focused on this age group.[26,41] Arora et al[26] evaluated the ME Panel in 62 infants 3 months or younger and reported a sensitivity of 100% and specificity of 93.4%. Blaschke et al,[41] however, reported mixed results for infants 60 days or younger, including two false-positive bacterial pathogens detected by the ME Panel. Additionally, larger number of infants had viruses detected with the ME Panel than with conventional methods, but it was unclear if these detections were true-positive or false-positive results.[41]

### Potential Benefits and Limitations

There are multiple potential benefits and limitations of the ME Panel (Table 3). Potential clinical benefits include the detection of CSF viruses and bacteria with high sensitivity and specificity, as noted previously.[12] Additional clinical benefits reported in the literature include shorter time to pathogen identification,[29,31,38] detection of organisms in CSF missed by other conventional studies such as Gram stain[43,54] or culture,[26,36,44,47,48] identification of organisms in samples of patients pretreated with antimicrobial

**TABLE 1.** Targets of the BioFire FilmArray ME Panel

| Viruses | Bacteria | Fungi |
|---|---|---|
| Cytomegalovirus | *Escherichia coli* K1 | *Cryptococcus neoformans/C. gattii* |
| EV | *Haemophilus influenzae* | |
| HSV-1 | *Listeria monocytogenes* | |
| HSV-2 | *Neisseria meningitidis* | |
| HHV-6 | *Streptococcus agalactiae* | |
| Human parechovirus | *Streptococcus pneumoniae* | |
| Varicella-zoster virus | | |

**TABLE 2.** Studies of the BioFire FilmArray ME Panel Included in the 2019 Meta-analysis

| Study | Study Population | Total No. of Samples in the Study | Type of Study | Overall Sensitivity | Overall Specificity | PPV | NPV | Positive Likelihood Ratio | Negative Likelihood Ratio |
|---|---|---|---|---|---|---|---|---|---|
| Leber et al[25] | Pediatrics and adults | 1560 | Prospective | 94.2% | 97.7% | 74.8% | 99.6% | 41.6 | 0.06 |
| Arora et al[26] | Pediatrics | 62 | Prospective | 100.0% | 93.4% | 55.6% | 100.0% | 15.3 | 0 |
| Lee et al[27] | Pediatrics and adults | 42 | Prospective | 60.0% | 100% | 100.0% | 86.7% | N/A | 0.40 |
| Radmard et al[24] | Pediatrics and adults | 705 | Retrospective | 85.7% | 98.3% | 36.8% | 99.9% | 52.2 | 0.13 |
| Hanson et al[28] | Pediatrics and adults | 342 | Retrospective | 91.8% | 88.3% | 88.4% | 91.7% | 7.8 | 0.09 |
| Messacar et al[29] | Pediatrics | 138 | Retrospective | 91.1% | 97.9% | 95.3% | 95.9% | 43.3 | 0.09 |
| Graf et al[30] | Pediatrics | 133 | Retrospective | 92.5% | 100.0% | 100.0% | 93.0% | N/A | 0.07 |
| Piccirilli et al[31] | Pediatrics and adults | 63 | Retrospective | 85.7% | 100.0% | 100.0% | 77.8% | N/A | 0.14 |

agents,[26,36,43,45,54] and enhanced implementation of chemoprophylaxis for close contacts.[45]

There is also a possible economic impact of using the ME Panel. Given the adverse consequences of delayed or misdiagnosed meningitis/encephalitis, patients suspected of having ME are often hospitalized for empiric antimicrobial therapy while awaiting the results of CSF culture.[9–11] Fast turnaround times of the ME Panel (approximately 1 hour) have the potential to optimize resource utilization by decreasing unnecessary hospitalizations,[9,10] number of other diagnostic tests,[9,10,13] length of stay,[9–11,13,38,42] and length of empiric antimicrobial therapy.[9,10,13] Theoretical models in pediatric and adult patients have suggested that the ME Panel can lead to cost savings when compared with current practice standards.[9,10] A study in adult patients found a significant difference between the median costs per treatment course of antimicrobials for patients who received standard-of-care testing compared with those in which the ME Panel was used.[46] Another study estimated cost savings of approximately $1750 per case with the use of the ME Panel in patients with suspected CNS infections, due to faster turnaround times compared with conventional methods.[11] These potential cost savings must be evaluated while also taking into account the cost of purchase of the ME Panel, the testing itself, and the service of the equipment.[11,46] The elevated cost of performing each test has been considered a limitation for the implementation of the ME Panel in low-income countries.[34]

The duration of antimicrobial therapy with the implementation of the ME Panel has also been evaluated. A study in a pediatric population found a shorter duration of antimicrobial therapy after the implementation of the ME Panel (2 vs 3 days).[38] Additionally, in a study focused on partially treated bacterial meningitis in adult and pediatric patients, the total duration of antimicrobial treatment was shorter with implementation of the ME Panel (9.5 vs. 15.2 days).[45] A shorter time to narrowing antimicrobials and a decrease in the number of acyclovir doses has also been reported with use of the ME Panel,[42] as has an increase in use of narrow-spectrum regimens.[45] Other studies, however, have provided conflicting results, including a study of adult patients that reported no difference in the duration of antimicrobial therapy with the use of the ME Panel.[49] As a possible mechanism for these findings, some investigations found that a significant proportion of patients with negative ME Panel results were still continued on antimicrobial therapy.[37,49] The potential impact of the implementation of the ME Panel on hospital length of stay has also been analyzed. While some studies have reported a shorter duration of hospitalization with use of the ME Panel,[11,38,42] others have found no difference.[45,49]

There are important limitations of the ME Panel. Some investigators have raised concerns for false-positive[12,15,25,55] and false-negative[12,15,25,51,57] results with use of the ME Panel. Case reports have described how false-positive and/or false-negative ME Panel results led to delayed diagnosis of the causative pathogen.[55,57] Studies have also suggested that the ME Panel should not replace the cryptococcal antigen test[12,15,47,57] and culture[12,57] for patients with suspicion of *Cryptococcus neoformans/Cryptococcus*

**TABLE 3.** Potential Benefits and Limitations of the BioFire FilmArray ME Panel

| Potential Benefits | Potential Limitations |
|---|---|
| -Faster turnaround time, diagnosis, and definitive treatment/treatment discontinuation[30,37,38] | -Concern for false-positive and false-negative tests[14,17,28,33,51–53] |
| -Pathogen identification in culture-negative CSF samples from patients with suspected bacterial meningitis[38,43–46] | -Not all pathogens able to cause CNS infections are detected by the panel[24,26,31,33,37,38,53,54] |
| -Detection of organisms in CSF obtained after antimicrobial pretreatment[38,43,47–49] | -Unable to provide antimicrobial susceptibilities[24,33] |
| -Enables simultaneous identification of coinfections on the same sample[9,50] | -Not intended for CSF samples obtained from indwelling CNS medical devices[24] |
| -Ability to test for multiple organisms simultaneously[24] | -Positive results do not exclude the possibility of a coinfection with an organism not in the panel[24] |
| -Facilitates proper administration of chemoprophylaxis for close contacts[49] | -Relatively high cost of purchase ($35,550–$50,000), service ($4000/y) and per test (~$200)[13,27,55] |
| -Relatively small amount of CSF sample (minimum 0.2 mL) required[24] | - Lower ability to detect viruses when compared with some singleplex assays[17,40,50,56] |
| -Limited hands-on time and technical expertise necessary[14,27] | -Positive results for herpesviruses may be due to latency or reactivation of the virus with or without disease[17,33] |

*gattii* ME. Specifically, some potential false-negative results of *C. neoformans/C. gattii* on ME Panel have occurred in patients with low burden of disease[28,57] and/or in patients on antifungal treatment.[12,22,25,57] Additionally, studies have suggested the possibility that positive antigen results after initiation of therapy may indicate persistence of antigen and not actual detection of live organisms.[22,25,52] False-negative results for viruses may be due to specimens containing low viral loads[31] and to the lower ability of the ME Panel to detect viruses when compared with some singleplex assays.[15,29,58,59] With regard to false-positive results, there are concerns for the potential of contamination during collection and processing of CSF samples.[12,25]

It is also important to highlight that all herpesviruses in the ME Panel (HSV-1, HSV-2, cytomegalovirus, varicella-zoster virus, HHV-6) can establish latent infections. Therefore, a positive result in the ME Panel may be due to a primary infection or alternatively to a latent infection present in the cells retrieved in the specimen (either the CSF or from peripheral blood in a traumatic tap) or reactivation of the virus (with or without true disease).[15,25,56] This accentuates the importance of evaluating the full clinical scenario when interpreting ME Panel results.[2,25,50,60] In addition, HHV-6 can be integrated into human chromosomes and transmitted vertically giving a positive ME Panel result.[31,50]

## PROMISING ADDITIONAL RAPID DIAGNOSTIC TECHNOLOGIES

Multiplexed PCR panels, like the ME Panel, are one of several rapid diagnostic approaches that have the potential to overcome some of the existing limitations in the diagnosis of CNS infections. Some of these diagnostics use different PCR-based techniques to improve the diagnostic yield such as the utilization of nested PCR (as in the BioFire FilmArray), loop-mediated isothermal amplification,[61] and 16S ribosomal RNA sequencing (broad-range PCR).[53] Others use different approaches for the identification of microorganisms such as matrix-assisted laser desorption ionization-time-of-flight mass spectrometry[62] and metagenomics next-generation sequencing.[63] All of these offer promising avenues to improve our current strategies to diagnose CNS infections, but require further research.

## CONCLUSIONS

The ME Panel is the first FDA-cleared multiplexed PCR capable of simultaneously detecting and identifying 14 organisms in CSF samples. This newer rapid diagnostic tool has an overall high sensitivity and specificity for CNS infections and has the potential to improve diagnosis and optimize utilization of health care resources for patients undergoing evaluation for ME. However, the ME Panel should not be used as the sole diagnostic tool in patients with suspected bacterial meningitis, and clinicians should interpret ME Panel results in combination with clinical, epidemiological, and laboratory data. Additionally, both false-positive and false-negative results have been reported. A negative ME Panel test does not indicate the absence of infection, as only 14 organisms are included in the panel, and a positive test may not necessarily reflect the true disease-causing organism, such as with latent viral infections. More research is needed to guide laboratories and clinicians in determining the optimal use of the ME Panel in clinical decision-making for pediatric and adult patients undergoing evaluation for CNS infections.

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