

# FilmArray Meningitis/ Encephalitis (ME) PCR Panel

*The recommendations in this guide are meant to serve as treatment guidelines for use at Michigan Medicine facilities. If you are an individual experiencing a medical emergency, call 911 immediately. These guidelines should not replace a provider's professional medical advice based on clinical judgment, or be used in lieu of an Infectious Diseases consultation when necessary. As a result of ongoing research, practice guidelines may from time to time change. The authors of these guidelines have made all attempts to ensure the accuracy based on current information, however, due to ongoing research, users of these guidelines are strongly encouraged to confirm the information contained within them through an independent source.*

*If obtained from a source other than [med.umich.edu/asp](https://med.umich.edu/asp), please visit the webpage for the most up-to-date document.*

- **Panel**

- Qualitative multiplex nucleic acid-based diagnostic test (<1 hr)

- **Patient**

- Any individual with S/S of meningitis and/or encephalitis

- **Specimen**

- CSF via LP (not indwelling medical devices)

| Bacteria  | Viruses  |
|---|--|
| <ul style="list-style-type: none"> <li>• <i>Escherichia coli K1</i></li> <li>• <i>Haemophilus influenzae</i></li> <li>• <i>Listeria monocytogenes</i></li> <li>• <i>Neisseria meningitidis</i></li> <li>• <i>Streptococcus agalactiae</i></li> <li>• <i>Streptococcus pneumoniae</i></li> </ul> | <ul style="list-style-type: none"> <li>• Cytomegalovirus (CMV)</li> <li>• Enterovirus</li> <li>• Herpes simplex virus 1 (HSV-1)</li> <li>• Herpes simplex virus 2 (HSV-2)</li> <li>• Human herpes virus 6 (HHV-6)</li> <li>• Human parechovirus</li> <li>• Varicella zoster virus (VZV)</li> </ul> |
| Yeast   |  |
| <ul style="list-style-type: none"> <li>• <i>Cryptococcus neoformans/gattii</i></li> </ul>   |  |

- *Only E. coli strains possessing the K1 capsular antigen will be detected. All other E. coli strains/serotypes will not be detected.*
- *Only encapsulated strains of N. meningitidis will be detected. Unencapsulated N. meningitidis will not be detected.*

# Takeaways from the Literature

- Pros
  - Good agreement with conventional methods for most included pathogens
  - Faster TAT than conventional tests (culture, stand-alone PCRs)
  - Broad coverage of multiple potential pathogens in one test
  - Utility in both acellular and pleocytic CSF
  - Utility in both pediatric and adult populations
  - Utility year-round
  - Utility in antibiotic-treated patients

# Takeaways from the Literature - Cryptococcus

- Con
  - Poor sensitivity when compared with Cryptococcus antigen and culture
    - FDA data:
      - 1 of 8 antigen pos – ME panel pos
      - 2 of 3 culture pos – ME panel pos
    - Mayo retrospective study (2018)
      - 26 of 50 antigen positive specimens were ME positive
      - 13 of 14 culture positive specimens were ME positive

# Takeaways from the Literature - HSV

- Cons

- Analytically lower sensitivity for HSV compared to our current stand-alone HSV PCR
  - LoD for the FilmArray ME panel HSV-1 and HSV-2 targets
    - ~1500 copies/ml and ~1300 copies/ml, respectively
  - LoD for our routine HSV-1/2 assay (Simplexa HSV 1&2 Direct)
    - ~150 copies/ml and ~900 copies/ml, respectively
  - 2 of 3 previous HSV-1 positives in our validation were negative by ME panel
    - CT values of original test were both 39 with test cutoff of 40
    - Retest by DiaSorin PCR also negative
- Mayo study (2018)
  - 19 of 26 previous HSV-1 positives were positive by ME panel
  - 48 of 55 previous HSV-2 positives were positive by ME panel
  - Discrepant analysis was performed on 10 of the 14 samples
    - 8 of the 10 testing negative for HSV-1/2 by an alternate molecular test
    - These 8 specimens had an initial  $C_T$  value of  $>37.5$  on routine testing

# Takeaways from the Literature – *S. pneumo*

- Cons

- Rare incidence of false positive issues with *S. pneumo* noted in FDA clearance study
  - 12/1556 – ME Panel + , Cx neg
    - 5 independent PCR +
    - 7 confirmatory Cx and independent PCR neg
  - One positive *S pneumo* in our validation of 32 prospective specimens
    - Confirmed by reference lab testing
- Confusion with how to interpret CMV and HHV-6 positives
  - Need to have ID aware of these results in particular

**Table 7. Demographic Summary for Prospective FilmArray ME Panel Clinical Evaluation**

| <b>Prospective Study Specimens (%)</b> |                                |
|--|--------------------------------|
| Fresh                                  | 1015 (65%)                     |
| Frozen                                 | 545 (35%)                      |
| Total Specimens                        | 1560                           |
| <b>Sex</b>                             | <b>Number of Specimens (%)</b> |
| Male                                   | 797 (51%)                      |
| Female                                 | 763 (49%)                      |
| <b>Age Group</b>                       | <b>Number of Specimens (%)</b> |
| < 2 mo.                                | 299 (19%)                      |
| 2-23 mo.                               | 143 (9%)                       |
| 2-17 years                             | 197 (13%)                      |
| 18-34 years                            | 224 (14%)                      |
| 35-64 years                            | 522 (33%)                      |
| 65+ years                              | 175 (11%)                      |
| <b>Status</b>                          | <b>Number of Specimens (%)</b> |
| Outpatient                             | 112 (7%)                       |
| Hospitalized                           | 920 (59%)                      |
| Emergency                              | 528 (34%)                      |

Table 9. FilmArray ME Prospective Clinical Performance Summary<sup>a</sup>

| Analyte                 |                | Sensitivity<br>(compared to culture) |            |                 | Specificity<br>(compared to culture) |             |                  |
|-------------------------|----------------|--------------------------------------|------------|-----------------|--------------------------------------|-------------|------------------|
|                         |                | TP/(TP + FN)                         | %          | 95% CI          | TN/(TN + FP)                         | %           | 95% CI           |
| <b>Bacteria</b>         |                |                                      |            |                 |                                      |             |                  |
| <i>E. coli</i> K1       | Fresh          | 1/1                                  | 100        | -               | 1014/1014                            | 100         | 99.6-100         |
|                         | Frozen         | 1/1                                  | 100        | -               | 543/544                              | 99.8        | 99.0-100         |
|                         | <b>Overall</b> | <b>2/2</b>                           | <b>100</b> | <b>34.2-100</b> | <b>1557/1558<sup>b,c</sup></b>       | <b>99.9</b> | <b>99.6-100</b>  |
| <i>H. influenzae</i>    | Fresh          | 1/1                                  | 100        | -               | 1013/1014                            | 99.9        | 99.4-100         |
|                         | Frozen         | 0/0                                  | -          | -               | 545/545                              | 100         | 99.3-100         |
|                         | <b>Overall</b> | <b>1/1</b>                           | <b>100</b> | <b>-</b>        | <b>1558/1559<sup>d</sup></b>         | <b>99.9</b> | <b>99.6-100</b>  |
| <i>L. monocytogenes</i> | Fresh          | 0/0                                  | -          | -               | 1015/1015                            | 100         | 99.6-100         |
|                         | Frozen         | 0/0                                  | -          | -               | 545/545                              | 100         | 99.3-100         |
|                         | <b>Overall</b> | <b>0/0</b>                           | <b>-</b>   | <b>-</b>        | <b>1560/1560</b>                     | <b>100</b>  | <b>99.8-100</b>  |
| <i>N. meningitidis</i>  | Fresh          | 0/0                                  | -          | -               | 1015/1015                            | 100         | 99.6-100         |
|                         | Frozen         | 0/0                                  | -          | -               | 545/545                              | 100         | 99.3-100         |
|                         | <b>Overall</b> | <b>0/0</b>                           | <b>-</b>   | <b>-</b>        | <b>1560/1560</b>                     | <b>100</b>  | <b>99.8-100</b>  |
| <i>S. agalactiae</i>    | Fresh          | 0/1                                  | 0.0        | -               | 1013/1014                            | 99.9        | 99.4-100         |
|                         | Frozen         | 0/0                                  | -          | -               | 545/545                              | 100         | 99.3-100         |
|                         | <b>Overall</b> | <b>0/1<sup>e</sup></b>               | <b>0.0</b> | <b>-</b>        | <b>1558/1559<sup>e</sup></b>         | <b>99.9</b> | <b>99.6-100</b>  |
| <i>S. pneumoniae</i>    | Fresh          | 2/2                                  | 100        | 34.2-100        | 1008/1013                            | 99.5        | 98.8-99.8        |
|                         | Frozen         | 2/2                                  | 100        | 34.2-100        | 536/543                              | 98.7        | 97.4-99.4        |
|                         | <b>Overall</b> | <b>4/4</b>                           | <b>100</b> | <b>51.0-100</b> | <b>1544/1556<sup>f</sup></b>         | <b>99.2</b> | <b>98.7-99.6</b> |



**Table 14. FilmArray ME Panel Archived Specimen Performance Data Summary**

| Analyte                 | Positive Percent Agreement |     |          | Negative Percent Agreement |     |          |
|-------------------------|----------------------------|-----|----------|----------------------------|-----|----------|
|                         | TP/(TP + FN)               | %   | 95% CI   | TN/(TN + FP)               | %   | 95% CI   |
| <b>Bacteria</b>         |                            |     |          |                            |     |          |
| <i>E. coli</i> K1       | 2/2                        | 100 | 34.2-100 | 35/35                      | 100 | 90.1-100 |
| <i>H. influenzae</i>    | 3/3                        | 100 | 43.9-100 | 39/39                      | 100 | 91-100   |
| <i>L. monocytogenes</i> | 1/1                        | 100 | -        | 41/41                      | 100 | 91.4-100 |
| <i>N. meningitidis</i>  | 7/7                        | 100 | 64.6-100 | 34/34                      | 100 | 89.8-100 |
| <i>S. agalactiae</i>    | 2/2                        | 100 | 34.2-100 | 40/40                      | 100 | 91.2-100 |
| <i>S. pneumoniae</i>    | 17/17                      | 100 | 81.6-100 | 21/21                      | 100 | 84.5-100 |

# Clinical Performance Summary - Bacteria

- 39 of 40 positive bacterial cultures detected by FA
  - 2/3 GBS, 4/4 E coli, 4/4 Hflu, 21/21 Spn, 1/1 Listeria, 7/7 Nmen.
- >99.9% specificity for all bacterial targets but *S. pneumoniae*
  - *S. pneumo* spec. 99.2%
    - 12/1556 – FA + , Cx neg
      - 5 independent PCR +
      - 7 confirmatory Cx and PCR neg isolates

**Table 10. Clinical Characteristics of Subjects with Unconfirmed False Positive *S. pneumoniae* Results**

| Subject age | CSF WBC | FilmArray Result | Comparator Culture/ Investigation PCR <sup>a</sup> | Diagnosis Reported in Medical Record                     |
|-------------|---------|------------------|--|--|
| <2 mo       | 3       | Pos              | Neg/Neg  | Infection, non-CNS ( <i>S. agalactiae</i> urine culture) |
| 65+         | 2       | Pos              | Neg/Neg  | Unable to obtain   |
| 2-17        | 0       | Pos              | Neg/Neg  | Infection, non-CNS (folliculitis)                        |
| <2 mo       | 3       | Pos              | Neg/Neg  | Infection, non-CNS (Parainfluenza virus)                 |
| 18-34       | 1       | Pos              | Neg/Neg  | CNS disease, non-infectious (epilepsy)                   |
| 35-64       | 1       | Pos              | Neg/Neg  | Infection, non-CNS (Hep B), multiple myeloma             |
| 18-34       | 1       | Pos              | Neg/Neg  | Infection, non-CNS (Bells' Palsy)                        |

<sup>a</sup> This PCR is the same as that described in footnote f of Table 9.

**Table 9. FilmArray ME Prospective Clinical Performance Summary<sup>a</sup>**

| Viruses |                |  |             |                  |  |             |                  |
|---------|----------------|--|-------------|------------------|--|-------------|------------------|
| Analyte |                | Positive Percent Agreement<br>(compared to PCR with bi-directional sequencing) |             |                  | Negative Percent Agreement<br>(compared to PCR with bi-directional sequencing) |             |                  |
|         |                | TP/(TP + FN)   | %           | 95% CI           | TN/(TN + FP)   | %           | 95% CI           |
| Viruses |                |  |             |                  |  |             |                  |
| CMV     | Fresh          | 2/2  | 100         | 34.2-100         | 1010/1013  | 99.7        | 99.1-99.9        |
|         | Frozen         | 1/1  | 100         | 20.7-100         | 544/544  | 100         | 99.3-100         |
|         | <b>Overall</b> | <b>3/3</b>   | <b>100</b>  | <b>43.9-100</b>  | <b>1554/1557<sup>g</sup></b>   | <b>99.8</b> | <b>99.4-99.9</b> |
| EV      | Fresh          | 43/44  | 97.7        | 88.2-99.6        | 965/971  | 99.4        | 98.7-99.7        |
|         | Frozen         | 1/2  | 50.0        | -                | 542/543  | 99.8        | 99.0-100         |
|         | <b>Overall</b> | <b>44/46<sup>h</sup></b>   | <b>95.7</b> | <b>85.5-98.8</b> | <b>1507/1514<sup>h</sup></b>   | <b>99.5</b> | <b>99.0-99.8</b> |
| HSV-1   | Fresh          | 1/1  | 100         | -                | 1013/1014  | 99.9        | 99.4-100         |
|         | Frozen         | 1/1  | 100         | -                | 543/544  | 99.8        | 99.0-100         |
|         | <b>Overall</b> | <b>2/2</b>   | <b>100</b>  | <b>34.2-100</b>  | <b>1556/1558<sup>i</sup></b>   | <b>99.9</b> | <b>99.5-100</b>  |
| HSV-2   | Fresh          | 6/6  | 100         | 61.0-100         | 1008/1009  | 99.9        | 99.4-100         |
|         | Frozen         | 4/4  | 100         | 51.0-100         | 540/541  | 99.8        | 99.0-100         |
|         | <b>Overall</b> | <b>10/10</b>   | <b>100</b>  | <b>72.2-100</b>  | <b>1548/1550<sup>j</sup></b>   | <b>99.9</b> | <b>99.5-100</b>  |
| HHV-6   | Fresh          | 13/15  | 86.7        | 62.1-96.3        | 997/1000   | 99.7        | 99.1-99.9        |
|         | Frozen         | 5/6  | 83.3        | 43.6-97.0        | 535/536  | 99.8        | 99.0-100         |
|         | <b>Overall</b> | <b>18/21<sup>k</sup></b>   | <b>85.7</b> | <b>65.4-95.0</b> | <b>1532/1536<sup>k</sup></b>   | <b>99.7</b> | <b>99.3-99.9</b> |
| HPeV    | Fresh          | 9/9  | 100         | 70.1-100         | 1003/1006  | 99.7        | 99.1-99.9        |
|         | Frozen         | 0/0  | -           | -                | 545/545  | 100         | 99.3-100         |
|         | <b>Overall</b> | <b>9/9</b>   | <b>100</b>  | <b>70.1-100</b>  | <b>1548/1551<sup>l</sup></b>   | <b>99.8</b> | <b>99.4-99.9</b> |
| VZV     | Fresh          | 3/3  | 100         | 43.9-100         | 1010/1012  | 99.8        | 99.3-99.9        |
|         | Frozen         | 1/1  | 100         | -                | 543/544  | 99.8        | 99.0-100         |
|         | <b>Overall</b> | <b>4/4</b>   | <b>100</b>  | <b>51.0-100</b>  | <b>1553/1556<sup>m</sup></b>   | <b>99.8</b> | <b>99.4-99.9</b> |

**Table 14. FilmArray ME Panel Archived Specimen Performance Data Summary**

| Viruses |                    |      |           |         |      |           |
|---------|--------------------|------|-----------|---------|------|-----------|
| CMV     | 7/8                | 87.5 | 52.9-97.8 | 181/181 | 100  | 97.9-100  |
| HSV-1   | 16/16              | 100  | 80.6-100  | 156/157 | 99.4 | 96.5-99.9 |
| HSV-2   | 33/34              | 97.1 | 85.1-99.5 | 136/136 | 100  | 97.3-100  |
| HHV-6   | 12/16 <sup>a</sup> | 75.0 | 50.5-89.8 | 168/168 | 100  | 97.8-100  |
| HPeV    | 2/3                | 66.7 | 20.8-93.9 | 187/187 | 100  | 98.0-100  |
| VZV     | 22/22              | 100  | 85.1-100  | 162/164 | 98.8 | 95.7-99.7 |

# Clinical Performance Summary - Viruses

- Negative percent agreement of >99.5% for all viruses
- Positive percent agreement
  - >95% for EV, HSV-1, HSV-2, and VZV
  - 10/11 for CMV
  - 30/37 for HHV-6
  - 11/12 HPeV

**Table 9. FilmArray ME Prospective Clinical Performance Summary<sup>a</sup>**

| Yeast                       |                |            |            |          |                              |             |                  |
|-----------------------------|----------------|------------|------------|----------|------------------------------|-------------|------------------|
| <i>C. neoformans/gattii</i> | Fresh          | 0/0        | -          | -        | 1015/1015                    | 100         | 99.6-100         |
|                             | Frozen         | 1/1        | 100        | -        | 540/544                      | 99.3        | 98.1-99.7        |
|                             | <b>Overall</b> | <b>1/1</b> | <b>100</b> | <b>-</b> | <b>1555/1559<sup>n</sup></b> | <b>99.7</b> | <b>99.3-99.9</b> |

**Table 14. FilmArray ME Panel Archived Specimen Performance Data Summary**

| Yeast                       |                    |     |          |         |     |          |
|-----------------------------|--------------------|-----|----------|---------|-----|----------|
| <i>C. neoformans/gattii</i> | 19/19 <sup>b</sup> | 100 | 83.2-100 | 171/171 | 100 | 97.8-100 |

**Table 11. FilmArray ME Panel *C. neoformans/gattii* assay performance relative to other comparator methods**

| <i>Cryptococcus</i> test comparator method | Positive Percent Agreement |      |           | Negative Percent Agreement |      |           |
|--|----------------------------|------|-----------|----------------------------|------|-----------|
|  | TP/(TP + FN)               | %    | 95% CI    | TN/(TN + FP)               | %    | 95% CI    |
| Cryptococcal Antigen                       | 1/8 <sup>a</sup>           | 12.5 | 2.2-47.1  | 187/188 <sup>b</sup>       | 99.5 | 97.0-99.5 |
| Standard Culture                           | 2/3 <sup>c</sup>           | 66.7 | 20.8-93.9 | 1554/1557 <sup>d</sup>     | 99.8 | 99.4-99.9 |
| Fungal Culture                             | 0/0                        | -    | -         | 22/23 <sup>e</sup>         | 95.7 | 79.0-99.2 |

Liesman, R. M., et al. (2018). "Evaluation of a Commercial Multiplex Molecular Panel for Diagnosis of Infectious Meningitis and Encephalitis." J Clin Microbiol 56(4): e01927-01917.

- Tested residual CSF samples (n =291) that previously tested positive by a routine method(s) (e.g., bacterial culture, individual real-time PCR assay) for a pathogen represented on the ME panel.
- The FilmArray ME panel demonstrated an overall percent positive agreement (PPA) of 97.5% (78/80) for bacterial pathogens, 90.1% (145/161) for viruses, and 52% (26/50) for *Cryptococcus neoformans/C. gattii*.
  - Despite the low overall agreement (52%) between the ME panel and antigen testing for detection of *C. neoformans/C. gattii*, the percent positive agreement of the FilmArray assay for *C. neoformans/C. gattii* was 92.3% (12/13) when the results were compared directly to the results of routine fungal smear or culture.
  - **7 FN results for HSV-1 and 7 FN results for HSV-2**
    - freeze / thaw issue in study

Chew, K. L., et al. (2018). "Culture-confirmed cryptococcal meningitis not detected by Cryptococcus PCR on the Biofire meningitis/encephalitis panel((R))." Clin Microbiol Infect 24(7): 791-792.

- 2 non-HIV-infected, non-transplant patients with culture-confirmed cryptococcal meningitis that was not detected on the Biofire ME panel.
- The cryptococcal antigen LFA titre was positive only in the undiluted sample for the first patient, and positive up to 1:20 dilution for the second patient, both of which suggest a low initial fungal burden of disease.
- Discrepant results between the Biofire ME panel and CrAG LFA have been previously reported on retrospective CSF samples
- According to the kit insert, the limit of detection of the assay is 100 CFU/mL for both *Cryptococcus* spp



Lewis, P. O., et al. (2019). "False negative diagnostic errors with polymerase chain reaction for the detection of cryptococcal meningoencephalitis." Med Mycol

- This retrospective review identified five patients with cryptococcal meningoencephalitis, 4 of whom had a negative ME panel for *Cryptococcus*.
- All five cases had positive serum cryptococcal antigens, and three of five had a positive cerebrospinal fluid (CSF) culture for *Cryptococcus*.

Arora, H. S., et al. (2017). "**Enhanced Identification of Group B Streptococcus and Escherichia Coli in Young Infants with Meningitis Using the Biofire Filmarray Meningitis/Encephalitis Panel.**" Pediatr Infect Dis J **36(7)**: 685-687.

- FilmArray Meningitis/Encephalitis (ME) polymerase chain reaction (PCR) panel was tested on 62 cerebrospinal fluid (CSF) samples from young infants (0-3 months) with suspected meningitis and compared with CSF cultures.
- **Twelve CSF samples from 9 infants were positive by ME PCR panel (10 Group B Streptococcus (GBS) and 2 Escherichia coli) of which only 5 were positive by culture.**
- The 7 CSF samples that were positive only by ME PCR panel were obtained from infants who had received **prior antibiotic treatment**. The ME PCR panel can be a useful tool in the rapid diagnosis of bacterial meningitis in pretreated young infants.

# Blaschke, A. J., et al. (2018). "Retrospective Evaluation of Infants Aged 1 to 60 Days with Residual Cerebrospinal Fluid (CSF) Tested Using the FilmArray Meningitis/Encephalitis (ME) Panel." J Clin Microbiol 56(7).

- Medical records for infants (aged 1 to 60 days) enrolled at three sites were reviewed for clinical, laboratory, and outcome data.
- **A total of 145 infants were reviewed.** The median age was 25 days. Most of the infants were hospitalized (134/145 [92%]) and received **antibiotics** (123/145 [85%]), and almost half (71/145 [49%]) received acyclovir.
- One infant had a bacterial pathogen (*Streptococcus pneumoniae*) identified and one had a fungal pathogen (*Cryptococcus neoformans*/*C. gattii*) identified by the FilmArray ME panel.
  - Neither child had abnormal CSF studies or positive conventional testing, and neither was diagnosed or treated for CNS infection. Secondary testing during the parent study could not confirm these detections, suggesting that these were both false-positive findings
- **Thirty-six infants (25%) had a viral pathogen detected, including 21 enteroviruses, 11 parechoviruses.**
  - Of these, 14 infants (39%) had CSF pleocytosis, defined as a CSF white blood cell (WBC) count of >14
  - **All infants with enteroviral meningitis detected by the FilmArray ME panel and conventional PCR were hospitalized, but 20% were discharged in less than 24 h when conventional PCR results became available.**
  - Only one infant was found to be CMV positive; this infant was not tested for CMV by conventional methods, did not have CSF pleocytosis, and was diagnosed with a urinary tract infection (UTI).
  - Four infants were positive for HHV-6, none of whom had conventional testing for HHV-6 performed

Lumley, S. F., et al. (2018). "Multiplex PCR reveals high prevalence of enterovirus and HHV6 in acellular pediatric cerebrospinal fluid samples." J Infect 77(3): 249-257.

- FilmArray ME panel was performed on the following sample types:
  - all neonate samples (age  $\leq 30$  days)
  - all infant (age 30 days–12 months) and child (age 12 months–16 years) samples if WCC  $> 5$  cells/uL (or cell count not possible)
  - all infant and child samples taken between April-October (seasonal enterovirus peak), irrespective of CSF cell count
  - adult (age  $\geq 17$  years) samples if CSF WCC  $> 5$  cells/uL or if immunosuppressed, selected adult samples after discussion with the clinical microbiologists
- Over 12 months, 637 samples were received in the lab of which 345 (54%) met the criteria for FilmArray testing.
- No sample was positive by bacterial culture, but of the samples tested by FilmArray a diagnostic result was obtained for 18/83 (22%) adults and 34/262 (13%) children ( Table 1 ). One infant sample was FilmArray positive for both *S.pneumoniae* and HHV6, all others were positive for a single organism.

Lee, S. H., et al. (2019). "Usefulness of the FilmArray meningitis/encephalitis (M/E) panel for the diagnosis of infectious meningitis and encephalitis in Taiwan." J Microbiol Immunol Infect.

- BioFire ME Panel in 42 subjects who presented to the emergency department with symptoms of M/E. The results were compared to conventional culture, antigen detection, PCR, and various laboratory fin
- The panel detected six positive samples, of which five were viral and one bacterial.
- We observed an overall agreement rate of 88% between the BioFire ME Panel results and the conventional methods.
- Five discordant results were observed for enterovirus, herpes simplex virus type 1, Escherichia coli, and Cryptococcus species.

**Table 2** Six patients with meningitis/encephalitis (M/E) caused by pathogens detected by both the FilmArray® M/E panel and comparator serological and molecular methods.

| No. | FilmArray            | Clinical diagnosis                      | Age/gender | CSF culture | RBC × 10 <sup>9</sup> /uL | WBC × 10 <sup>9</sup> /uL | Lymphocyte/<br>neutrophil | Total protein<br>mg/dL | Glucose<br>mg/dL | CSF/blood<br>glucose | Serology/molecular<br>method (specimen)                       |
|-----|----------------------|---|------------|-------------|---------------------------|---------------------------|---------------------------|------------------------|------------------|----------------------|---|
| 1   | HSV-2                | HSV M/E                                 | 27 yr/F    | Negative    | 36                        | 389                       | 99/1                      | 170.6                  | 50               | 0.51                 | HSV IgM+, HSV-1 IgG+,<br>HSV-2 IgG- (serum)                   |
| 2   | VZV                  | Ramsay Hunt<br>syndrome<br>with VZV M/E | 40 yr/M    | Negative    | 4                         | 252                       | 249/3                     | 42.3                   | 49               | —                    | VZV PCR+ (CSF)<br>VZV IgG+, IgM- (serum)                      |
| 3   | HSV-2                | HSV M/E                                 | 27 yr/F    | Negative    | 1                         | 340                       | 290/50                    | 83.4                   | 51               | 0.49                 | HSV PCR+ (CSF)  |
| 4   | HSV-2                | HSV M/E                                 | 28 yr/M    | Negative    | 2                         | 629                       | 100/0                     | 122.9                  | 46               | 0.36                 | HSV PCR+ (CSF)<br>HSV-1 IgG-, HSV-2 IgG-,<br>HSV IgM+ (serum) |
| 5   | HSV-1                | HSV M/E                                 | 21 yr/M    | Negative    | 111                       | 226                       | 223/3                     | 62.9                   | 69               | 0.56                 | HSV PCR+ (CSF)  |
| 6   | <i>S. agalactiae</i> | <i>S. agalactiae</i><br>sepsis          | 29 d/M     | Negative    | 1                         | 1                         | 0/1                       | 113.4                  | 64               | 0.79                 | <i>S. agalactiae</i> (blood)                                  |

**Table 4** Five patients with M/E diagnosed by serological and comparative molecular methods but negative by FilmArray M/E panel tests due to pathogens that were included in the FilmArray<sup>®</sup> meningitis/encephalitis (M/E) panel.

| No. | Clinical diagnosis   | Age/gender | CSF bacterial culture | CSF viral culture | RBC (10 <sup>9</sup> /uL) | WBC (10 <sup>9</sup> /uL) | No. (10 <sup>9</sup> /uL) of lymphocyte/<br>neutrophil | Total protein mg/dL | Glucose mg/dL | CSF/blood glucose ratio | Serology/molecular method/culture (specimen)   |
|-----|----------------------|------------|-----------------------|-------------------|---------------------------|---------------------------|--|---------------------|---------------|-------------------------|--|
| 1   | HSV M/E              | 63 yr/F    | Negative              | Negative          | 84                        | 144                       | 144/0  | 162.7               | 43            | —                       | HSV DNA+ (CSF)                                 |
| 2   | Systemic enterovirus | 42 yr/F    | Negative              | Negative          | 243                       | 0                         | 0/0  | 26.8                | 54            | 0.56                    | Enterovirus PCR+ (throat)                      |
| 3   | <i>E. coli</i> M/E   | 1 mo/M     | <i>E. coli</i>        | —                 | 297                       | 18                        | 11/7   | 86.1                | 54            | 0.61                    | <i>E. coli</i> (urine) Blood culture: negative |
| 4   | Cryptococcosis       | 45 yr/M    | Negative              | Negative          | 1350                      | 118                       | 117/1  | 289.6               | 48            | —                       | Cryp. Ag 1:16 (CSF);<br>Cryp. Ag 1:512 (serum) |
| 5   | Cryptococcosis       | 54 yr/M    | Negative              | —                 | 0                         | 30                        | 26/4   | 86.4                | 75            | 0.73                    | Cryp. Ag 1:2 (CSF)                             |

—, not performed; HSV, herpes simplex virus.  
Cryp. Ag, cryptococcal antigen.

# Takeaways from the Literature

- Pros

- Good agreement with conventional methods for most included pathogens
- Faster TAT than conventional tests (culture, stand-alone PCRs)
- Broad coverage of multiple potential pathogens in one test
- Utility in both acellular and pleocytic CSF
- Utility in both pediatric and adult populations
- Utility year-round

- Cons

- Poor sensitivity when compared with Cryptococcus antigen and culture
- Analytically lower sensitivity for HSV compared to our current HSV PCR
  - The reported LoD for the FilmArray ME panel HSV-1 and HSV-2 targets (250 TCID<sub>50</sub>/ml and 50 TCID<sub>50</sub>/ml, respectively) is ~10-fold higher (less sensitive) than the reported LoD for our routine HSV-1/2 assay (Simplexa HSV 1&2 Direct)
- Rare incidence of false positive issues with *S. pneumo*
- Questionable interpretation of CMV and HHV-6 positives – utility of having ID aware of all orders