



Multiplex PCR for Microbial Detection in Spinal Fluid (BIOFIRE FILMARRAY Meningitis/Encephalitis Panel)

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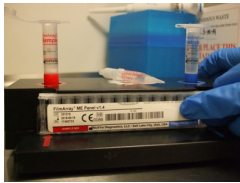
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Disclosures

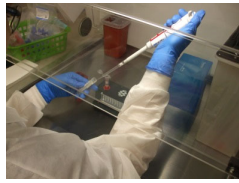
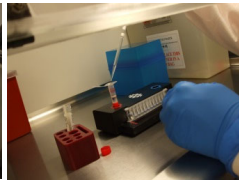
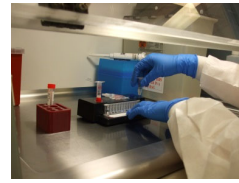
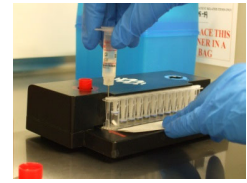
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FDA-Approved Multiplex PCR Assay - Spinal Fluid BIOFIRE FILMARRAY Meningitis/Encephalitis Panel

Viruses	Bacteria	Fungus
Cytomegalovirus	<i>Escherichia coli</i> K1	<i>Cryptococcus neoformans/gattii</i>
Enterovirus	<i>Haemophilus influenzae</i>	
Herpes simplex virus 1	<i>Listeria monocytogenes</i>	
Herpes simplex virus 2	<i>Neisseria meningitidis</i>	
Human herpes virus 6	<i>Streptococcus agalactiae</i>	
Human parechovirus	<i>Streptococcus pneumoniae</i>	
Varicella zoster virus		



Pre-inoculation

Specimen inoculation
into sample bufferHydration buffer
inoculationSample buffer
inoculation

Load instrument

Evaluation of BIOFIRE FILMARRAY Meningitis/ Encephalitis Panel

- 291 clinical, residual CSF samples positive by routine method(s) (e.g., bacterial culture, individual real-time PCR)
 - 76 collected during prevaccine era (March 1975 to June 1997); positive for bacterial pathogen
- Overall percent positive agreement
 - 90.1% (145/161) viruses
 - 97.5% (78/80) bacteria
 - 52% (26/50) *Cryptococcus neoformans*/*Cryptococcus gattii*

Liesman et al. J Clin Microbiol 2018;56:e01927-17

Comparison of BIOFIRE FILMARRAY Meningitis/Encephalitis Panel to Routine Testing

Target	No. of cerebrospinal fluid specimens with:						PPA (95% CI)	Adjusted PPA (95% CI)
	Expected positive result	Positive result by BIOFIRE FILMARRAY Meningitis /Encephalitis panel	TP result	FP result	FN result			
Enterovirus	43	41	41	0	2	95.4 (83.7, 99.6)	95.4 (83.7, 99.6)	
Herpes simplex virus 1	26	20	19	1	7	73.1 (53.7, 86.5)	82.6 (62.2, 93.6)	
Herpes simplex virus 2	55	49	48	1	7	87.3 (75.7, 94.0)	96.0 (85.8, 99.7)	
Cytomegalovirus	3	3	3	0	0	100 (38.3, 100)	100 (38.3, 100)	
Varicella zoster virus	29	30	29	1	0	100 (86.1, 100)	100 (86.5, 100)	
Human herpes virus 6	5	7	5	2	0	100 (51.1, 100)	100 (55.7, 100)	

Liesman et al. J Clin Microbiol 2018;56:e01927-17

Comparison of BIOFIRE FILMARRAY Meningitis/Encephalitis Panel to Routine Testing, continued

Target	No. of cerebrospinal fluid specimens with:						PPA (95% CI)	Adjusted PPA (95% CI)
	Expected positive result	Positive result by BIOFIRE FILMARRAY Meningitis /Encephalitis panel	TP result	FP result	FN result			
<i>Streptococcus agalactiae</i>	2	3	2	1	0	100 (29.0, 100)	100 (29.0, 100)	
<i>Streptococcus pneumoniae</i>	27	30	27	3	0	100 (85.2, 100)	100 (85.7, 100)	
<i>Neisseria meningitidis</i>	10	10	9	1	1	90.0 (57.4, 99.9)	100 (67.9, 100)	
<i>Haemophilus influenzae</i>	40	39	39	0	1	97.5 (86.0, 99.9)	100 (89.3, 100)	
<i>Listeria monocytogenes</i>	0	1	0	1	0	UTC	UTC	
<i>Escherichia coli</i> K1	1	1	1	0	0	100 (16.8, 100)	100 (16.8, 100)	
<i>Cryptococcus neoformans/C. gattii</i>	50	26	26	0	24	52.0 (38.5, 65.2)	57.8 (43.3, 71.0)	

Liesman et al. J Clin Microbiol 2018;56:e01927-17

Apparent Coinfections

Case	Expected result from routine testing	Result(s) of BIOFIRE FILMARRAY Meningitis/Encephalitis panel	Result(s) following confirmatory testing
1	<i>Haemophilus influenzae</i>	<i>H. influenzae</i> , <i>Listeria monocytogenes</i>	<i>H. influenzae</i>
2	<i>Cryptococcus neoformans</i>	<i>C. neoformans</i> / <i>C. gattii</i> , <i>S. pneumoniae</i>	<i>C. neoformans</i> / <i>C. gattii</i>
3	<i>Neisseria meningitidis</i>	<i>N. meningitidis</i> , <i>S. pneumoniae</i>	<i>N. meningitidis</i>
4	<i>H. influenzae</i>	<i>H. influenzae</i> , HHV-6	<i>H. influenzae</i>
5	<i>C. neoformans</i>	<i>C. neoformans</i> / <i>C. gattii</i> , HSV-1	<i>C. neoformans</i> / <i>C. gattii</i>
6	HSV-1	HSV-1, HHV-6	HSV-1, HHV-6
7	CMV	CMV, VZV	CMV, VZV
8	<i>H. influenzae</i>	<i>S. pneumoniae</i> , <i>N. meningitidis</i>	<i>S. pneumoniae</i> , <i>N. meningitidis</i>

Liesman et al. J Clin Microbiol 2018;56:e01927-17

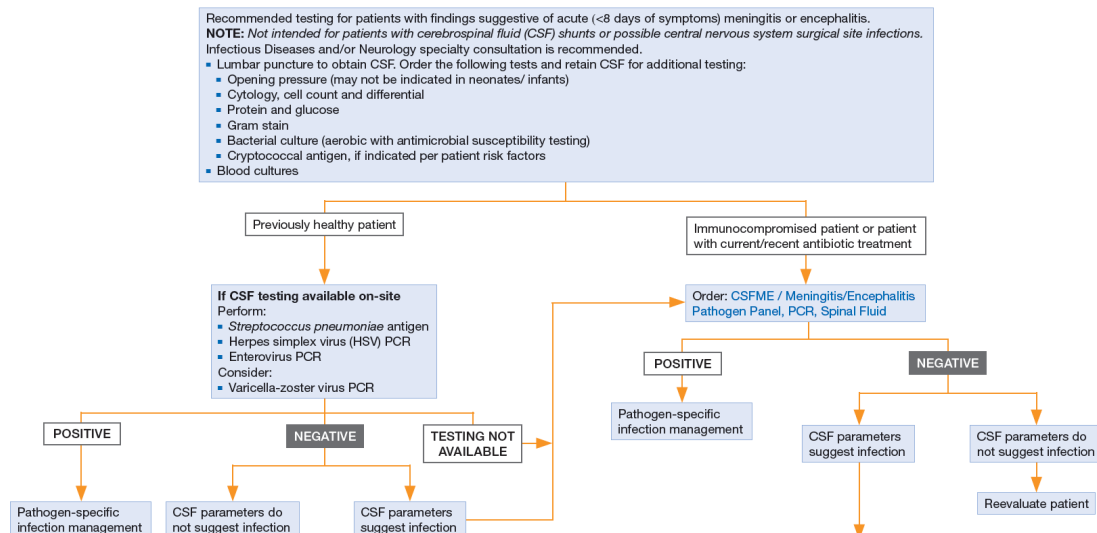
Limitations

- HHV-6 & CMV unusual in immunocompetent; may be clinically insignificant
 - Radmard et al. Frontiers in Neurology 2019;10:281
- HHV-6 detection may result from germline integration
 - Green et al. Clin Infect Dis 2018;67:1125–1128
- Off-panel organisms...
 - *Staphylococcus epidermidis*, *Cutibacterium acnes*, many Gram-negative bacilli, *Mycobacterium tuberculosis*, *Borrelia burgdorferi*, *Histoplasma capsulatum*, *Coccidioides immitis/posadasii*, *Blastomyces* species, West Nile virus, Powassan virus, Jamestown Canyon virus, California encephalitis virus, Eastern Equine encephalitis virus, St. Louis encephalitis virus, Western Equine encephalitis virus, *Ehrlichia* species, *Naegleria fowleri*, *Balamuthia mandrillaris*, *Toxoplasma* and *Acanthamoeba* species, etc.

Limitations, continued

- Potential false-positive *S. pneumoniae*
 - Possibly due to amplified DNA contamination or *S. pneumoniae* colonization in healthcare workers or laboratory staff handling samples
 - Leber et al. J Clin Microbiol 2016;54:2251-61
 - Radmard et al. Frontiers in Neurology 2019;10:281
- Tuberculous meningitis diagnosis delayed because of false-positive HSV-1 result
 - Gomez et al. Open Forum Infect Dis 2016;doi:10.1093/ofid/ofw245

Meningitis/Encephalitis Panel Algorithm



Additional testing should be tailored based on clinical presentation, risk factors, CSF parameters, and exposure history.

- If not previously performed, consider:
 - CLFA / *Cryptococcus* Antigen Screen with Titer, Spinal Fluid
 - HSV6 / Herpes Simplex Virus (HSV), Molecular Detection, PCR, Spinal Fluid
- Syphilis testing
 - SYPGR / Syphilis IgG Antibody with Reflex, Serum
 - VDRL / VDRL, Spinal Fluid
- Fungal and mycobacterial testing
 - FGEN / Fungal Culture, Routine
 - FS / Fungal Smear
 - CTB / Mycobacteria and *Nocardia* Culture
 - SAFB / Acid-Fast Smear for *Mycobacterium*
 - MTBRP / *Mycobacterium tuberculosis* Complex, Molecular Detection, PCR
 - HBRP / *Histoplasma capsulatum*/*Blastomyces* species, Molecular Detection, PCR, Varies
 - HICBL / *Histoplasma*/*Blastomyces* Panel, Spinal Fluid
 - SHSTO / *Histoplasma* Antibody, Serum
 - FUNSF / Fungitell, CSF (1,3-beta-D-glucan)
 - BLAST / *Blastomyces* Antibody by EIA, Serum
 - COXIS / *Coccidioides* Antibody with Reflex, Serum
 - CCOC / *Coccidioides* Antibody, Spinal Fluid
 - CIMRP / *Coccidioides immitis/posadasii*, Molecular Detection, PCR

- Vector-borne testing
 - Mosquito-borne pathogens
 - WNS / West Nile Virus Antibody, IgG and IgM, Serum
 - WNC / West Nile Virus Antibody, IgG and IgM, Spinal Fluid
 - LCWNV / West Nile Virus, Molecular Detection, PCR, Spinal Fluid
 - ABOPC / Arbovirus Antibody Panel, IgG and IgM, Spinal Fluid
 - ARBOP / Arbovirus Antibody Panel, IgG and IgM, Serum
 - Tick-borne pathogens
 - LNBAB / Lyme Central Nervous System Infection IgG with Antibody Index Reflex, Serum and Spinal Fluid (see Lyme Neuroborreliosis Diagnostic Algorithm)
 - PBORR / Lyme Disease, Molecular Detection, PCR, Varies
 - For emerging vector-borne diseases (eg, Powassan virus, Jamestown Canyon virus) contact your local public health laboratory for more information
- Neuroimmunology testing (consider if antibody prevalence in epilepsy and encephalopathy [APE2] score is ≥ 4)
 - ENS1 / Encephalopathy, Autoimmune Evaluation, Serum
 - ENC1 / Encephalopathy, Autoimmune Evaluation, Spinal Fluid
- Parasitic testing
 - FLARP / Free-Living Amebae, Molecular Detection, PCR, Spinal Fluid, Fresh and Paraffin Tissue
 - PTOX / *Toxoplasma gondii*, Molecular Detection, PCR
 - TXMGP / *Toxoplasma gondii* Antibody, IgM and IgG (Separate Determinations), Serum
- Other considerations
 - BRBPS / Broad Range Bacterial PCR and Sequencing, Varies
 - HIVDX / HIV-1 and HIV-2 Antigen and Antibody Diagnostic Evaluation, Plasma
 - LCJC / JC Virus, Molecular Detection, PCR, Spinal Fluid



Thank You