Comparison in Enterovirus Detection in Cerebrospinal Fluid Patient Samples with the FilmArray® Meningitis/Encephalitis System, Cepheid® Gene Xpert® EV, and ARUP® Laboratory Developed Test

Tatum Lunt[2], Susan Slechta, Ph.D.[2], Eric Lo B.S.[1], Kimberly Hanson, M.D.[2], Andrew C. Hemmert Ph.D.[1]

[1]BioFire Diagnostics, LLC, Salt Lake City, UT, [2]ARUP, Salt Lake City, UT

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INTRODUCTION/BACKGROUND

Infections of the central nervous system (CNS) are potentially life-threatening requiring urgent and appropriate treatment. One of the most common CNS infections, Enterovirus (EV), can be difficult to empirically diagnose as it presents with similar symptoms to more serious infections. Without accurate diagnosis, patients with EV infections may be unnecessarily treated with antibiotics and hospitalized until a more serious infection can be ruled out. A common method for detecting EV is PCR, either using Laboratory Developed Tests (LDT) or with an U.S. Food and Drug Administration (FDA) cleared test such as the Cepheid® Xpert® EV test.

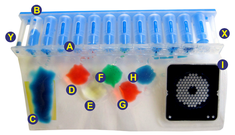
BioFire Diagnostics has developed the FilmArray® (FA) Meningitis/Encephalitis (ME) panel to aid in the diagnosis of CNS infections. This rapid, user-friendly panel simultaneously tests for 6 bacterial, 8 viral and 2 fungal targets using approximately 200 µL of CSF, with a comprehensive result in about 1 hour.

The FilmArray System

The FilmArray is a lab-in-a-pouch medium-scale fluid manipulation test performed in a self-contained, disposable, thin-film plastic pouch. The FilmArray platform processes a single sample, from nucleic acid purification to result, in a fully automated fashion.

The FilmArray ME pouch has a fitment (B) containing freeze-dried reagents and plungers that plunge liquids to the film portion of the pouch. This portion consists of stations for cell lysis (C), magnetic-bead based nucleic acid purification (D & E), first-stage multiplex PCR (F & G) and an array of 102, second-stage nested PCRs (I).

PCR primers are dried into the wells of the array and each primer set amplifies a unique product of the first-stage multiplex PCR. The second-stage PCR product is detected in a melting analysis using a fluorescent double-stranded DNA binding dye, LCGreen®.



A. Fitment with freeze-dried reagents
B. Plungers- deliver reagents to blisters
C. Sample lysis and bead collection
D. Wash station
E. Magnetic bead collection blister
F. Elution Station
G. Multiplex Outer PCR blister
H. Dilution blister
I. Inner Nested PCR array

THE FILMARRAY MENINGITIS/ENCEPHALITIS (ME) PANEL

Simultaneous detection of 15 targets:

Bacteria

- *Escherichia coli* K1
- *Haemophilus influenzae*
- *Listeria monocytogenes*
- *Neisseria meningitidis*
- *Streptococcus agalactiae*
- *Streptococcus pneumoniae*

Viruses

- Cytomegalovirus
- Enterovirus
- Epstein-Barr virus
- Herpes simplex virus 1
- Herpes simplex virus 2
- Human herpesvirus 6
- Human parechovirus
- Varicella zoster virus

Yeast

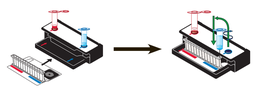
- *Cryptococcus neoformans/gattii*

MATERIALS AND METHODS

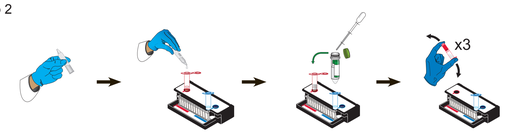
Sixty (60) CSF samples previously tested by the validated ARUP LDT were evaluated using the FA ME and Xpert EV tests. Of the 60 CSF samples, 50 were positive by the ARUP LDT for EV. Residual specimens were then split and tested simultaneously using a research use only (RUO) FA ME panel and the Xpert EV test. Each sample was tested per the manufacturer's instructions.

FilmArray Pouch Loading Instruction

Step 1



Step 2



Testing requires minimal pre-processing of specimens. CSF and FA Sample Buffer are combined in a novel filter-injection vial and then loaded into the FilmArray ME pouch. The user enters the sample and pouch type (using a barcode reader) into the software and initiates a run.

Cepheid Xpert EV WorkFlow

RESULTS

FA ME was concordant with the ARUP LDT and detected EV in all 50 samples (50/50). Results for Xpert EV were concordant with the ARUP LDT test and FA ME system in 47/48 cases. One missed EV detection was observed and 2 probe check errors occurred in the Xpert test. Additionally, since the FA ME panel is a comprehensive panel, it identified additional pathogens in the 60 clinical CSF samples (2 *S. pneumoniae*, 2 HSV2, and 1 EBV). Additional detections were not confirmed by an alternative method.

Figure 1. EV Detection in sample EVcomp_20 with ARUP LDT, Cepheid Xpert EV, and FilmArray ME Panel

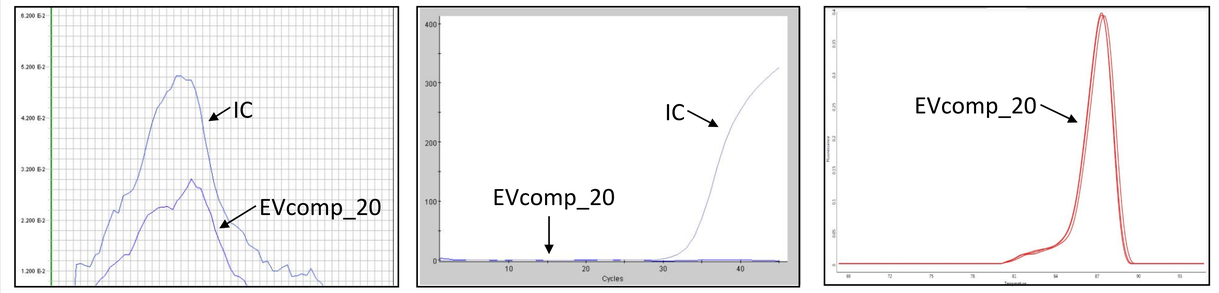


Figure 2. EV Detection in sample EVcomp_45 with ARUP LDT, Cepheid Xpert EV, and FilmArray ME Panel

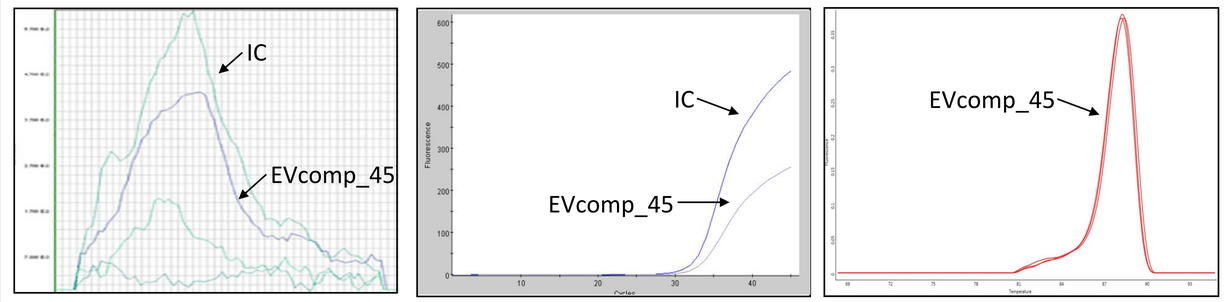


Figure 3. EV and *S. pneumoniae* Detection in sample EVcomp_14 with FilmArray ME Panel

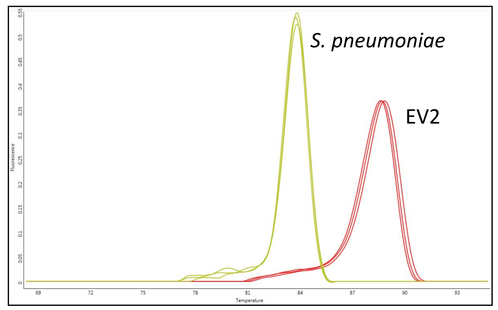


Table 1. Enterovirus Detection in Frozen, Archived, De-identified Patient CSF Samples

Test	EV Detection	Error	Additional Detection
ARUP LDT	50/50	NA	NA
FA ME	50/50	0/50	*S. pneumoniae* (2), HSV2 (2), EBV (1)
GX-EV	47/48	2/50	NA

ME: Meningitis/Encephalitis; LDT: Laboratory Developed Test

CONCLUSIONS

These data demonstrate similar performance for EV detection in clinical specimens between the ARUP LDT, the Xpert EV test and the FA ME system. Further, the FA ME system detected additional pathogens in some samples.

Disclaimer: "The FilmArray ME Panel has not been approved for in vitro diagnostic use by the FDA or any other regulatory agencies."

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CONTACT INFORMATION
Eric Lo
BioFire Diagnostics
Eric.Lo@BioFireDX.com