

# Impact of Implementing the Cerebrospinal Fluid FilmArray Meningitis/Encephalitis Panel on Duration of Intravenous Acyclovir Treatment

Madison Clague,<sup>1,○</sup> Carla Kim,<sup>1</sup> Jason Zucker,<sup>2,○</sup> Daniel A. Green,<sup>3</sup> Yifei Sun,<sup>4</sup> Susan Whittier,<sup>3</sup> and Kiran T. Thakur<sup>1</sup>

<sup>1</sup>Department of Neurology, Columbia University Irving Medical Center/New York Presbyterian Hospital, New York, New York, USA, <sup>2</sup>Division of Infectious Diseases, Department of Medicine, Columbia University Irving Medical Center/New York Presbyterian Hospital, New York, New York, USA, <sup>3</sup>Department of Pathology and Cell Biology, Columbia University Irving Medical Center/New York Presbyterian Hospital, New York, New York, USA, and <sup>4</sup>Department of Biostatistics, Columbia University Mailman School of Public Health, New York, New York, USA

**Background.** Herpes simplex virus–1 is the most common cause of sporadic encephalitis worldwide and requires prompt antiviral treatment. Traditionally, herpes simplex virus–1 (HSV-1) cerebrospinal fluid (CSF) testing is conducted using standalone polymerase chain reaction (PCR). The BioFire CSF FilmArray Meningitis/Encephalitis Panel (BioFire ME Panel) was introduced in 2015 at our institution, providing an alternative method of HSV-1 CSF testing. This study assesses the impact of the BioFire ME Panel on duration of intravenous acyclovir treatment.

**Methods.** A retrospective review of electronic medical records between 2010 and 2019 was performed. Information on intravenous acyclovir treatment and HSV-1 CSF testing was collected and analyzed. Our descriptive analysis included Mann-Whitney tests, 2 proportion Z-tests, and logistic regression.

**Results.** Our CSF HSV-1-negative cohort included 524 BioFire patients (125 pediatric, 399 adult) and 287 standalone PCR patients (115 pediatric, 172 adult). Across both pediatric and adult groups, patients who were tested for HSV-1 with the BioFire ME Panel had shorter average (SD) durations of intravenous acyclovir treatment (pediatric: 2.00 [5.71] days; adult: 3.26 [6.59] days) compared with patients tested with standalone PCR (pediatric: 4.83 [8.62] days; adult: 4.93 [8.46] days;  $P < .001$ ). Time from lumbar puncture collection to HSV-1 results was additionally faster on average for the BioFire ME Panel than the standalone PCR ( $P < .001$ ).

**Conclusions.** The implementation of the BioFire ME Panel shortened CSF HSV-1 PCR result time and intravenous acyclovir duration. The shortened treatment and testing times from the BioFire ME Panel implementation may reduce hospital treatment costs and unnecessary use of antiviral treatments.

**Keywords.** acyclovir; meningitis; encephalitis; HSV-1.

Herpes simplex virus–1 (HSV-1) is the most common cause of sporadic encephalitis worldwide, with an incidence between 2 and 4 cases per 1 000 000 [1]. Without prompt antiviral treatment, mortality and morbidity rates are 70% and 50%, respectively [2]. Currently, the only Food and Drug Administration (FDA)–approved treatment for herpes simplex encephalitis (HSE) is acyclovir, with a recommended dosing of 10 mg/kg intravenously (IV) every 8 hours for 14–21 days [3]. Prior studies

have demonstrated that administration of acyclovir on the first day of admission for patients with suspected HSE resulted in 68.6% of patients having a favorable outcome at discharge, whereas delay in initiation was associated with an unfavorable outcome, defined as a modified Rankin Score  $>2$  [2]. Therefore, acyclovir is commonly prescribed empirically for any patient with possible CNS infection [4] and discontinued upon negative CSF HSV-1 result or determination of other cause.

Acyclovir is generally well tolerated, though acyclovir-induced nephrotoxicity is a known adverse effect [5]. A study of renal dysfunction in children receiving IV acyclovir treatment demonstrated that renal dysfunction was seen in 35% of treatment courses and occurred within 48 hours of initiation of acyclovir [6]. A UK study of acute kidney injury (AKI) in adults treated with IV acyclovir found that incidence of AKI was 13% and higher total doses conferred greater risk [7]. Given the potential nephrotoxic side effects of extended IV acyclovir treatment, it is important to discontinue empiric treatment as soon as possible once HSV-1 encephalitis has been ruled out.

The duration of IV acyclovir treatment depends in part on the turnaround time for CSF HSV-1 PCR testing results. As

Received 10 May 2022; editorial decision 12 July 2022; accepted 21 July 2022; published online 22 July 2022

Correspondence: K. T. Thakur, MD, Division of Critical Care and Hospitalist Neurology, Department of Neurology, Columbia University Irving Medical Center–New York Presbyterian Hospital, 177 Fort Washington Avenue, Milstein Hospital, 8GS-300, New York, NY 10032 (ktt2115@cumc.columbia.edu).

## Open Forum Infectious Diseases®

© The Author(s) 2022. Published by Oxford University Press on behalf of Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<https://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com  
<https://doi.org/10.1093/ofid/ofac356>

compared with traditional standalone PCR testing, the BioFire CSF FilmArray Meningitis/Encephalitis Panel (BioFire ME Panel) has been found to reduce turnaround time [8] and hospital stay [9]. Studies have demonstrated that the multiplex PCR ME Panel had 75% positive agreement with clinical consensus [10] and had concordant results with traditional testing methods in 97% of cases [8]. Furthermore, a study has shown that the ME Panel has a negative predictive value of >99% for HSV-1 and HSV-2 [11].

In this study, we aimed to compare acyclovir treatment trends between patients who were tested with the traditional CSF standalone quantitative PCR (qPCR) or CSF BioFire ME Panel test and received IV acyclovir.

## METHODS

### Patient Population

Patients who presented between 2010 and 2019 to Columbia University Irving Medical Center (CUIMC)/New York-Presbyterian (NYP) and Morgan Stanley Children's Hospital of New York (CHONY/NYP) were included in our study. Cases were included if patients received IV acyclovir and underwent CSF standalone PCR or CSF BioFire testing for HSV-1 during the respective admission. Standalone PCR testing was conducted between 2010 and 2016 and was either conducted in-house (2010–2013) or sent to external labs (2014–2016). The in-house assay was a laboratory-developed real-time PCR assay using the Roche LightCycler (Roche Molecular Systems, Branchburg, NJ, USA). Of the cases included in our study, ~87% of tests were conducted in-house. The BioFire panel was introduced in 2016 and was only conducted in-house. Based on the estimated effect size of 0.5, it was determined that a ~2:1 ratio of BioFire to standalone PCR cases would provide sufficient power.

### Data Collection

A retrospective review of electronic medical records was performed. Information on hospitalization dates, number of lumbar punctures (LPs), LP collection time, the number of CSF HSV-1 tests conducted, the result time of CSF HSV-1 tests, and IV acyclovir administration dates was collected. We also collected information on creatinine values at admission and the highest creatinine value after acyclovir administration.

### Analysis

Our primary focus was on the duration of IV acyclovir treatment. For CSF HSV-1 PCR testing results, we calculated the time from LP to CSF HSV-1 PCR results, the time from acyclovir administration to CSF HSV-1 PCR results, and the time from acyclovir administration to LP. In analyzing acyclovir treatment trends, we calculated the duration of IV acyclovir treatment, the time from admission to IV acyclovir administration, the time

from LP to IV acyclovir discontinuation, and the time from HSV result to IV acyclovir discontinuation.

We were additionally interested in analyzing the effect of the acyclovir usage on trends in renal function. To investigate this, we collected the number of patients with abnormal creatinine after acyclovir administration, the time from admission to highest creatinine, and the time from acyclovir administration to highest creatinine.

Mann-Whitney tests were conducted for an exploratory analysis to compare the events of interest between the CSF standalone PCR HSV-1-negative and BioFire HSV-1-negative groups. Proportions were compared using a 2-proportion Z-test. Binary logistic regression was also performed with age and gender as covariates to analyze the relationship between HSV-1 test type and our events of interest. Significance was set at  $P = .05$ . All statistical testing was performed using IBM SPSS Statistics, version 28. Due to the small sample sizes of the CSF HSV-1-positive standalone PCR and BioFire groups, we present these comparisons descriptively.

## RESULTS

The HSV-1-negative BioFire ( $n = 524$ ) and standalone PCR ( $n = 287$ ) groups were demographically similar apart from age ( $P < .001$ ) (Table 1). For this reason, we separated both HSV-1-negative groups into pediatric (18 and under; BioFire  $n = 125$ , standalone PCR  $n = 115$ ) and adult (age >18; BioFire  $n = 399$ , PCR  $n = 172$ ) patient cohorts. In comparing the pediatric populations for the BioFire and standalone PCR HSV-1-negative groups, we found no difference between the groups for duration of hospitalization, time from CSF HSV-1 result to acyclovir discontinuation, or time from admission to highest creatinine (Tables 2 and 3). The mean time from LP to CSF HSV-1 result ( $P < .001$ ) (Tables 2 and 3), time from acyclovir administration to CSF HSV-1 result ( $P < .001$ ) (Tables 2 and 3), and duration of acyclovir ( $P < .001$ ) (Tables 2 and 3) were all longer in the standalone PCR group compared with the BioFire group. The mean time from admission to acyclovir administration ( $P < .001$ ) (Tables 2 and 3) and time from LP to acyclovir discontinuation ( $P < .001$ ) (Tables 2 and 3) were also longer in the standalone PCR group compared with the BioFire group. The mean time from acyclovir administration to LP was shorter in the standalone PCR group than the BioFire group ( $P < .001$ ) (Tables 2 and 3). The proportion of patients with newly abnormal creatinine after acyclovir administration was higher in the standalone PCR group compared with the BioFire group ( $P = .021$ ) (Tables 2 and 3).

For the adult HSV-1-negative groups, we found no difference between the BioFire and standalone PCR groups for time from admission to highest creatinine or time from acyclovir administration to highest creatinine (Tables 2 and 3). Average duration of hospitalization ( $P < .001$ ) (Tables 2 and

**Table 1. Demographics**

	BioFire (n = 537)		PCR (n = 289)	
	HSV- (n = 524)	HSV+ (n = 13)	HSV- (n = 287)	HSV+ (n = 2)
Female, %	46.0	15.4	41.5	50.0
Male, %	54.0	84.6	58.5	50.0
Mean age (SD), y	43.6 (27.6)*	48.5 (27.09)	33.1 (28.2)*	68; 65
	BioFire HSV-	PCR HSV-		
	≤18 y (n = 125)	>18 y (n = 399)	≤18 y (n = 115)	>18 y (n = 172)
Female, %	46.4	45.9	33.0	47.1
Male, %	53.6	54.1	67.0	52.9
Mean age (SD), y	4.33 (6.48)	55.88 (18.75)	2.68 (4.73)	53.42 (16.57)

Abbreviations: HSV, herpes simplex virus; PCR, polymerase chain reaction.

\*Signifies statistical significance at  $\alpha = .05$ .

3), time from LP to CSF HSV-1 PCR result ( $P < .001$ ) (Tables 2 and 3), and time from acyclovir administration to CSF HSV-1 result ( $P < .001$ ) (Tables 2 and 3) were all longer in the standalone PCR group compared with the BioFire group. Acyclovir administration was started, on average, earlier in the standalone PCR group than the BioFire group ( $P < .001$ ) (Tables 2 and 3). The mean duration of acyclovir treatment ( $P < .001$ ) (Tables 2 and 3), time from admission to acyclovir administration ( $P < .001$ ) (Tables 2 and 3), and time from LP to acyclovir discontinuation ( $P < .001$ ) (Tables 2 and 3) were all longer in the standalone PCR group compared with the BioFire group. Time from HSV result to acyclovir discontinuation, however, was shorter in the standalone PCR group compared with the BioFire group ( $P < .001$ ) (Tables 2 and 3). The proportion of patients with newly abnormal creatinine values after acyclovir administration was higher in the standalone PCR group than the BioFire group but was not statistically significant ( $P = .163$ ) (Tables 2 and 3).

We conducted logistic regression to explore the relationship between our outcomes of interest and type of HSV-1 test (BioFire vs standalone PCR) after adjusting for age and gender. After adjusting for these covariates, average duration of hospitalization, time from HSV result to acyclovir discontinuation, and time from acyclovir administration to highest creatinine did not remain significant predictors of which HSV test type was conducted. Average time from LP to HSV, time from acyclovir administration to HSV result, duration of acyclovir, and time from LP to acyclovir discontinuation, however, did remain significant predictors of HSV-1 test type in both the pediatric and adult data. Average time from acyclovir administration to LP remained significant only in the adult data. Average time from admission to highest creatinine was not significant before or after controlling for age and gender. Of note, in the adult group, age had a significant effect on average time from acyclovir administration to HSV result. In the pediatric group, age had a significant effect on average acyclovir duration, average time from acyclovir administration to HSV result, and average time from LP to acyclovir discontinuation.

Increasing age was associated with a lower chance of being in the standalone PCR group for these outcomes.

Longer average time from LP to HSV results was predictive of being in the standalone PCR group (adult: odds ratio [OR], 32.259;  $P < .001$ ; pediatric: OR, 37.742;  $P < .001$ ). Having a longer average time from acyclovir administration to HSV results was also predictive of being in the standalone PCR group (adult: OR, 1.351;  $P < .001$ ; pediatric: OR, 1.451;  $P < .001$ ). Additionally, longer duration of acyclovir (adult: OR, 1.032;  $P = .020$ ; pediatric: OR, 1.088;  $P = .006$ ) and longer time from LP to acyclovir discontinuation (adult: OR, 1.045;  $P = .001$ ; pediatric: OR, 1.348;  $P < .001$ ) were predictive of being in the standalone PCR group.

The CSF HSV-1-positive BioFire and standalone PCR groups differed in terms of demographics. The BioFire HSV-1-positive group was majority male and on average younger than the standalone PCR HSV-1-positive patients (Tables 2 and 3). Duration of hospitalization was similar for the BioFire and standalone PCR HSV-1-positive patients (Tables 2 and 3). The mean time from LP to HSV result and time from acyclovir administration to HSV result were shorter in the BioFire group compared with the standalone PCR group (Tables 2 and 3). The mean time from acyclovir administration to LP was slightly longer in the BioFire group compared with the standalone PCR group (Tables 2 and 3). Duration of acyclovir treatment, time from admission to acyclovir administration, and time from LP to acyclovir discontinuation varied between the 2 standalone PCR patients, which limits comparison with the BioFire group (Tables 2 and 3). However, for both standalone PCR patients, acyclovir was discontinued before receiving the HSV result, whereas it was on average discontinued after receiving the HSV result in the BioFire group (Tables 2 and 3). Only 1 of the 2 standalone PCR patients and 4 (30.8%) of the BioFire patients had newly abnormal creatinine after acyclovir administration (Tables 2 and 3).

## DISCUSSION

This study demonstrated that the implementation of the BioFire ME Panel resulted in shorter duration of acyclovir

**Table 2. Key HSV-1-Negative and -Positive Results**

	BioFire HSV- (n = 524)		PCR HSV- (n = 287)		P		BioFire HSV+ (n = 13)	PCR HSV+ (n = 2)
	≤18 y (n = 125)	>18 y (n = 399)	≤18 y (n = 115)	>18 y (n = 172)	≤18 y	>18 y	All Ages	All Ages
Duration of hospitalization	16.11 (37.49)	17.28 (24.63)*	14.28 (21.96)	22.27 (25.91)*	.205	<.001	21.00 (13.89)	15; 27
HSV testing								
LP to HSV results	0.16 (0.38)*	0.24 (0.38)*	3.69 (3.21)*	4.56 (9.63)*	<.001	<.001	0.19 (0.17)	20.14; 3.80
Acyclovir administration to HSV results	1.21 (4.21)*	1.03 (2.16)*	4.48 (4.96)*	3.99 (7.69)*	<.001	<.001	0.22 (1.31)	19.96; 3.80
Acyclovir administration to LP	1.04 (4.23)*	0.78 (2.14)*	0.79 (4.11)*	-0.56 (6.78)*	<.001	<.001	0.03 (1.22)	-0.18; 0
Acyclovir treatment								
Duration of acyclovir	2.00 (5.71)*	3.26 (6.59)*	4.83 (8.62)*	4.93 (8.46)*	<.001	<.001	12.15 (8.42)	15.04; 0.64
Admission to acyclovir administration	1.56 (6.40)*	2.99 (10.33)*	2.85 (9.02)*	5.19 (11.05)*	<.001	<.001	2.45 (2.77)	0.5; 7.76
LP to acyclovir discontinuation	0.96 (3.67)*	2.48 (6.44)*	4.04 (7.64)*	5.49 (13.06)*	<.001	<.001	12.12 (8.04)	15.22; 0.64
HSV result to acyclovir discontinuation	0.79 (3.50)	2.23 (6.45)*	0.35 (8.12)	0.93 (8.23)*	.154	<.001	11.93 (7.97)	-4.92; -3.15
Abnormal creatinine								
No. with abnormal creatinine at admission (%)	2 (1.6)	126 (31.6)	3 (2.6)	57 (33.1)	-	-	1 (7.6)	0 (0)
No. with abnormal creatinine after acyclovir (%)	3 (2.4)	157 (39.3)	8 (7.0)	74 (43.0)	-	-	5 (38.5)	1 (50.0)
No. with newly abnormal creatinine after acyclovir administration (%)	1 (0.8)*	49 (12.3)	7 (6.1)*	29 (16.9)	.021	.163	4 (30.8)	1 (50)
Admission to highest creatinine	4.73 (2.51)	9.85 (13.17)	23.46 (33.75)	11.39 (13.75)	.776	.197	11.90 (8.74)	15.49; -
Acyclovir administration to highest creatinine	1.66 (0.73)*	6.62 (10.12)	8.50 (9.53)*	6.03 (8.30)	.012	.380	8.62 (7.62)	14.99; -

All values presented except for “No. with abnormal creatinine” are mean (SD), with the unit days. All BioFire+ results except for “No. with abnormal creatinine” are mean (SD), with the unit days. For standalone PCR+ results, the actual values for each case are presented.

Abbreviations: HSV, herpes simplex virus; LP, lumbar puncture; PCR, polymerase chain reaction.

\*Signifies statistical significance at  $\alpha=0.05$ .

treatment and shorter times to results compared with the CSF HSV-1 standalone PCR. These results may be because the BioFire ME Panel allowed for a more streamlined lab workflow due to the implementation of a sample-to-answer platform compared with the prior in-house PCR testing. These study results are consistent with previous studies that have demonstrated that implementation of the BioFire ME Panel results in decreased acyclovir duration [12–14]. This finding has held true across multiple populations. A pediatric study conducted by Messacar et al. demonstrated that in the post-ME Panel implementation period acyclovir initiation was unaffected, but acyclovir duration decreased [12]. A multicenter study by Evans et al. [14] and a cohort study by Broadhurst et al. [13] additionally found that implementation of the ME Panel resulted in decreased duration of IV acyclovir. While our study did not demonstrate significant differences in renal injury between patients tested with the BioFire panel and the standalone PCR, previous studies have shown that nephrotoxicity with intravenous acyclovir is associated with higher dosing [6, 7] and shorter duration of intravenous acyclovir treatment may reduce this risk. This reduction in duration of treatment could reduce the cost of HSE care for hospitals [15]. Soucek et al. [15] found that the potential savings in antimicrobial treatment offset the increased cost of testing associated with the ME Panel. Reduced acyclovir duration is additionally beneficial given that IV acyclovir is vulnerable to drug shortage [16].

Prior studies have demonstrated that the BioFire ME Panel is a comparable alternative to standalone PCR testing. A study by

Liesman et al. [17] found that the ME Panel detected 97.5% of bacterial pathogens and 90.1% of viruses that routine methods identified. Additionally, Tansarli and Chapin [11] conducted a review of 8 ME Panel studies and found that the ME Panel had high diagnostic accuracy compared with other standard testing methods. It is important to note that while the ME Panel is highly specific and sensitive, there are concerns about false-positive and false-negative results [11, 17]. This has been particularly emphasized with reference to false-negative results for HSV-1/2, indicating that while the panel has a high positive predictive value for these viruses, it still requires diagnostic stewardship [11, 17]. Overall, implementing the BioFire ME Panel provides a rapid, in-house alternative to standalone PCR testing [17].

Our study did have an unexpected finding in that time from CSF HSV-1 result to acyclovir discontinuation was shorter in the standalone PCR HSV-1-negative groups compared with the BioFire HSV-1-negative groups. This result may be due to several factors including the resolution of patient symptoms before receiving standalone PCR results or the determination of an alternative diagnosis through imaging and other diagnostic testing before receiving standalone PCR test results.

This study has multiple strengths. The first is the large sample size for the HSV-1-negative patients that spans multiple years, which provided sufficient power for investigating multiple outcomes. This study adds to the existing literature on the impact of the BioFire ME Panel on acyclovir treatment and time to test result for both adult and pediatric patients. Furthermore, the use of regression analysis to control for demographic variables

**Table 3. Key HSV-1-Negative and -Positive Results (Median and IQR)**

	BioFire HSV- (n = 524)		PCR HSV- (n = 287)		P		BioFire HSV+ (n = 13)	PCR HSV+ (n = 2)
	≤18 y (n = 125)	>18 y (n = 399)	≤18 y (n = 115)	>18 y (n = 172)	≤18 y	>18 y	All Ages	All Ages
Duration of hospitalization	5 (9.5)	9 (14)*	5 (13)	16 (20)*	.205	<.001	25 (41)	15; 27
HSV testing								
LP to HSV results	0.07 (0.14)*	0.16 (0.16)*	2.93 (2.82)*	3.19 (2.56)*	<.001	<.001	0.18 (0.18)	20.14; 3.80
Acyclovir administration to HSV results	0.25 (0.60)*	0.42 (1.08)*	3.20 (3.52)*	3.34 (3.55)*	<.001	<.001	0.22 (0.32)	19.96; 3.80
Acyclovir administration to LP	0.11 (0.33)*	0.19 (1.06)*	0.01 (0.60)*	0.01 (0.90)*	<.001	<.001	0.04 (0.12)	-0.18; 0
Acyclovir treatment								
Duration of acyclovir	0.27 (1.07)*	1.04 (3.23)*	2.48 (2.66)*	2.67 (3.93)*	<.001	<.001	12.56 (13.06)	15.04; 0.64
Admission to acyclovir administration	0.80 (0.67)*	0.93 (1.14)*	1.06 (1.09)*	1.43 (1.93)*	<.001	<.001	2.43 (1.04)	0.5; 7.76
LP to acyclovir discontinuation	0.10 (0.62)*	0.57 (1.88)*	2.47 (2.05)*	2.78 (3.83)*	<.001	<.001	12.53 (12.95)	15.22; 0.64
HSV result to acyclovir discontinuation	0.02 (0.41)	0.26 (1.81)*	0.04 (2.24)	-0.25 (2.77)*	.154	<.001	12.34 (12.77)	-4.92; -3.15
Abnormal creatinine								
No. with abnormal creatinine at admission (%)	2 (1.6)	126 (31.6)	3 (2.6)	57 (33.1)	-	-	1 (7.6)	0 (0)
No. with abnormal creatinine after acyclovir (%)	3 (2.4)	157 (39.3)	8 (7.0)	74 (43.0)	-	-	5 (38.5)	1 (50.0)
No. with newly abnormal creatinine after acyclovir administration (%)	1 (0.8)*	49 (12.3)	7 (6.1)*	29 (16.9)	.021	.163	4 (30.8)	1 (50)
Admission to highest creatinine	3.35 (4.40)	5.04 (11.77)	5.25 (39.96)	6.71 (12.38)	.776	.197	13.42 (11.90)	15.49; -
Acyclovir administration to highest creatinine	1.68 (1.46)*	2.82 (7.29)	3.93 (13.12)*	2.74 (6.74)	.012	.380	10.03 (8.62)	14.99; -

All values presented except for "No. with abnormal creatinine" are median (IQR), with the unit days. All BioFire+ results except for "No. with abnormal creatinine" are median (IQR), with the unit days. For standalone PCR+ results, the actual values for each case are presented.

Abbreviations: HSV, herpes simplex virus; IQR, interquartile range; LP, lumbar puncture; PCR, polymerase chain reaction.

\*Signifies statistical significance at  $\alpha = .05$ .

strengthens our ability to draw conclusions from these data. While this study did not present significant results for hospital duration or creatinine values, it adds to the understanding of the BioFire panel's impact on these outcomes. This study is limited by data availability and sample size for HSV-1-positive patients as well as the retrospective design. There was limited availability of data on acyclovir dosing for standalone PCR cases, and due to the rarity of the condition, the number of HSV-1-positive patients in our patient population was small. This limited our ability to statistically compare the BioFire and standalone PCR HSV-1-positive groups as well as the total dosing between groups. The retrospective design additionally required us to rely on EMR time stamps for test result times and acyclovir administration times. However, we established consistent end point calculations by standardizing which time points were collected.

Future work is necessary to fully understand the impact of the BioFire ME Panel on unnecessary medication usage and hospital costs. Further studies with larger HSV-1-positive samples would additionally improve the understanding of the impact of the BioFire ME Panel on clinical outcomes in patients with confirmed HSV-1 encephalitis or meningitis and the clinical impact of the BioFire ME Panel.

### Acknowledgments

We would like to acknowledge the support of our funder, bioMerieux.

**Financial support.** This work was supported by bioMerieux (BFD-ME-10-007 to K.T.T.).

**Potential conflicts of interest.** K.T.T. is funded as a Principal Investigator by bioMerieux and by the National Institutes of Health and Centers for

Disease Control and Prevention for additional projects. D.A.G. has received an investigator-initiated grant from BioFire for unrelated work and has also served on scientific advisory panels for BioFire. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**Author contributions.** M.C. contributed to data collection, data analysis, and writing of the manuscript. C.K. contributed to data collection and the review and revision of the manuscript. J.Z. contributed to the review of the manuscript. D.A.G. helped identify cases and contributed to review of the manuscript. Y.S. provided statistical guidance and contributed to review of the manuscript. S.W. contributed information on testing practices. K.T.T. directed the study, provided guidance, and contributed to the review and revision of the manuscript.

**Patient consent.** This study does not include factors necessitating patient consent and has been approved by the Columbia University Institutional Review Board.

### References

- Bradshaw MJ, Venkatesan A. Herpes simplex virus-1 encephalitis in adults: pathophysiology, diagnosis, and management. *Neurotherapeutics* **2016**; 13:493-508.
- Singh TD, Fugate JE, Hocker S, Wijdicks EFM, Aksamit AJ, Rabinstein AA. Predictors of outcome in HSV encephalitis. *J Neurol* **2016**; 263:277-89.
- Whitley RJ. Herpes simplex virus infections of the central nervous system. *Contin Minneap Minn* **2015**; 21:1704-13.
- Solomon T, Michael BD, Smith PE, et al. Management of suspected viral encephalitis in adults—Association of British Neurologists and British Infection Association National Guidelines. *J Infect* **2012**; 64:347-73.
- Gaensbauer JT, Birkholz M, Pfannenstern K, Todd JK. Herpes PCR testing and empiric acyclovir use beyond the neonatal period. *Pediatrics* **2014**; 134:e651-6.
- Rao S, Abzug MJ, Carosone-Link P, et al. Intravenous acyclovir and renal dysfunction in children: a matched case control study. *J Pediatr* **2015**; 166:1462-8.e1-4.
- Ryan L, Heed A, Foster J, Valappil M, Schmid ML, Duncan CJA. Acute kidney injury (AKI) associated with intravenous aciclovir in adults: incidence and risk factors in clinical practice. *Int J Infect Dis* **2018**; 74:97-9.

8. Chong BSW, Kennedy KJ. Comparison of a commercial real-time PCR panel to routine laboratory methods for the diagnosis of meningitis-encephalitis. *Pathology (Phila)* **2021**; 53:635–8.
9. DiDiodato G, Bradbury N. Cerebrospinal fluid analysis with the BioFire FilmArray meningitis/encephalitis molecular panel reduces length of hospital stay in patients with suspected central nervous system infections. *Open Forum Infect Dis* **2019**; 6:XXX–XX.
10. Waldrop G, Zucker J, Boubour A, Radmard S, Green DA, Thakur KT. Clinical significance of positive results of the BioFire cerebrospinal fluid FilmArray meningitis/encephalitis panel at a tertiary medical center in the United States. *Arch Pathol Lab Med* **2022**; 146:194–200.
11. Tansarli GS, Chapin KC. Diagnostic test accuracy of the BioFire® FilmArray® meningitis/encephalitis panel: a systematic review and meta-analysis. *Clin Microbiol Infect* **2020**; 26:281–90.
12. Messacar K, Gaensbauer JT, Birkholz M, et al. Impact of FilmArray meningitis encephalitis panel on HSV testing and empiric acyclovir use in children beyond the neonatal period. *Diagn Microbiol Infect Dis* **2020**; 97:115085.
13. Broadhurst MJ, Dujari S, Budvytiene I, Pinsky BA, Gold CA, Banaei N. Utilization, yield, and accuracy of the FilmArray meningitis/encephalitis panel with diagnostic stewardship and testing algorithm. *J Clin Microbiol* **2020**; 58:e00311-20.
14. Evans M, Merkel K, Harder J, Rose D. Impact of the implementation of a rapid meningitis/encephalitis multiplex polymerase chain reaction panel on IV acyclovir duration: multicenter, retrospective cohort of adult and pediatric patients. *Diagn Microbiol Infect Dis* **2019**; 96:114935.
15. Soucek DK, Dumkow LE, VanLangen KM, Jameson AP. Cost justification of the BioFire FilmArray meningitis/encephalitis panel versus standard of care for diagnosing meningitis in a community hospital. *J Pharm Prac*. **In press**.
16. McLaughlin MM, Sutton SH, Jensen AO, Esterly JS. Use of high-dose oral valacyclovir during an intravenous acyclovir shortage: a retrospective analysis of tolerability and drug shortage management. *Infect Dis Ther* **2017**; 6:259–64.
17. Liesman RM, Strasburg AP, Heitman AK, Theel ES, Patel R, Binnicker MJ. Evaluation of a commercial multiplex molecular panel for diagnosis of infectious meningitis and encephalitis. *J Clin Microbiol* **2018**; 56:e01927-17.