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ORIGINAL PAPER

Economic analysis of rapid multiplex polymerase chain reaction testing for meningitis/encephalitis in adult patients

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Abstract

Purpose Many patients with suspected meningitis do not require hospitalization yet are admitted, often resulting in unnecessary care and additional cost. We assessed the possible economic impact of a rapid multiplex test for suspected adult community-acquired meningitis/encephalitis.

Methods A model simulated diagnosis, clinical decisions, resource use/costs of standard of care (SOC) and two cerebrospinal fluid (CSF) testing strategies using the FDA-cleared BioFire® FilmArray® System (FA) which provides results in approximately one hour.

Results Pathogens detected by FA caused approximately 74% of cases, 97% of which would be accurately diagnosed with FA. False positives and false negatives more often led to extended/unnecessary admission than inappropriate discharge/missed admission. Mean cost per case ranged from 16829 to 20791. A strategy of testing all suspected cases yielded greater savings (2213/case) than testing only those with abnormal CSF (812/case) and both were less expensive than SOC.

Conclusion This economic analysis demonstrates that FA can inform more appropriate clinician decisions resulting in cost savings with greater economic benefits achievable with syndromic testing of all cases, rather than SOC or targeted syndromic testing.

Keywords Cost · Encephalitis · FilmArray · Meningitis

Introduction

Infectious meningitis and encephalitis (ME) warrant early diagnosis and identification of disease etiology given the potentially serious consequences associated with these conditions. The severity and trajectory of the disease vary by etiology with bacterial and fungal infections having the highest mortality rates but occurring less often than viral ME [1]. Holmquist et al. estimated that there were approximately 72,000 meningitis hospitalizations in the United States (US) in 2006 costing in excess of $1.2 billion (mean cost per case of $17,100) [2]. Over half of these hospitalizations were for viral meningitis with only 22% having a bacterial etiology. However, this analysis was conducted in the midst of changing ME epidemiology due to the routine or increasing use of *Haemophilus influenzae* type b, pneumococcal, and meningococcal vaccines [3]. Substantial reductions in the incidence of bacterial ME have occurred in the pediatric population (by 60% or more) [4, 5], with the majority (at least 74%) of all ME cases occurring in adults [2].

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Because of the morbidity and mortality associated with ME [1], especially when diagnosis is delayed or incorrect, suspected cases typically are hospitalized for empiric antibiotic therapy and diagnostic testing—primarily bacterial culture of cerebrospinal fluid (CSF) and, increasingly, polymerase chain reaction (PCR) tests of the CSF for viruses and arboviral serologies (i.e., West Nile virus or St. Louis encephalitis virus). Although molecular tests have much more rapid turnaround times than culture, until recently, only US Food and Drug Administration (FDA)-cleared test for one [enterovirus (EV)] or two [herpes simplex virus (HSV)-1 and HSV-2] specific viral pathogens was available [6, 7]. As an alternative, laboratories rely on laboratory-developed tests conducted in house or, more often, by a reference laboratory. Consequently, the majority of suspected ME cases incur, at a minimum, the costs of a 1–3 day hospitalization, empiric antibiotic therapy, and numerous diagnostic tests [8–10].

The BioFire® FilmArray® System (FA; BioFire/bioMérieux, Salt Lake City, UT, USA) is a US FDA-cleared multiplex PCR system that performs, in a single pouch device, extraction, amplification, and detection of syndromically related pathogens. The BioFire® Meningitis–Encephalitis (ME) Panel tests CSF for 14 of the most prevalent bacterial, viral, and fungal pathogens (Table 1) associated with community-acquired ME, in approximately 1 h. The key FA attributes—rapid turnaround time, comprehensive pathogen array, and high sensitivity and specificity [11, 12]—allow clinicians to accurately diagnose suspected ME patients, make more informed clinical decisions, and provide appropriate care.

Recently, we published an analysis exploring the potential economic impact of FA if used as a component of the testing and diagnosis paradigm in cases of suspected pediatric ME [13]. Our simulation model-based analysis demonstrated that avoidance of inappropriate patient hospitalizations, reductions in length of stay, and more appropriate use of medications and diagnostic tests more than offset the cost of the FA ME Panel, resulting in cost savings compared to current standard of care (SOC). Because ME epidemiology and costs differ between adults and infants or children, the purpose of the present study was to conduct a similar analysis, assessing the possible economic impact of a rapid, sensitive, and specific test for immunocompetent adult patients with suspected community-acquired ME.

Methods

The simulation model developed for this analysis is based largely on published epidemiological literature and analyses of a large hospital administrative database. The results of our economic analysis in a pediatric population, as well as the hospital database analysis that underpins many of the model inputs, have been recently published [8, 13] and detailed methodology is available in those references and in the Supplementary Material available on the Cambridge Core website. As the study used a de-identified database, it was exempt from Institutional Review Board approval.

A brief overview of the model and the associated analytic approach are described below.

Table 1 Estimated FilmArray meningitis/encephalitis panel performance characteristics

Pathogen type or group	Sensitivity/PPA (%)[a]	Specificity/NPA (%)[a]
Escherichia coli K1	100.0	99.9
Haemophilus influenzae	100.0	99.9
Listeria monocytogenes	97.5	100.0
Neisseria meningitidis	97.5	100.0
Streptococcus agalactiae	97.5	99.9
Streptococcus pneumoniae	100.0	99.2
Cytomegalovirus	100.0	99.8
Enterovirus	95.7	99.5
Herpes simplex virus 1	100.0	99.9
Herpes simplex virus 2	100.0	99.9
Human herpesvirus 6	85.7	99.7
Human parechovirus	100.0	99.8
Varicella zoster virus	100.0	99.8
Cryptococcus neoformans/gattii	100.0	99.7

Data extracted from [11, 12]

ME meningitis/encephalitis, *NPA* negative percentage of agreement, *PPA* positive percentage of agreement

[a]Due to no observations of *Listeria monocytogenes* and *Neisseria meningitidis* in the multicenter FilmArray panel study [11] and only one specimen of *Streptococcus agalactiae* (a false negative result by FilmArray), the sensitivity estimates used in the model are based on the combined results for all bacteria from the FilmArray study and archived specimens. The performance measures of sensitivity and specificity only refer to bacterial analytes for which the gold standard of CSF bacterial culture was used as the reference method. Performance measures of positive percentage of agreement and negative percentage of agreement refer to all other analytes, for which PCR/sequencing assays were used as comparator methods

Model overview

Figure 1 is a schematic of the Excel-based (version 2016; Microsoft Corporation; Redmond, WA, USA) model we developed to simulate the diagnosis, clinical decisions, medical resource use, and acute costs associated with suspected community-acquired ME in immunocompetent adult patients (age ≥ 18 years). Patients are assumed to present with signs and symptoms consistent with suspected primary ME at either a hospital outpatient/emergency department (ED) or during a hospitalization (inpatient). In the model, patients undergo testing by one of three strategies: standard

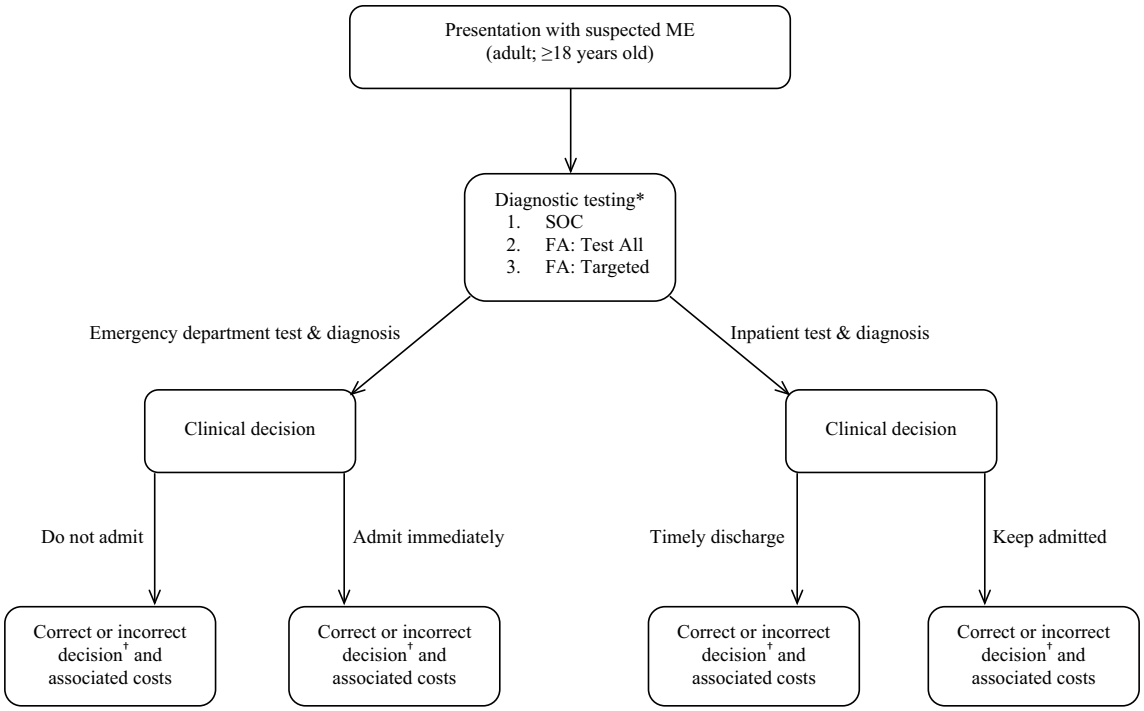

Fig. 1 Meningitis/encephalitis (ME) economic model schematic. *Strategy 1: SOC includes LP, CSF analysis, and other diagnostic tests; Strategy 2:FA test All includes an LP and conventional CSF analysis plus FA for all patients; Strategy 3: FA targeted test includes an LP and conventional CSF analysis plus FA only in patients with an initial abnormal CSF result. †The determination of correct or incorrect clinical decision making was applicable only to the two FA strategies. The costs associated with SOC were based on observed data and actual clinical and diagnostic decisions, whether correct or incorrect. *CSF* cerebrospinal fluid, *FA* FilmArray, *LP* lumbar puncture, *ME* meningitis/encephalitis, *SOC* standard of care

of care (SOC); FA test all (TA); or FA targeted testing (TT). SOC includes the seminal diagnostic test for suspected ME—a lumbar puncture (LP) with CSF analysis as well as a variety of other possible tests [14–16]. Both FA strategies include CSF analysis but differ from SOC in that some diagnostic tests may be avoided (such as viral culture and urine antigen tests). In addition, the TA strategy uses FA in all suspected ME patients while, in the TT strategy, FA is utilized only in patients with abnormal CSF (defined as a white blood cell count > 5 plus a ratio of red/white blood cells < 1000) [17–19].

Based on the test results, an initial diagnosis and clinical decision is made to either immediately admit or not admit the patient (ED LP/testing) or to keep the patient admitted or discharge them in a timely fashion (inpatient LP/testing). Given clinician practice to admit patients with suspected ME for an LP and empiric medical therapy, SOC was composed largely of inpatient-based decisions and costs. Owing to the high sensitivity and specificity of FA for the most common ME pathogens [11, 12], we assumed that clinical decision making for majority of the cases in the FA strategies would originate in the ED setting.

Finally, the model evaluates whether the correct clinical decision is made for the causative ME pathogen. Costs associated with SOC strategy were based on actual cases and clinical decisions as observed in a large hospital database (see "Model inputs"). However, because the FA strategies required clinical decisions to be informed by FA test results, simulating the ME pathogen distribution, test results, clinical decisions, and costs was required.

Model inputs

Parameter estimates for the model were based on several sources including a retrospective observational analysis of a large hospital database [8, 13], a multicenter evaluation of FA performance [11, 12], published epidemiological literature [5, 20, 21], and input from infectious disease experts (RH, CCG, JMB-L, SAB). Further details are described below, in Tables 1 and 2, the Supplementary Material text, and Supplementary Tables S1–S5 available on the Cambridge Core website.

A retrospective observational analysis of 26,388 adult (age 18+) patients admitted in the US during 2011–2014 with discharge data available in the Premier Healthcare Database (PHD) was conducted to assess ME pathogen distribution, resource use, and costs [22]. Approximately 47% of adult patients were male. Despite most (77%) having an

Table 2 Pathogen/group prevalence for the FilmArray meningitis/encephalitis panel model

Pathogen type or group	Prevalence for the SOC and FA test all strategies (%)[a]	Percent of pathogens with abnormal CSF result (%)[b]	Prevalence for the FA targeted strategy (abnormal CSF) (%)[c]	Prevalence for the FA targeted strategy (normal CSF) (%)[c]
Escherichia coli K1	0.56	97.0	0.55	0.02
Haemophilus influenzae	0.99	97.0	0.96	0.03
Listeria monocytogenes	0.42	97.0	0.41	0.01
Neisseria meningitidis	2.67	97.0	2.60	0.08
Streptococcus agalactiae	1.41	97.0	1.37	0.04
Streptococcus pneumoniae	8.04	97.0	7.79	0.24
Cytomegalovirus	0.96	80.0	0.77	0.19
Enterovirus	33.83	60.0	20.30	13.53
Herpes simplex virus 1	2.89	92.0	2.66	0.23
Herpes simplex virus 2	5.78	92.0	5.32	0.46
Human herpesvirus 6	0.96	80.0	0.77	0.19
Human parechovirus	1.82	80.0	1.45	0.36
Varicella zoster virus	8.67	80.0	6.94	1.73
Cryptococcus neoformans/gattii	4.78	90.0	4.30	0.48
Non-FilmArray bacteria	5.89	97.0	5.71	0.18
Non-FilmArray virus	12.64	90.0	11.38	1.26
Non-FilmArray fungus	2.68	90.0	2.41	0.27
Not ME	5.00	5.0	0.25	4.75

CSF cerebrospinal fluid, *FA* FilmArray, *ME* meningitis/encephalitis, *SOC* standard of care

[a]Calculated using the Premier prevalence data and assumptions about redistribution into the FilmArray ME panel model categories (Supplementary Table S1)

[b]Based on the prospective FA study (data on file) and input from infectious disease experts

[c]Patients with abnormal and normal CSF are calculated to make up 76% and 24%, respectively, of all suspected ME cases in the model. Patients with normal CSF in the FA targeted test strategy are not tested with FA but are assigned SOC costs

LP initially performed in a hospital outpatient/ED setting, 83% of all subjects were hospitalized.

The sensitivity (true positive rate) and specificity (true negative rate) used in the model for the FA ME Panel are presented in Table 1 and are estimated based on a multicenter evaluation of 1560 prospectively collected CSF specimens and archived CSF samples [11, 12]. These estimates were used in the simulation model of the FA testing strategies, determining whether the correct diagnosis and clinical decision would be made given the FA test results (Supplementary Table S1).

Table 2 shows the prevalence estimates in the modeled adult cohort including the 14 pathogens identifiable using the FA ME Panel, groups of pathogens not included in the FA test, and 'Not ME' (patients who ultimately are determined to have had a condition other than ME). Additional transformation of the prevalence data for the model (Supplementary Table S2) was informed by literature [5, 20, 21] as well as input from infectious disease experts (RH, CCG, JMB-L, SAB).

Cost estimates from the PHD included those for hospitalization, intensive care unit stay, medications, and diagnostic testing which were inflated to 2015 US dollars using the inpatient hospital services Consumer Price Index [23]. Potential cost offsets associated with the FA ME panel test strategies included avoided resource use (i.e., less informative diagnostic tests and medications used inappropriately) and benefits accrued due to a faster diagnosis (i.e., avoided unnecessary inpatient admissions or more timely discharge). Overall, cost offsets likely are underestimated because we were not able to quantify the frequency and costs of send-out tests that would be avoided using FA [22]. Incremental costs for the TA and TT strategies included those related to incorrect clinical decisions in the case of false positive (FP) or false negative (FN) test results as well as the $193 list price for the disposable FA ME Panel pouch. The capital cost of the FilmArray Instrument, once amortized over its expected lifetime, is nominal and not included in the analysis. Furthermore, staff time for running the FA test (less than 2 min) or that associated with any avoided medical resource use (e.g., unnecessary tests or inappropriate antibiotic use) was judged to be nominal, likely non-differential, and not relevant for the analysis perspective. All cost parameter estimates are presented in Supplementary Tables S3–S5.

Economic model analyses

In the base case analyses, the model uses the default parameter estimates and, based on the prevalence of the different pathogen types or groups, simulates individual ME cases. For SOC, costs are assigned based on the pathogen or group (including Not ME), while for the FA strategies, 1 of the 18 possible FA test scenarios (e.g., single positive, multiple positive, all negative) is simulated and costs assigned, including an economic 'penalty' should the FA test result and subsequent clinical decision be incorrect (Supplementary Tables S1, S3–S5). The mean costs of the overall strategies can then be compared, allowing for possible shifts in the settings of ME diagnostic testing, to determine the economic impact of the use of the FA test.

Comprehensive sensitivity analyses varying a single parameter or groups of estimates were conducted to evaluate the impact of model assumptions, parameter uncertainty, and the overall robustness of results [24].

Results

Base case model analyses

Based on a mean of 1000 simulated adult cases of suspected community-acquired ME, the model estimates that approximately 737 and 742 cases of ME would be potentially identifiable with FA in the TA and TT strategies, respectively (Supplementary Tables S6, S7); over 97% of these cases were accurately diagnosed with FA in both strategies. Due to the high positive and negative predictive value of FA, there were very low rates of inaccurate diagnosis, pathogen misidentification, and incorrect clinical decision making. For example, in the TA strategy, approximately 4.4% of all cases were either misidentified as an FA pathogen (FP = 0.7%) or not identified correctly if the true pathogen was an FA pathogen (either FP = 1.9% or FN = 1.7%) (Supplementary Table S6). These misidentifications more often led to a clinical decision that resulted in an unnecessary admission or unnecessarily extended an existing admission (3.8% of all cases)—representing missed opportunities for cost savings—rather than premature hospital discharge or a missed admission (3.2% of all cases) which could lead to poorer clinical outcomes and increased treatment costs. Targeting FA use only to those with abnormal CSF resulted in a similar level of misidentifications with the exception that there were almost no instances (0.2% of all cases) of premature discharge/missed admission (Supplementary Table S7).

The economic results of the SOC and FA testing strategies are presented in Table 3 and Supplementary Figure S1. The mean cost per case ranged from $16,829 to $20,791 and varied based on the testing strategy and setting of the initial LP (ED vs. inpatient). LP and testing in the ED was less costly than in the inpatient setting, because an ED test allows for a reduction in the number of hospitalizations. Yet, as documented in the PHD analysis, a relatively small proportion of ME patients (17%) currently receive an LP in a hospital outpatient/ED setting without subsequent admission. Our base case assumed that the majority of patients (75%) would be tested with FA in the ED setting given that the FA test yields results rapidly that can be utilized for diagnosis (although this assumption was tested extensively in sensitivity analyses). Comparing the costs of SOC and the FA strategies—weighted by the LP setting distribution—demonstrated that the implementation of either FA

Table 3 Economic impact of the FilmArray meningitis/encephalitis panel testing strategies compared with standard of care

	Standard of care costs		FA panel costs			
			Test all strategy		Targeted test strategy (abnormal CSF)	
	Inpatient result	ED result	Inpatient result	ED result	Inpatient result	ED result
Mean cost	$19,651	$17,076	$17,518	$16,829	$20,791	$20,356
Distribution of LP and 'testing' location (%)	83	17	25	75	25	75
Weighted average cost of strategy	$19,214		$17,001		$20,465	
	SOC vs. FA comparative analysis					
Cost of SOC and FA test all strategy	$19,214		$17,001			
Cost addition (savings) of FA ME panel			($2213)			
Cost of SOC and FA test abnormal strategy	$19,274[a]				$18,462[b]	
Cost addition (savings) of FA ME panel					($812)	

CSF cerebrospinal fluid, *ED* emergency department, *FA* FilmArray, *LP* lumbar puncture, *ME* meningitis/encephalitis, *SOC* standard of care

[a]Calculated based on the following weighed average costs for SOC: abnormal CSF ($21,533) and normal CSF ($12,119)

[b]Calculated based on the weighted average FA cost for abnormal CSF ($20,465) and weighted average SOC cost for normal CSF ($12,119)

testing strategy was cost saving relative to SOC. The FA TA strategy yielded greater cost savings ($2213 per case) than a strategy of using the FA test only in patients with abnormal CSF ($812 per case).

Model sensitivity analyses

Sensitivity analyses were performed by varying FA performance characteristics, pathogen prevalence, costs, LP/FA test setting distribution, and other variables (Supplementary Table S8; Fig. 2). Changes to a single type of parameter did not impact the results materially. The inclusion of FA testing resulted in incremental costs (rather than cost savings) only in an analysis with combinations of extreme values. All other scenarios, including all ED/inpatient setting distributions for FA testing, remained cost saving. A more detailed discussion of these results is included in the Supplementary Text available on the Cambridge Core website.

Discussion

Due to the potential significant acute and long-term complications associated with bacterial ME, most patients with signs and symptoms of ME are admitted to the hospital despite the low prevalence of the bacterial etiology in immunocompetent patients. As a result, patients with viral meningitis (for example, EV, which is usually self-limiting) often experience unnecessary hospital stays, antibiotic use, and diagnostic testing, all of which contribute to a substantial cost burden. Our current modeled analysis of the immunocompetent adult population demonstrates findings similar to our evaluation of pediatric ME cases [13]: that the use of a highly sensitive and specific multiplex PCR test with a broad diagnostic spectrum for numerous ME pathogens can yield substantial cost savings of up to 12% (~$2200 per case) compared to current standard practice. In addition, our analysis suggests that this testing paradigm does not sacrifice good clinical practice and outcomes to achieve a more efficient use of medical resources and cost savings with missed admissions or inappropriate discharges being uncommon with FA (3.2% of all cases in a TA strategy) or rare (0.2% of all cases in a TT strategy). These findings are consistent with other studies documenting positive clinical and economic benefits associated with EV PCR testing [25–30], yet the results are more compelling given the numerous additional pathogens included in the FA test.

While our analyses in both pediatric and adult populations suggest that the FA ME panel can yield cost savings compared to the current practice, the magnitude of the savings is approximately $1300 lower (per patient) in adults [13]. Largely, this is due to higher treatment costs in children that yield greater cost offsets when inappropriate inpatient admissions are shortened or avoided. In addition, EV prevalence is higher in children, thus yielding more opportunity for early discharge than in adults. Nevertheless, the total number of ME cases is approximately three times greater in the adult population [2] and, therefore, the overall potential cost savings are likely larger as well, despite the lower per patient cost savings in adults.

In addition to our pediatric research, one other economic evaluation has explored the potential economic benefits of FA [31]. Soucek et al. quantified the cost of empiric antimicrobial treatment using data from the electronic medical records of 33 adults admitted to a community teaching hospital for a presumed meningitis diagnosis between

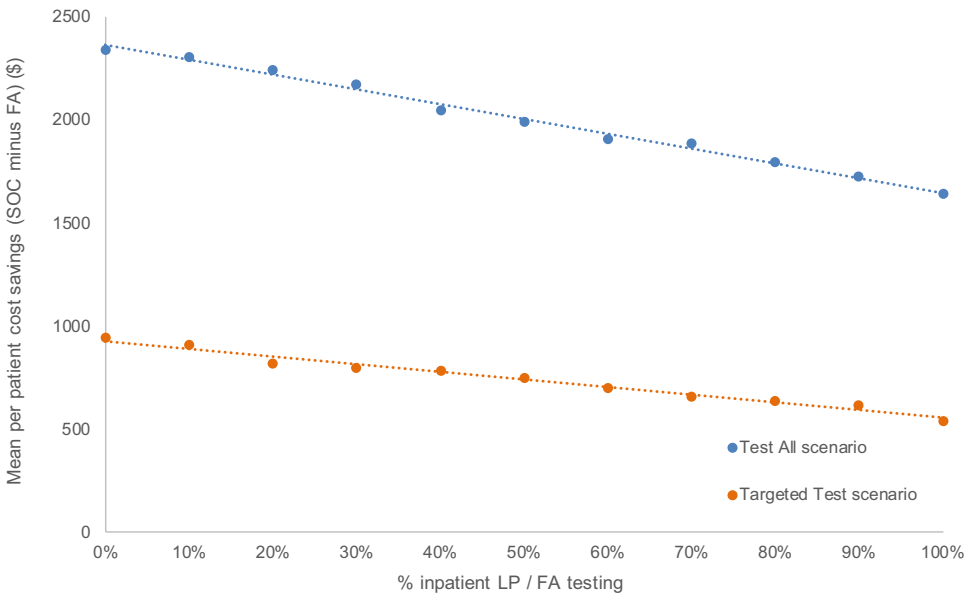

Fig. 2 Mean per patient cost savings by % of lumbar puncture/FilmArray testing conducted in the inpatient setting (remainder conducted in emergency department setting) and testing scenario. The base case analysis assumed 25% inpatient LP/FA testing. *FA* FilmArray, *LP* lumbar puncture

1 January 2015 and 31 December 2015. Actual costs were compared to estimated costs had FA been used for diagnosis and treatment decisions in the same 33 patients. The authors reported that antimicrobial cost would be reduced by 61% per treatment course with FA use due to its more rapid time to final results. When diagnostic testing supply costs were also included, the median per patient costs of SOC ($239.64) and the FA estimate ($239.14) were basically equivalent; in other words, the incremental cost of FA was entirely offset by the antimicrobial savings. While Soucek et al. only analyzed several medical resource components of the overall cost of care, their results offer compelling support of the potential cost savings predicted by our more comprehensive modeled analyses of both pediatric and adult populations.

Our analyses suggest that a broader use of the FA ME Panel will produce greater cost savings than its targeted use. This is largely explained by missed opportunities to avoid a costly admission or discharge a patient much earlier when testing only those with abnormal CSF. For example, in the US, many adults with the most prevalent ME pathogen (EV) and a normal CSF cell count are admitted as common practice. Had these patients been tested with FA, nearly all would have received a rapid EV diagnosis and been managed more efficiently.

Given the potential clinical benefits of attaining rapid and comprehensive results to more accurately diagnose suspected ME cases, institutions may employ an 'enhanced testing' strategy in which a battery of 4–5 additional individual PCR tests are used for the most common and/or most lethal pathogens. However, in most instances, labs must send out these tests with turnaround times measured in days rather than hours, thus diminishing the ability to make a timely clinical decision in the ED and reduce costs, both of which can be achieved with a rapid test. A sensitivity analysis designed to evaluate such a strategy demonstrated that institutions utilizing numerous send-out tests to diagnose ME would achieve even greater savings with both FA testing strategies compared to current SOC. For example, the mean per case cost savings increased from $2213 (base case) to $2492 (enhanced testing scenario) for the FA TA strategy.

Although FA use may obviate the need for some other diagnostic tests, it is not a replacement for bacterial or fungal culture. The FA package insert clearly states that laboratories should continue to perform a Gram stain and culture to provide detection of pathogens not present in the panel, pathogens that may be present in numbers below the assay limit of detection, and to provide essential and comprehensive antimicrobial susceptibility data [12]. The benefit of the panel for bacterial pathogens lies in the rapidity of the test result and the detection of bacterial pathogens that are difficult to grow (e.g., *Haemophilus influenzae*) or in cases where the patient has been pretreated with antimicrobials and both Gram stain and culture can become negative after as little as a single dose of ceftriaxone and vancomycin [32].

Our research has several strengths that support the rigor of the findings and conclusions. First, the FA ME Panel performance characteristics for all but three pathogens (*Listeria monocytogenes*, *Neisseria meningitidis*, and *Streptococcus agalactiae*) are based on a large multicenter study of prospectively collected CSF samples and archived CSF samples [11, 12]. Varying these parameters to the extreme 95% confidence intervals in sensitivity analyses resulted in only moderate changes in the cost results. Second, cost estimates were based on analyses of one of the largest hospital databases containing detailed data on medications, diagnostic tests, and timing of resource use, allowing more accurate estimation of possible cost offsets with FA testing.

However, as with all economic models, limitations of our research also warrant further discussion. By necessity, our model oversimplifies true clinical decision making by relying solely on the result of a single FA test, possibly also knowing the status (normal or abnormal) of a CSF sample. Furthermore, we were not able to analyze other medical, social and ethical aspects or perform sub-analyses based on age groups and comorbidities. A greater wealth of information is available to inform real-world decisions and FA's intended use is as a component of testing and an aid in the diagnosis process, not as the sole basis for patient management decisions. Nevertheless, current clinical practice and decisions often are clearly suboptimal, exposing many suspected ME patients to an unnecessary hospitalization. Our analysis demonstrates the possible economic benefits that can be achieved if a comprehensive multiplex assay for ME is incorporated into the diagnostic paradigm.

Similarly, for pragmatic purposes, some elements of our model rely on a hospital database analysis that used International Classification of Disease (ICD) coding to identify potential cases. The reliability of this approach has been questioned [33], but the results of sensitivity analyses designed to explore this issue remain favorable and suggest that FA test use would be cost saving over wide ranges of ME pathogen/Not ME distribution.

Some pathogen-specific parameter estimates were based on clinical experience of infectious disease experts rather than published evidence given data gaps in the literature. For example, our estimate of human herpesvirus (HHV)-6 prevalence may be an overestimate in this immunocompetent patient population, although the lack of routine screening for this pathogen limits a more precise estimate. Although we varied this parameter and others widely in sensitivity analyses and observed only one scenario in which our cost-saving conclusion would change, more robust prevalence and cost estimates for individual pathogens may make our conclusions more definitive.

Finally, we conducted our analysis from the perspective of the US healthcare system over the acute hospitalization period. While the benefits of a rapid and comprehensive FA ME panel that can improve clinical decision making and patient care may translate to other healthcare systems, the economic results of this analysis may not be generalizable given differences in relative costs and financing mechanisms in other countries. Furthermore, we did not explicitly attempt to simulate or quantify improved clinical outcomes associated with better diagnostics or possible poorer clinical outcomes associated with incorrect clinical diagnoses that could occur during or after an admission. Although the occurrence of the types of clinical decisions most likely to lead to poor outcomes is very low in our analyses, we have only evaluated costs, not morbidity or mortality, for either SOC or FA testing. With high mortality rates for many bacterial and fungal pathogens [5, 34, 35], especially in older adults [2], and delays in diagnosis increasing mortality [36], this potential benefit, left unexplored by our analysis, should be considered in future evaluations. Finally, it remains a challenge deciding the true role of HHV-6 cases in cases outside the classic encephalitis seen after bone marrow transplantation [3, 37].

Corroborating our findings with a real-world prospective study with both clinical and economic outcome measures would be ideal. However, the rarity of highly lethal and high-cost ME pathogens makes such research impractical. Our comprehensive economic analysis of a multiplex assay for ME suggests that its use can inform more appropriate clinical decisions yielding cost savings compared to current clinical practice. Furthermore, greater economic benefits may be achieved if testing is used more broadly rather than only in a narrow subset of patients with abnormal CSF results. This new testing paradigm in ME patients should also increase confidence in clinical management while benefiting all stakeholders by using scarce medical resources more wisely and appropriately.

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Compliance with ethical standards

Conflict of interest SD is a paid consultant to bioMérieux and an employee of Veritas Health Economics Consulting; RH and JMBL are consultants to bioMérieux and speakers for BioFire Diagnostics; CCG is an employee of bioMérieux and BioFire Diagnostics and owns bioMérieux stock; LZ is an employee of bioMérieux; SAB was an employee of bioMérieux at the time the research was conducted.

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