FILMARRAY: CAN IT MAKE A DIFFERENCE FOR CSF TESTING

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MMUH

Level 4 teaching hospital based in Dublin's north inner city

Over 600 in-patient beds

Adults, range of frontline and specialist services on a regional and national level

In 2016

- 21,500 in-patients
- 58,900 emergency department visits

CSF STATS

524 CSF samples processed in 2016

53 had white cell counts greater than 5

Microbiology 8am to midnight, multi disciplinary post midnight

- Cell count
- Differential WCC on samples with a WCC >5
- Gram stain (only up to midnight Mon-Sun)
- Culture
- Referral of samples to NVRL and/or IMMRL

LIMITATIONS OF CURRENT SERVICE

35 week pregnant lady with Bechets disease presented to ED on Saturday 14/5 @ 2am with headache and fever

LP revealed raised WCC 250 (50% poly, 50% mono) with raised protein and glucose

Empiric treatment commenced (ceftriaxone + amox IV + acyclovir)

DD: enterovirus, Bechets aseptic meningitis, Listeria, HSV and then other bacterial and viral causes

Patient remained on empiric antimicrobials until 17/5 @ 17:19 when a report of Enterovirus PCR pos was received from NVRL

ME PANEL TARGETS

FilmArray
Meningitis / Encephalitis (ME) Panel - IVD

BIOFIRE
www.BioFireDx.com

Run Summary			
Sample ID:	910313	Run Date:	01 Jul 2016 3:22 PM
Detected:	Enterovirus	Controls:	Passed

Result Summary	
Bacteria	
Not Detected	*Escherichia coli* K1
Not Detected	*Haemophilus influenzae*
Not Detected	*Listeria monocytogenes*
Not Detected	*Neisseria meningitidis*
Not Detected	*Streptococcus agalactiae*
Not Detected	*Streptococcus pneumoniae*
Viruses	
Not Detected	Cytomegalovirus
✓ Detected	Enterovirus
Not Detected	Herpes simplex virus 1
Not Detected	Herpes simplex virus 2
Not Detected	Human herpesvirus 6
Not Detected	Human parechovirus
Not Detected	Varicella zoster virus
Yeast	
Not Detected	*Cryptococcus neoformans/gattii*

Run Details			
Pouch:	ME Panel v1.4	Protocol:	CSF v2.0
Run Status:	Completed	Operator:	louise o sullivan (louise)
Serial No.:	04364997	Instrument:	ITI FA "FA3409"
Lot No.:	262216		

MMUH VERIFICATION

ZeptoMetrix NATrol Meningitis/Encephalitis Panel + NEQAS isolates and ATCC isolates			Patient samples previously tested in NVRL		
Escherichia coli K1	HSV-1	Haemophilus influenzae	Positive Enterovirus patient sample	Positive Enterovirus patient sample	Negative CSF patient sample
CMV	Neisseria meningitidis	HSV-2			
EnterovirusType 11	Streptococcus agalactiae	VZV			
Streptococcus pneumoniae	Cryptococcus gattii	Listeria monocytogenes			
HHV-6	Haemophilus influenzae ATCC	HPeV			
Listeria monocytogenes NEQAS	Streptococcus pneumoniae ATCC	Cryptococcus neofomans (patient)			
Streptococcus agalactiae NEQAS		Neisseria meningitidis NEQAS			

33 patient samples tested
26 negative results were in agreement with Ref Labs
8 detection in 7 samples from different patients

Detected	FA	NVRL	IMMRL
VZV	4	1	NA
STRPN	1	NA	0
EV	2	1	NA
HHV6	1	Insuf	NA

CASE STUDY 1

Previously physically well, immunocompetent adult presented with the worst headache she ever had, neck stiffness and intermittent photophobia.

Acute meningitis was not immediately suspected as she had the headache for 4 days and she had managed to continue to cycle and attend a social function.

Risk factors for neurological disease-long term antipsychotic medications.

MRI ruled out the possible neurological diagnoses.

CASE STUDY 1

LP revealed a raised white cell count in CSF (predom monos), raised protein and FilmArray gave a positive PCR for Varicella Zoster Virus two hours later.

Started on acyclovir immediately thereafter.

Diagnosis was a somewhat unexpected finding but fit the clinical picture. In light of the result, the patient was examined thoroughly for skin lesions and a single herpetic lesion was discovered in the lumbar region.

Infection prevention and control precautions were initiated at this point.

BENEFITS OF FILMARRAY FOR CASE STUDY 1

As meningitis was not the working diagnosis on admission, IV antibacterials were not started.

However, it is likely that in the absence of the FilmArray result, medical team would have started antibacterial therapy based on the raised white cell count, while awaiting a diagnosis of cause.

Interestingly, the sample sent to the NVRL returned a negative result for VZV, so this diagnosis may never have come and the patient may have remained an inpatient for longer for further investigations

CASE STUDY 2

HIV positive patient, poorly compliant with antiretroviral therapy and clinic appointments, presented with acute red eye and visual disturbance on a background of feeling generally unwell for a couple of weeks.

Hx of shingles one month earlier

Ophthalmology review diagnosed pan-uveitis, retinitis and areas of retinal necrosis.

Opportunistic infection was suspected, in particular CMV, which is a known common cause of retinitis in HIV positive patients.

CASE STUDY 2

LP performed and vitreous and aqueous samples collected in OT.

LP revealed raised white cell count(100% monos), raised protein and FilmArray was positive for VZV and Strep. pneumo within 2 hours.

Treatment for VZV and STRPN immediately commenced.

VZV and STRPN were not detected by NVRL and IMMRL respectively. However, the vitreous and aqueous samples submitted to NVRL were positive for VZV.

BENEFITS OF FILMARRAY FOR CASE STUDY 2

Initiation of appropriate therapy is critical in retinitis cases as lack of treatment may result in irreversible visual loss.

It is likely that another agent e.g. ganciclovir would have been started, which is not first line for VZV. Acyclovir is first line for VZV and cheaper than ganciclovir. Antibacterial therapy is unlikely to have been started.

Importance of ruling out other opportunistic causes of retinitis which could be diagnosed in CSF, in particular Cryptococcus neoformans. This spares the patient unnecessary antifungal therapy and is a potential cost reduction for the hospital(€1267 per day).

CASE STUDY 3

Previously well young woman presented to ED with severe headache, neck stiffness and photophobia.

A differential diagnosis of meningitis or sub-arachnoid haemorrhage was made. Ceftriaxone and vanc initiated

CT ruled out haemorrhage and a lumbar puncture was performed.

CSF was positive with a raised white cell count (mononuclear predominance) and raised protein. FilmArray was positive for Enterovirus

BENEFITS OF FILMARRAY FOR CASE STUDY 3

Result was discussed with the medical registrar on call at 00:30 at which time he confirmed that the patient was on antibacterials due to the classical meningitic presentation, was not neurologically compromised and was already beginning to feel somewhat better.

Antibacterial therapy was stopped and the patient was discharged to recover at home less than 24 hours after registration at ED. In the absence of FilmArray, patient would have been admitted.

Risk of healthcare associated complications for the patient was minimised.

Financial savings of a minimum of one bed day, likely two, and the same duration of antibacterials =€858-1716.

CASE STUDY 4

HIV and Hep C positive patient presented with ischaemic stroke

Commenced on ceftriaxone and vanc for ?? Meningitis or Infective Endocarditis

LP revealed raised WCC 14 (100% monos), raised protein and FilmArray gave a positive result for VZV @ 3am

Acyclovir commenced on basis of FilmArray result

BENEFITS OF FILMARRAY FOR CASE STUDY 4

Diagnosis of VZV was missed by the less sensitive test performed by the NVRL.

Immunocompromised patient commenced appropriate treatment for VZV, unnecessary antimicrobials were discontinued and amphotericin B was not initiated.

As this was an unexpected result, initiation of appropriate treatment reduced the risk of further strokes and greatly improved the patient's prognosis.

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Multicenter Evaluation of BioFire FilmArray Meningitis/Encephalitis Panel for Detection of Bacteria, Viruses, and Yeast in Cerebrospinal Fluid Specimens

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PAPER OVERVIEW

Leber et al report the results of a large multicenter trial designed to support FDA clearance of the ME panel.

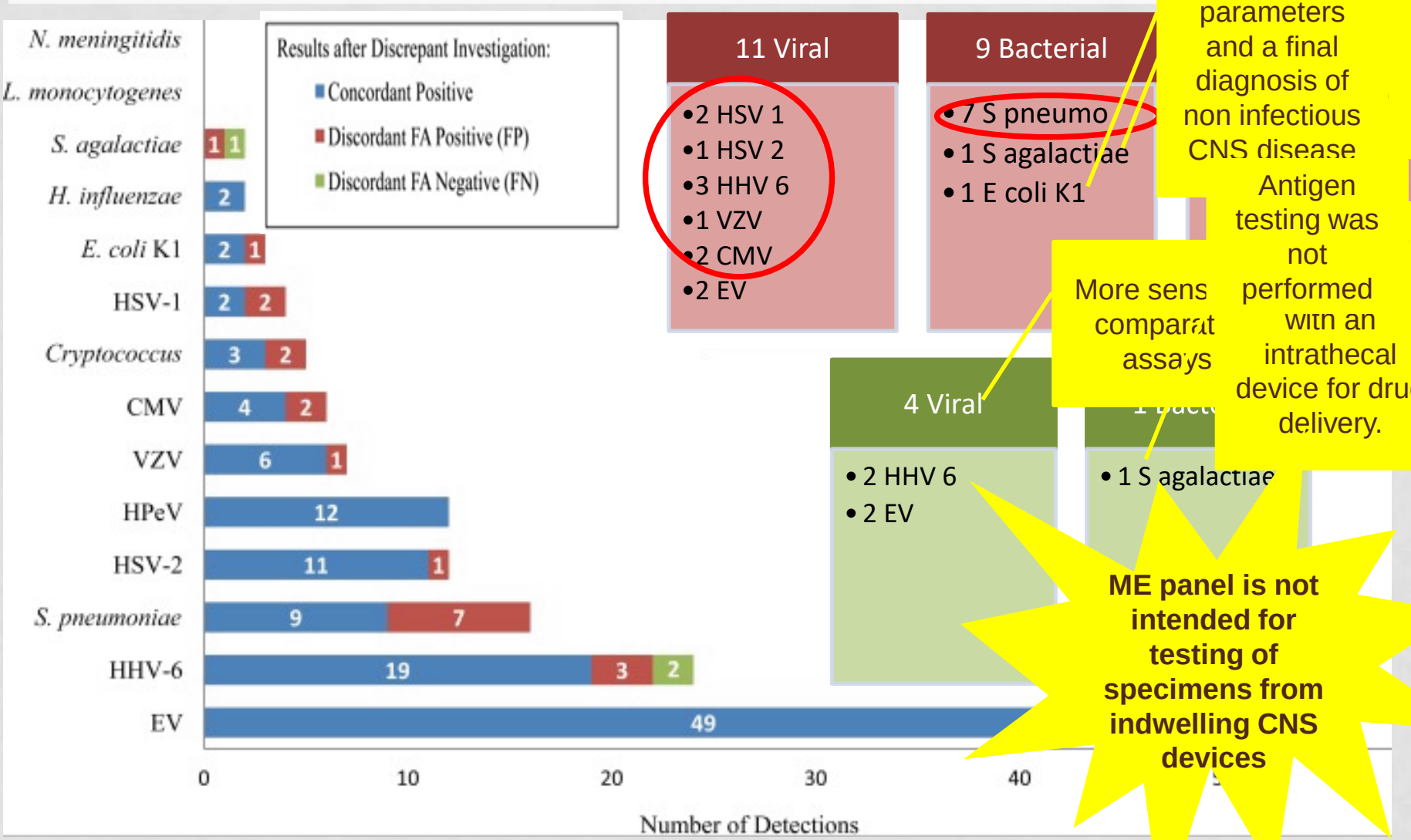
1,560 residual CSF specimens obtained as a part of routine clinical care were tested at 11 different sites in the US.

The ME panel test performance was assessed through comparisons to conventional culture for bacteria or with PCR followed by sequencing for the viral and yeast targets.

Discordant results across methods were resolved by repeat molecular analysis (when possible) combined with a blind review of study subject demographic, clinical, and laboratory information.

Following adjudication of discrepant results there was 84.4% positive and >99% negative agreement between the ME panel and conventional methods.

PERFORMANCE OF FILMARRAY ME PANEL V'S COMPARATOR ASSAYS



HERPES VIRUSES

All of the herpesviruses included in the ME panel are known to establish latency so detection may represent a recent primary infection, reactivation with disease, reactivation without disease or latent detection in cells present in the CSF.

Caution should be taken with evidence of bloody traumatic taps and contamination of the CSF with peripheral blood cells

STREPTOCOCCUS PNEUMO

The number of false positive S. pneumo results were concerning.

Investigators speculated it was possibly due to contamination during aliquoting-control material or oral flora from operators or collectors.

Complacency when testing is performed outside dedicated molecular sections of the laboratory.

Ideally a biological safety cabinet that can be kept clean and separate from control material should be used when loading the FilmArray pouches. Face masks for collectors.

LIMITATIONS OF STUDY

Full clinical data was not available on all patients

Imperfect diagnostic gold standard as a comparator for bacterial targets

There was no remaining sample for retesting in some instances

The study design did not select subjects with a high pretest probability of CNS infection, as enrolment was based solely on a sample being submitted for CSF culture with sufficient volume left over for study testing

WHICH PATIENTS SHOULD BE TESTED

Immunocompromised patients - Herpesviridae and Cryptococcus species can cause significant disease

Paediatric and adult patients with a high clinical suspicion for bacterial infection. Also useful where patients have received antibiotics prior to LP

Targeted testing (in MMUH immunocompetent patients with WCC >5 or immunocompromised/ immunocompetent patients with high protein and a high clinical suspicion of encephalitis

AUTHORS RECOMMENDATIONS

Laboratory consultation services are needed to help clinicians interpret results and testing should be scrutinised closely in context of all available medical history.

False negative results due to organisms not included in the panel or pathogens below the levels of detection suggest empiric antibiotics and/or acyclovir should be initiated when the clinical suspicion for bacterial infection or HSV encephalitis is high and the ME panel is negative.

ME panel will not replace Gram staining or culture or CSF cryptococcal antigen

CONCLUSION FROM A MMUH PERSPECTIVE

Big thanks to Dr Deirdre Brady and Dr Edel O' Regan.
Thanks also bioMerieux for allowing us to trial the instrument


ANY
QUESTIONS
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