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ORIGINAL ARTICLE

Clinical Metagenomic Sequencing for Diagnosis of Meningitis and Encephalitis

Wilson *et al*. June 13, 2019

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Background

- A cause for acute meningoencephalitis cases is not identified in approximately 50% of patients.
- Poor patient outcomes, increased patient and family anxiety, high cost burden to the health care system.
- Metagenomic next-generation sequencing is a promising approach

comprehensive spectrum of potential causes in a single assay

- **Aim**: to evaluate the real-life clinical performance of the metagenomic NGS assay in comparison with conventional microbiologic testing.

Methods

- 1-year, multicenter, prospective case series
- Target condition: clinical syndrome of meningitis, encephalitis, or myelitis without etiologic diagnosis at time of enrollment
- Index test: metagenomic NGS assay of CSF
- Study enrollment target: 300 patients

Methods

- Results reported in the patient EMR and discussed in the clinical microbial sequencing board
- Final clinical diagnoses were adjudicated by retrospective, in-depth chart review
- Orthogonal confirmation of discrepant results was performed
- Standardized physician surveys before and after reporting of metagenomic NGS results

Results

482 Patients were assessed for eligibility
213 Were identified by chart review
165 Were identified by physician referral
58 Were identified by automated EMR report
46 Were identified by provider-order entry

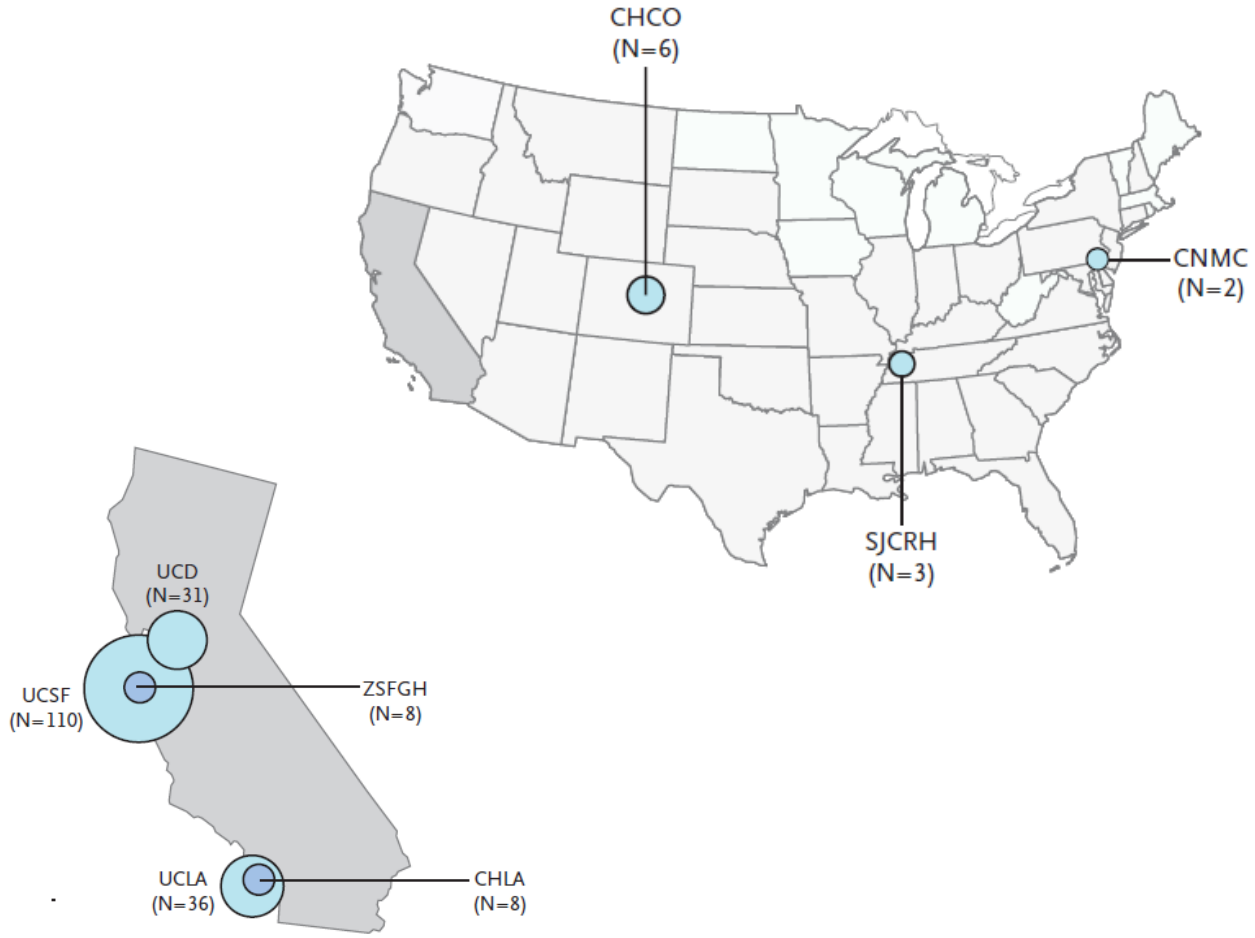
197 Did not meet criteria for enrollment

285 Met criteria for enrollment

71 Were not enrolled in study
34 Had inadequate CSF volume (<0.5 ml)
19 Declined to participate
18 Were discharged from hospital or could not be contacted

214 Were enrolled in study

204 Completed the study
10 Withdrew or were withdrawn
6 Did not provide written consent or could not be contacted
3 Were withdrawn by surrogate
1 Withdrew



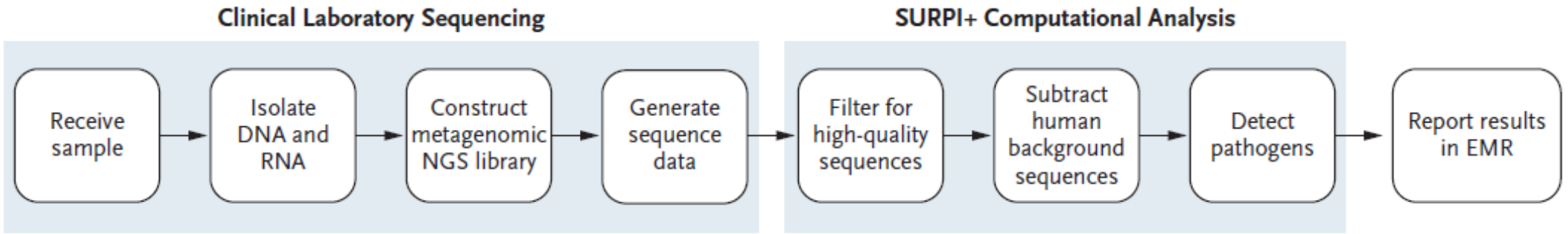
- June 2016 - July 2017
- Eight participating sites in USA
- 214 Patients enrolled → 204 completed the study

Table 1. Demographic and Clinical Characteristics of the 204 Patients.*

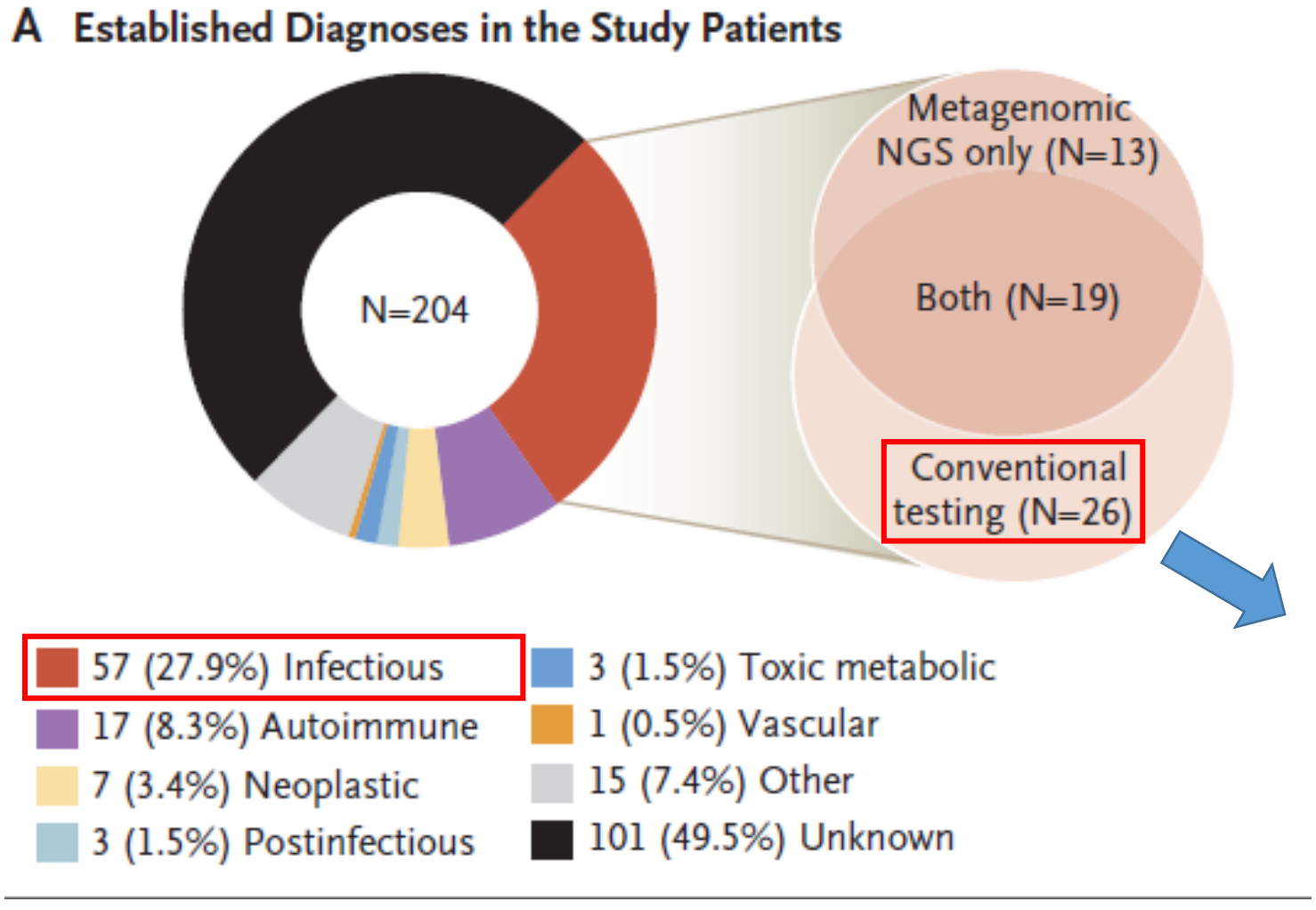
Characteristic	Value
Age	
Mean — yr	39.6
Distribution — no. (%)	
0–2 yr	5 (2.5)
3–12 yr	25 (12.3)
13–18 yr	16 (7.8)
19–25 yr	17 (8.3)
26–40 yr	40 (19.6)
41–60 yr	53 (26.0)
>60 yr	48 (23.5)
Male sex — no. (%)	114 (55.9)
Syndrome — no. (%)	
Meningitis alone	70 (34.3)
Encephalitis with or without meningitis	130 (63.7)
Myelitis with or without meningitis	4 (2.0)
Exacerbation of chronic condition — no. (%)†	28 (13.7)
Immunocompromised — no. (%)	83 (40.7)
HIV-1	21 (10.3)
Solid-organ transplant	14 (6.9)
Bone marrow transplant	13 (6.4)
Chemotherapy	14 (6.9)
Immunosuppression for non-neoplastic condition	14 (6.9)
Congenital condition	3 (1.5)
Other	4 (2.0)
Existing CNS hardware — no. (%)‡	27 (13.2)
ICU admission — no. (%)	99 (48.5)
Death within 30 days — no. (%)	23 (11.3)
Mean Karnofsky performance-status score at time of discharge§	64.6
Mean length of stay (range) — days	
In hospital	27.9 (1–246)
In ICU¶	17.8 (1–71)
Percentage of hospitalization time spent in ICU¶	32.2
Median no. of days after hospital admission that CSF was collected for metagenomic NGS (range) — days‖	3.0 (0–219)

46 (22.5%)

41%



Mean laboratory turnaround time: 90 hours



- 11 Serologic testing alone
- 7 Samples other than CSF
- 8 Low titers of pathogens

Clinical microbial sequencing board

- Modeled after the “tumor board” concept in oncology
- Weekly teleconferences for review of metagenomic NGS results in clinical context
- Among the 13 cases diagnosed solely by metagenomic NGS:
  - Results favorably affected clinical reasoning in 8 cases
  - In 7 cases guided therapy

E Clinical Effect (13 cases diagnosed by metagenomic NGS only)

- 7 (54%) Enabled appropriate and targeted treatment
  - *N. farcinica* — long-term treatment with oral moxifloxacin and minocycline
  - *Candida tropicalis* — treatment with high-dose fluconazole and liposomal amphotericin B (started empirically for elevated 1,3-β-D-glucan level)
  - HEV — successful treatment with IV ribavirin after patient was readmitted with liver failure and consideration of liver transplantation
  - *E. aerogenes* — narrowing of antibiotic therapy to IV cefepime and oral trimethoprim–sulfamethoxazole
  - *Enterococcus faecalis* — narrowing of antibiotic therapy to IV vancomycin; discontinuation of meropenem
  - *S. mitis* — narrowing of antibiotic therapy to IV cefepime; continuation of antibiotics for 4 wk to treat CNS infection
  - *S. agalactiae* — treatment with an additional 4 wk of therapy with IV ceftriaxone and vancomycin
- 1 (8%) Helped to rule out coinfections; enabled patient to proceed with chemotherapy (EBV-associated lymphoma)
- 1 (8%) Supported clinical decisions to narrow coverage (neisseria)
- 2 (15%) Had no effect, because patient already discharged from hospital (enterovirus)
- 1 (8%) Had no effect, because clinical significance unclear (MW polyomavirus)
- 1 (8%) Provided reassurance to patient or surrogate (SLEV)

Hepatitis E virus meningoencephalitis

- 58 y/o woman
- Bilateral lung transplant, multiple sclerosis on chronic immunosuppression
- Fever, headache, nausea, vomiting, neck stiffness, and photophobia
- Transaminitis beginning at the time of her lung transplant. Deterioration of liver function
- CSF profile: lymphocytic pleocytosis, normal glucose and protein levels. All microbiologic studies returned negative
- mNGS testing: Hepatitis E virus infection
- Treatment with IV ribavirin, with resolution of both neurologic symptoms and liver failure
- Lung donor: previously unrecognized HEV infection → first reported case of HEV infection transmitted by lung transplant

Nocardia farcinica meningoencephalitis

- 66 y/o man
- Lung transplantation
- Fever, altered mental status, sepsis, and pneumonia following a flu-like illness
- Empirically treated with meropenem, vancomycin, azithromycin, and oseltamivir
- Brain MRI revealed ventriculitis and multiple T2 hyperintense lesions throughout the cerebral hemispheres
- CSF 126 WBCs (78% N, 20% L, 2% M), normal glucose, and elevated protein. Microbiological testing was negative
- mNGS testing: Nocardia farcinica
- Initial treatment with IV imipenem followed by long-term treatment with oral moxifloxacin and minocycline

Discussion

Advantages

- Unbiased approach → ability to detect many potential infectious agents in a single assay
- Earlier and more targeted treatments
- Identification of emerging infections
- Earlier workup and treatment for noninfectious causes (e.g. suspected autoimmune encephalitis)
- Concordance with conventional testing: reassurance, immunocompromised patients (ruling out co-infections)
- Clinical microbial sequencing board → precision medicine

Limitations

- Cost, accessibility, and turnaround time
- The preferred timing and patient population for clinical metagenomic NGS testing remain to be defined
- High host background → higher risk of false negative results
- Clinical thresholds for reporting a positive test on metagenomic NGS
  - ➢ more liberal reporting thresholds for high-priority pathogens?

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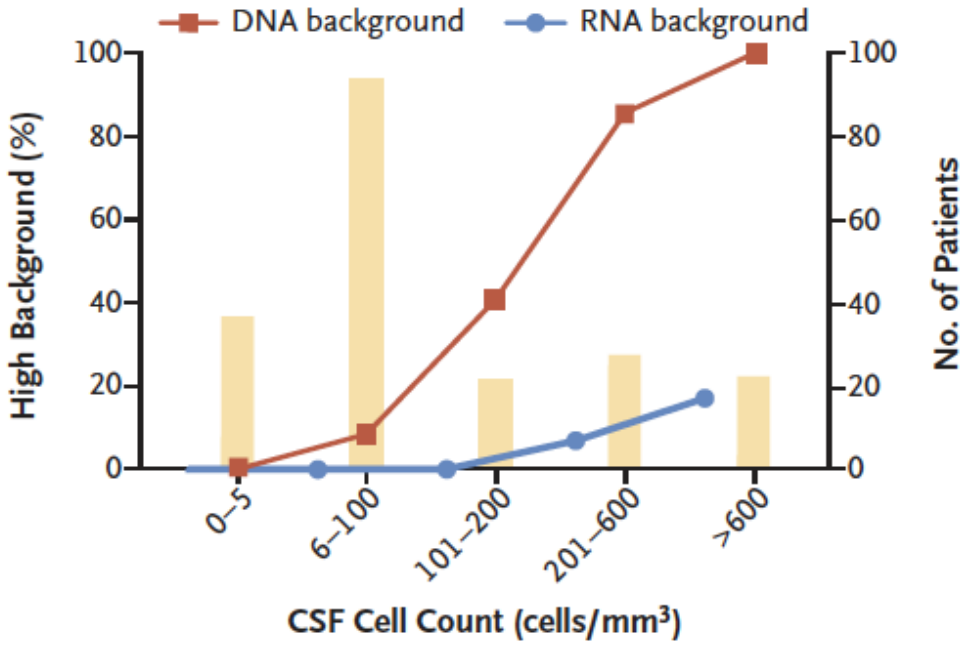

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Conclusions

- Clinical metagenomic NGS of CSF represents a potential step forward in the diagnosis of meningoencephalitis.
- The highest diagnostic yield resulted from a combination of metagenomic NGS of CSF and conventional testing