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Evaluating the Clinical Impact of Metagenomic Next-Generation Sequencing in CNS Infections: A Diagnostic Pathway and Resource Utilization Modeling Study

Gerome Vallejos MD MMSc, Carla Kim, Kathryn B. Holroyd MD , Kiran T Thakur MD

Program in Neuroinfectious Diseases, Department of Neurology, Columbia University Irving Medical Center, New York Presbyterian Hospital, New York, NY USA

BACKGROUND

Diagnosing meningitis and encephalitis remains challenging due to non-specific clinical presentations and the limitations of traditional microbiological methods. Metagenomic next-generation sequencing (mNGS) offers a broad approach to detect pathogens, but its real-world impact on clinical decision-making remains undefined.

OBJECTIVES

To address this, we developed a probabilistic Bayesian modeling framework to estimate the potential clinical utility of a mNGS test that detects RNA and DNA pathogens in CSF in ~48h, and we analyzed the potential reductions in total number of microbiological tests, number of LPs, and days to diagnosis.

METHODS

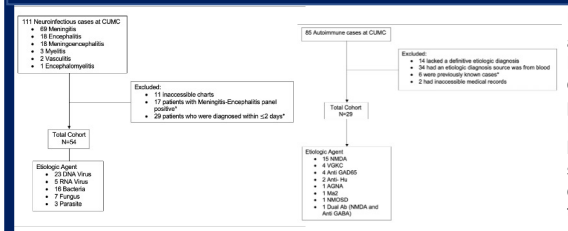

Figure 1: Infectious Cohort

Figure 2: Autoimmune Cohort

Using prevalence estimates as priors, we applied a Bayesian framework to adjust the PPV/NPV of an mNGS test and compared outcomes with the observed diagnostic pathway. For infectious cases, the adjusted PPV estimated true positives that would have been identified early, and each was assigned a simplified mNGS scenario (1 LP, 1 test, 2 diagnostic days) to calculate avoided LPs, tests, and days. For autoimmune cases, adjusted NPV estimated true negatives with 1 LP, no further tests, and 2 diagnostic days, assuming mNGS would have ended further workup. All analyses were performed in R v4.3.2.

RESULTS

The cohort included 29 autoimmune encephalitis cases and 54 infectious cases: 23 DNA viral, 5 RNA viral, 16 bacterial, 7 fungal, and 3 parasitic cases. **In the modeled scenario using mNGS (48h turnaround) after first LP, there were potential microbiological tests saved, fewer days to diagnosis, and LPs avoided. For the infectious encephalitis cohort impact:**

•DNA viral (n=23): ↓ 88 tests, ↓ 145 days, ↓ 2 LPs
•Bacterial (n=16): ↓ 30 tests, ↓ 144 days, ↓ 12 LPs
•Fungal (n=7): ↓ 29 tests, ↓ 61 days, ↓ 3 LPs
•RNA viral (n=5): ↓ 4 tests, ↓ 11 days, 0 LPs
•Parasitic (n=3): ↓ 9 tests, ↓ 9 days, 0 LPs

For the autoimmune encephalitis cohort impact:

↓ 126 microbiological tests, ↓ 297 days to diagnosis, ↓ 2 LPs

DATA

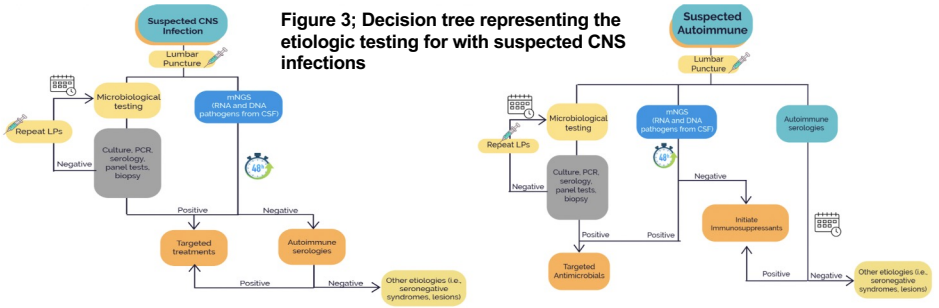

Figure 3; Decision tree representing the etiologic testing for with suspected CNS infections

Table 1 Impact of Adjusted mNGS PPV on Modeled Diagnostic Efficiency and Resource Use by Pathogen Type

Infectious Cases	Adjusted mNGS PPV	Total number of patients	Total number of patients that will test positive with mNGS	Total number of LP avoided	Total Number of Etiologic tests avoided	Total number of days to diagnosis saved
DNA Virus	0.984	23	~ 22	2	88	145
RNA Virus	0.895	5	~ 4	0	4	11
Bacteria	0.974	16	~ 15	12	30	144
Fungus	0.928	7	~ 6	3	29	61
Parasite	0.846	3	~ 2	0	9	9

Table 2 Impact of Adjusted mNGS NPV on Modeled Diagnostic Efficiency and Resource Use by Pathogen Type

	Adjusted mNGS NPV	Total number of patients	Total number of patients that will test negative with mNGS	Total number of LP avoided	Total Number of Etiologic tests avoided	Total number of Days to Diagnosis reduced
Autoimmune Cases	0.984	29	~ 27	2	126	297

CONCLUSIONS

mNGS as a complementary tool. mNGS may complement existing meningoencephalitis (ME) diagnostics, potentially reducing tests and time to diagnosis. **Limitations.** This analysis assumed equivalent pathogen detection, though CSF mNGS can increase yield by >20%, and results are based on modeled scenarios rather than real-world data. **Future directions.** Prospective studies are needed to assess real-world diagnostic impact, clinical outcomes, and cost-effectiveness of mNGS in ME. **Funding:** Supported by Delve Bio.