



Metagenomic Next-Generation Sequencing of Cerebrospinal Fluid in Culture-Negative Meningoencephalitis: A Review of Diagnostic Yield and Clinical Impact

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Abstract

A large minority of meningoencephalitis is never explained. Culture, targeted polymerase chain reaction and serology each require the clinician to have guessed the organism before the test is ordered, and when the guess is wrong the patient is treated empirically and the cause is never established. Metagenomic sequencing inverts that logic by asking what nucleic acid is present rather than whether a named pathogen is.

Objectives: To review the published evidence on the diagnostic yield, accuracy and clinical impact of metagenomic next-generation sequencing of cerebrospinal fluid in patients with meningoencephalitis undiagnosed by conventional testing, and to set out what is required to interpret a result.

Material and Methods: A narrative review. MEDLINE, Embase and the Cochrane Library were searched from January 2013 to May 2026 for prospective and retrospective cohorts, diagnostic accuracy studies, validation reports and society guidance on metagenomic sequencing in central nervous system infection. Values were extracted from the primary reports and tabulated without pooling.

Results: Cause remains unknown in 37% of encephalitis after extensive conventional testing. In the largest prospective study, 204 hospitalised patients yielded 58 nervous system infections, of which sequencing alone identified 13 (22%) while conventional testing alone identified 26 (45%). Pooled sensitivity across twelve studies and 1,249 patients is 77% with specificity of 96%. Yield is concentrated in the undiagnosed, immunocompromised and pretreated, and the dominant interpretive problem is distinguishing genuine low-abundance signal from reagent and environmental contamination.

Conclusion: Metagenomic sequencing is a supplement to conventional testing rather than a replacement for it: the two modalities identify substantially different infections. Its value is greatest in the culture-negative, immunocompromised or antibiotic-pretreated patient, and it should be reported against negative controls and confirmed orthogonally before treatment is changed.

Abbreviations: CSF – Cerebrospinal Fluid, mNGS – Metagenomic Next-Generation Sequencing, CNS – Central Nervous System, PCR – Polymerase Chain Reaction, HSV – Herpes Simplex Virus, ICU – Intensive Care Unit.

Keywords: Metagenomic Sequencing; Meningoencephalitis; Cerebrospinal Fluid; Culture-Negative Infection; Diagnostic Yield

Introduction

Encephalitis is a neurological emergency in which the cause is frequently never established. In a population-based English cohort of 203 patients investigated more thoroughly than routine practice allows, an infectious cause was identified in 42%, an immune-mediated cause in 21%, and 37% were left unexplained – a larger share than any single identified aetiology [1]. Systematic

review across non-outbreak settings reaches the same conclusion, and the California Encephalitis Project, which applied an unusually broad panel, still failed to identify a pathogen in the majority of children referred to it [2,3,4]. Contemporary series comparing infectious with autoimmune presentations show the two are now diagnosed at broadly similar rates, which makes separating them the practical task [31,32].

The reason is structural rather than technical. Culture detects only organisms that grow under the conditions provided, and is compromised by antibiotics given before the sample was taken. Polymerase chain reaction is highly sensitive but pathogen-specific: it answers the question asked and is silent on every organism not on the requisition. Multiplex panels widen the question modestly, and a diagnostic accuracy meta-analysis of the commonest such panel shows good performance against the targets it contains and none at all against those it does not [5,6]. Serology is retrospective and cross-reactive. Each modality therefore requires the clinician to have guessed correctly in advance.

It is worth being clear about what the technique is and is not. Clinical metagenomics sequences everything in the sample and assigns reads to organisms by comparison against reference databases [26]. It is not culture-independent identification of a suspected organism, which targeted amplification already does well, and it is not whole-genome sequencing of an isolate. The distinguishing feature is that the differential diagnosis is set by the database rather than by the requisition, which is also the source of most of its interpretive difficulty.

Metagenomic next-generation sequencing removes that requirement. All nucleic acid in a sample is sequenced, human sequence is computationally subtracted, and what remains is compared against reference databases. The approach is hypothesis-free, so an organism nobody suspected can be identified without being named in advance. Its clinical debut was a child with fourteen months of undiagnosed meningoencephalitis in whom sequencing identified *Leptospira* and directed a treatment that produced recovery [7].

A decade on, the technique is available in accredited laboratories and the question has moved from whether it can work to where it belongs. This review examines what the published cohorts show about its yield in culture-negative disease, how accurate it is against conventional testing, what it changes in management, and what is required to interpret a result responsibly.

Material and Methods

Search strategy:

MEDLINE, Embase and the Cochrane Library were searched from January 2013 to May 2026. Terms combined controlled vocabulary and free text for metagenomic sequencing, next-generation sequencing, cerebrospinal fluid, meningitis, encephalitis, central nervous system infection and diagnostic yield. Reference lists of validation reports and society guidance were hand-searched.

Eligibility and synthesis:

Prospective and retrospective cohorts reporting patient-level diagnostic outcomes, diagnostic accuracy studies with a composite or adjudicated reference standard, analytical validation reports and

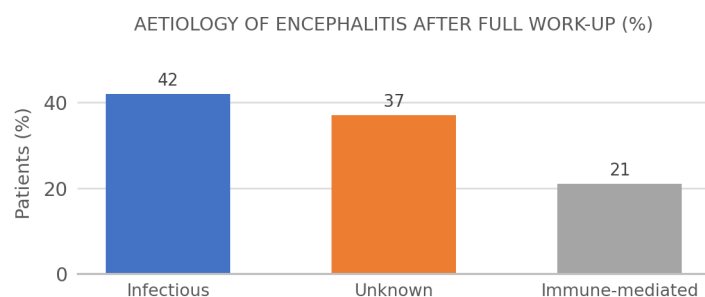


Figure 1: Aetiology established in a population-based cohort of 203 patients with encephalitis investigated to protocol [1].

Modality	Scope	Turnaround	Principal limitation
Culture	Organisms that grow	1–5 days	Lost after antibiotic pretreatment
Targeted PCR	One named pathogen	Hours	Answers only the question asked
Multiplex panel	Fixed target set	About 1 hour	Silent on anything off-panel
Serology	Host response	Days	Retrospective; cross-reactive
Metagenomic sequencing	Any nucleic acid present	1 day to weeks	Background contamination; cost

Table 1: Diagnostic modalities in suspected central nervous system infection.

multisociety guidance were eligible. Single case reports were used only where they document a first application or a distinct interpretive problem. Values were extracted by one reviewer and checked by a second. The included studies differ in platform, wet-lab protocol, bioinformatic threshold and reference standard, so results are presented descriptively and no pooling was attempted. No individual patient data were accessed and ethics approval was not required.

Results

The size of the undiagnosed group

The clinical problem is quantified in Figure 1 and Table 1. Even with protocolised testing, 37% of the English cohort had no identified cause, and case fatality was 12% overall, rising to 30% in tuberculous disease [1]. Consensus case definitions published subsequently standardised what counts as encephalitis but did not narrow the diagnostic gap [8]. Work comparing inflammatory mediator profiles found that unexplained cases resemble infectious rather than immune-mediated ones, which is indirect evidence that a proportion of the unknown group is infectious and simply undetected [9].

That matters because the therapeutic consequences diverge sharply. An undiagnosed patient is typically maintained on broad antimicrobial cover while immunosuppression for a possible autoimmune cause is withheld or given empirically, and both errors carry cost. Where autoimmune encephalitis is the true diagnosis, established clinical criteria allow treatment without waiting for antibody confirmation, but only once infection has been excluded

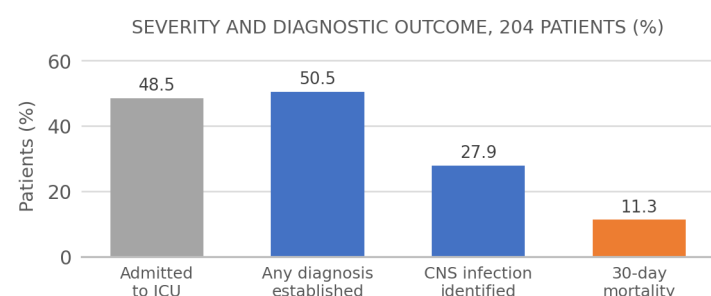


Figure 4: Illness severity and diagnostic outcome in the pivotal cohort of 204 hospitalised patients [12].

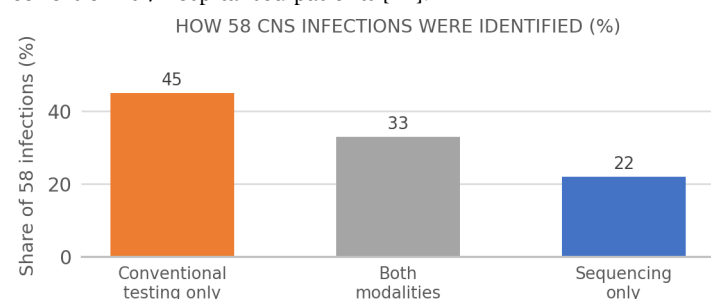


Figure 2: How 58 nervous system infections were identified in the pivotal prospective cohort of 204 patients, by testing modality [12]. convincingly [10,11]. The value of a test that can close the infectious question is therefore larger than its yield alone suggests.

Yield in the largest prospective cohort

The pivotal study enrolled 204 hospitalised adults and children with suspected meningoencephalitis across eight hospitals and sequenced their cerebrospinal fluid alongside the full conventional work-up [12]. The population was severely ill: 48.5% required intensive care and 30-day mortality was 11.3% (Figure 4). A diagnosis of any kind was established in 103 of 204 (50.5%), and 58 nervous system infections were identified in 57 patients (27.9%).

How those 58 infections were found is the central result (Figure 2). Sequencing and conventional testing agreed on 19 (33%). Conventional testing alone accounted for 26 (45%) — eleven diagnosed serologically, seven from tissue other than cerebrospinal fluid, and eight simply negative on sequencing. Sequencing alone accounted for 13 (22%), infections that would otherwise have been missed. The two approaches are therefore complementary rather than competing, and a service that replaced conventional testing with sequencing would have lost nearly half its diagnoses.

Other cohorts are consistent in direction if not in magnitude. A prospective multicentre Chinese series of 213 patients reported a positive detection rate of 57.0% among definite central nervous system infections, with performance varying substantially by pathogen class and by the read-count threshold applied [13]. Retrospective series in the undiagnosed and immunocompromised report higher incremental yield, which is expected: the technique performs best precisely where conventional testing has already failed [14,15].

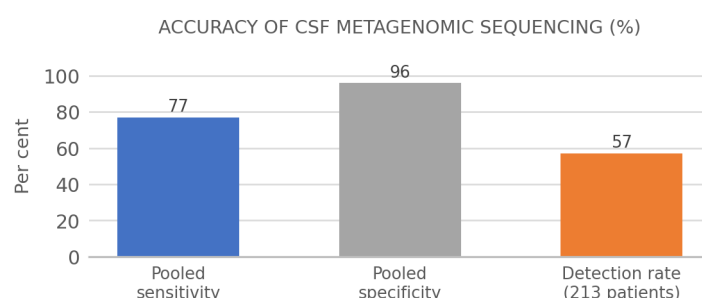


Figure 3: Pooled diagnostic accuracy of metagenomic sequencing across twelve studies and 1,249 patients, with the detection rate reported in a separate multicentre cohort [5,13].

Accuracy against a reference standard

Formal accuracy is summarised in Figure 3. A meta-analysis of twelve studies and 1,249 patients gives a pooled sensitivity of 77% and specificity of 96% across all pathogens [5]. Specificity is the reassuring figure and sensitivity the limiting one: roughly a quarter of true infections are missed, for reasons that are mechanistic rather than remediable by better software. Pathogen nucleic acid may be absent from cerebrospinal fluid when infection is confined to parenchyma; organisms with thick cell walls resist extraction; and a high human background from pleocytosis crowds out microbial reads.

Analytical validation studies report limits of detection in the range of a few hundred genomic copies per millilitre under favourable conditions, degrading sharply as human background rises [16,17]. Both DNA and RNA workflows are needed to cover the plausible range of central nervous system pathogens, which roughly doubles cost. The practical consequence is that a negative sequencing result carries much less information than a positive one, and should never be used to exclude infection in a patient whose clinical course suggests it. Comparable performance in other fluids and in the lower respiratory tract suggests the limits are a property of the method rather than of cerebrospinal fluid specifically [30].

The interpretive problem

The dominant difficulty is not detection but attribution (Table 2). Sequencing recovers nucleic acid from reagents, extraction kits, laboratory environment and the sequencing run itself, and these background organisms are not rare curiosities but a routine feature of every run. Distinguishing a genuine low-abundance pathogen from background requires no-template controls processed in parallel, quantitative thresholds established during validation, and a documented interpretation pathway [16,18,19]. European guidance on bacterial meningitis assumes a culture-based pathway throughout and predates routine availability of sequencing, so the interpretive rules have had to come from the laboratory literature rather than from clinical guidelines [27].

The pivotal study handled this by confirming every positive orthogonally and by convening a clinical microbial sequencing board — microbiologists, infectious disease physicians and

Requirement	Purpose	Basis
No-template controls in parallel	Establishes the reagent and environmental background	Validation guidance [16,18]
Quantitative threshold set at validation	Separates signal from background reads	Accuracy studies [13,17]
Orthogonal confirmation	Verifies a finding before treatment changes	Pivotal cohort [12]
Multidisciplinary review	Weighs the organism against the clinical picture	Sequencing board [12,19]
Explicit negative reporting	Prevents a negative being read as exclusion	Sensitivity near 77% [5]

Table 2: Requirements for interpreting a metagenomic result, drawn from the validation and cohort literature.

bioinformaticians reviewing results against the clinical picture before they were released [12]. That structure is as much a part of the intervention as the assay, and a laboratory offering sequencing without it is offering something materially different from what was studied. Professional guidance on validating metagenomic assays makes the same point about controls, thresholds and reporting [18].

A second interpretive trap is the organism that is genuinely present but not causal. Sequencing detects colonisation, latent virus and incidental viraemia as readily as invasive disease, and human herpesviruses in particular are frequently recovered without being responsible for the illness. The question a result answers is what nucleic acid was in the tube, which is not the same question as what is making the patient ill.

Two adjacent developments bear on where the test sits. Sequencing of brain tissue at biopsy or autopsy has resolved cases in which cerebrospinal fluid was uninformative, which reinforces the point that a negative fluid result reflects sampling as much as absence [28]. And unexpected organisms recovered in individual patients —neurobrucellosis identified in a child after months of negative conventional testing is a representative example — illustrate the specific situation in which the hypothesis-free approach earns its cost [29].

Where it changes management

Impact is concentrated in identifiable groups (Table 3). Patients pretreated with antibiotics before lumbar puncture lose culture yield but retain nucleic acid. Immunocompromised patients present with an unusually wide differential in which conventional panels perform poorly, and are the group in whom unexpected organisms are most often found [14,20]. Chronic meningitis, where months of investigation frequently end without an answer, is a setting in which sequencing has produced diagnoses that changed treatment [15]. Conversely, a patient with typical herpes simplex encephalitis and a positive polymerase chain reaction gains nothing from sequencing, and routine use in that setting would be an expensive way of confirming what is already known [21,22].

Setting	Expected value	Reason
Undiagnosed after full conventional work-up	High	The alternative is no diagnosis [12]
Immunocompromised host	High	Wide differential; panels perform poorly [14,20]
Antibiotics before lumbar puncture	High	Culture yield lost, nucleic acid retained
Chronic meningitis	Moderate to high	Prolonged undiagnosed illness [15]
Typical HSV encephalitis, PCR positive	Low	Targeted testing already definitive [21,22]

Table 3: Clinical settings in which metagenomic sequencing of cerebrospinal fluid is most and least likely to alter management.

Turnaround is the other determinant of usefulness. Sequencing performed and reported within 48 hours can alter antimicrobial choice while it still matters; the same result at three weeks is of academic interest in an acute illness, though it may still stop unnecessary treatment or redirect a chronic case. Reported turnaround has fallen substantially as workflows have matured, and real-time platforms have shortened it further [23,24].

Cost and access shape practice as much as performance does. Running both DNA and RNA workflows on a single sample, with the controls and orthogonal confirmation that interpretation requires, puts the per-test cost well above any conventional assay, and the expertise to interpret the output is concentrated in a small number of centres [19,24]. Send-out testing spreads access but lengthens turnaround, which erodes precisely the advantage that matters in acute illness. Services adopting the test therefore have to decide not only who to test but how quickly a result can be acted on, and a pathway that cannot return an answer inside the window in which treatment decisions are made will deliver epidemiology rather than care.

Discussion

The evidence supports a specific and fairly narrow position. Metagenomic sequencing of cerebrospinal fluid identifies infections that conventional testing misses, in a group of patients where the alternative is often no diagnosis at all. It also misses infections that conventional testing finds, at a comparable or higher rate. Those two facts together make it a supplement rather than a replacement, and any service model built on substitution misreads the evidence.

The sensible deployment is therefore selective. Sequencing should be requested when conventional testing has failed and the clinical picture still suggests infection; when the patient is immunocompromised and the differential is correspondingly wide; when antibiotics preceded sampling; or when a decision to start immunosuppression turns on excluding infection. It should not be a first-line test in a patient with a syndrome that targeted testing handles well.

A positive result also carries obligations. Because the method detects nucleic acid rather than viable organism, and because latent and colonising species appear readily, the finding has to be reconciled with the syndrome, the imaging and the cerebrospinal fluid profile before it is treated as the cause [20,26]. Where it fits, it can shorten a long diagnostic odyssey and redirect therapy decisively; where it does not, the safer reading is that an organism was present in the sample and its significance is undetermined. Reporting that distinction explicitly, rather than leaving it to the requesting clinician to infer from a read count, is what separates a useful service from a confusing one.

Three requirements follow from the interpretive difficulties rather than from the technology. Negative controls must be processed and reported alongside every clinical sample, since without them a low-read result cannot be assessed at all. Positive findings that will change management should be confirmed by an orthogonal method. And results should be interpreted against the clinical picture by people who can weigh both, rather than released as a list of organisms with read counts. None of these is technically demanding, and all three were present in the study that produced the best evidence.

What remains genuinely unresolved is cost-effectiveness. No adequately powered study has compared a strategy of early sequencing against extended conventional testing on patient outcomes rather than diagnostic yield, and yield is a surrogate: a diagnosis matters only if it changes what is done. The related question of whether plasma microbial cell-free DNA can substitute for cerebrospinal fluid in some presentations is also open, with encouraging but not definitive data [25].

Study limitations

This is a narrative rather than a systematic review: studies were selected against stated criteria but without duplicate screening of the full yield, and no risk-of-bias instrument was applied. The accuracy literature is heterogeneous in platform, protocol and threshold, so pooled figures describe a moving target. Most cohorts derive from specialist centres with high pre-test probability and are likely to overstate yield elsewhere. Publication bias favours series in which sequencing succeeded. The review addresses diagnosis and does not cover antimicrobial resistance prediction, host transcriptomic classifiers or paediatric practice separately.

Conclusion

In meningoencephalitis that conventional testing has failed to explain, metagenomic sequencing of cerebrospinal fluid identifies a meaningful minority of infections that would otherwise be missed, with high specificity and moderate sensitivity. It does not replace culture, targeted amplification or serology, which between them still account for the larger share of diagnoses. Its place is as a second-line test in the undiagnosed, the immunocompromised and the pretreated, delivered with negative controls, orthogonal

confirmation and clinical interpretation. A negative result does not exclude infection, and a positive one identifies nucleic acid rather than causation.

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