Reply to correspondence: Integrating metagenomic sequencing into diagnostic pathways for tuberculous meningitis

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Lin and colleagues highlight the emerging role of metagenomic next-generation sequencing (mNGS) as a diagnostic adjunct for tuberculous meningitis.[1] The diagnosis of tuberculous meningitis is notoriously challenging and new diagnostic approaches, such as mNGS, are much needed.[2] However, the use and integration of mNGS into routine diagnostic practice must overcome the considerable challenges of cost and global availability.[3] When we developed the scope of our practice guideline in 2021, these challenges had not been met; mNGS was therefore not included.

Lin and colleagues refer to a study of Nanopore targeted sequencing (NTS), used to test cerebrospinal fluid (CSF) of 100 individuals with intracranial tuberculosis, of whom 41/100 had tuberculous meningitis.[4] Diagnostic sensitivities of CSF smear microscopy, Xpert MTB/RIF (Xpert) and mycobacterial culture were extremely low (0%, 5%, and 2%, respectively), suggesting low CSF volumes were tested. The performance of these three tests substantially increases if large CSF volumes (>6mls) are tested. mNGS does however have an advantage: the ability to identify other treatable infectious causes of meningoencephalitis at the same time.

For tuberculous meningitis, a test that detects all true cases – avoiding missed opportunities to initiate anti-tuberculosis chemotherapy and thereby save lives – remains the diagnostic goal. In the absence of a single test that can reliably ‘rule-out’ tuberculous meningitis when negative, combined host-pathogen approaches may present a solution. The addition of host transcriptomic classifiers further strengthens the value proposition of mNGS and continued research in this area is warranted across a variety of populations. Additionally, host transcriptomic approaches may allow the development of a blood test that uses transcriptional signatures to distinguish tuberculous meningitis from other brain infections.[5]

Integration of mNGS into future diagnostic pathways is likely to add value as these techniques become more widely used. We therefore agree with Lin and colleagues that optimising pre-analytics is important. Standardised approaches to CSF sampling, processing, storage, and read-interpretation would be welcome, and could be incorporated into future guidelines for healthcare professionals who have access to these techniques.

In summary, we recognise mNGS as an emerging adjunct for tuberculous meningitis diagnosis. Whilst cost and availability currently limit its use, the emerging role of mNGS requires the development of standardised approaches. We suspect the application and availability of mNGS will be sufficiently advanced for inclusion in subsequent updates to the tuberculous meningitis practice guideline.

Competing Interests

We declare no competing interests

References

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