

## **Improving Tuberculous Meningitis Diagnostics - A Combined Host and Pathogen Classifier**

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### **Objectives**

To assess the diagnostic performance of metagenomic next-generation sequencing (mNGS) combined with host differential gene expression for tuberculous meningitis (TBM) versus other causes of meningitis.

### **Background**

GeneXpert RIF/MTB Ultra is ~70% sensitive for definite/probable TBM. Definite TBM is microbiologically proven. Probable TBM has negative microbiology but scores  $\geq 10$  points on the case definition scale. 90-98% of mNGS sequencing data reflect host gene expression. Host transcriptomic signatures may differ by pathogen and thus, enhance diagnostic utility. We assessed CSF mNGS and transcriptomics for identifying TBM and other pathogens misclassified as TBM.

### **Design/Methods**

**Cohort:** 157 HIV-infected Ugandan adults with sub-acute meningitis: Definite (n=15), probable (n=7), and possible (n=53) TBM; non-TB meningitis (n=82).

**Method:** Unbiased RNA and DNA libraries were sequenced. We performed metagenomic analysis through a custom bioinformatics pipeline. Transcriptomic diagnostic classifier was developed using 22 samples (11 TB + 11 other), which, along with cases with co-infections, were not included in the final analysis.

### **Results**

mNGS was 80% concordant (12/15) against definite TBM with 3 additional cases of TBM detected (1 probable and 2 possible). Host transcriptomics displayed 100% (6/6) sensitivity (inclusive of mNGS-positive TBM), 87% (67/77) specificity, with an Area Under the ROC Curve of 0.95 (0.90-1.0). Among probable TBM cases the host transcriptomic classifier predicted 71% (5/7) were TBM including the 1 mNGS-positive TBM case. Within possible TBM, mNGS identified 9 other pathogens (4 viral, 2 bacterial, 2 toxoplasmosis and 1 TBM-viral co-infection). The host transcriptomic signature classified 5/53 possible TBM cases as TBM, including the 1 mNGS-positive TBM case.

**Conclusion**

mNGS and host transcriptomics combined for 77% (17/22) sensitivity against definite/probable TBM. mNGS alone detected TB or alternate pathogens in 19% (10/53) of possible TBM cases. This is the first study to utilize both pathogen detection and the host response to diagnose CNS infections from CSF.