Study Demonstrates GeneXpert Ultra's Ability to Improve TB Meningitis Detection

Sep 25, 2017 | John Gilmore

Premium

NEW YORK (GenomeWeb) – Researchers from a joint international team have found that Cepheid's GeneXpert Ultra platform detects tuberculous meningitis (TBM) much more accurately than other standards of detection, including its predecessor Xpert and culture-based methods.

In 2013, the World Health Organization began recommending the Xpert MTB/RIF as an initial diagnostic test for TBM. Cepheid's Xpert is cartridge-based fully automated PCR test. Accurate diagnosis for *T. meningitis* still remains difficult because the current tools, Xpert and culture, only have sensitivities of about 50 to 70 percent and about 60 percent, respectively.

In an interview, Keertan Dheda, Head of Pulmonology at the University of Cape Town, who was not part of the new study, emphasized that the GeneXpert conventional cartridge is "still being largely used throughout the world, and they are slowly moving to the Ultra cartridge."

In terms of the device's simplicity, the study's lead author Nathaniel Bahr, an infectious disease specialist at the University of Kansas, explained that "the GeneXpert apparatus [is] the same one used for the Xpert Ultra TB test, so if people want to use the new test, they [just] have to buy new cartridges and upgrade the software."

In the study, published earlier this month in *The Lancet*, researchers evaluated the diagnostic performance of the Xpert MTB/RIF Ultra (Xpert Ultra) for TBM compared with Xpert or culture. From February 2015 to November 2016, the researchers screened 129 HIV-infected adults in Mbarara, Uganda with suspected meningitis for tuberculosis.

Obtaining cerebrospinal fluid (CSF) specimens during screenings, the researchers classified 23 participants as probable or definite TBM by uniform case definition, excluding Xpert Ultra results. The team centrifuged CSF, resuspended the pellet in 2 ml of CSF, and tested 0.5 ml with mycobacteria growth indicator tube culture, 1ml with Xpert, and prospectively cryopreserved 0.5 ml. When the Xpert Ultra finished development, the researchers thawed the remaining CSF and ran the assay.

Bahr and his collaborators then assessed the Xpert Ultra's diagnostic performance against any positive CSF tuberculous tests and a consensus clinical case definition, not including the Xpert Ultra result. They categorized the study's participants as definite, probable, possible, and not tuberculous meningitis.

Xpert Ultra sensitivity was 70 percent for probable or definite TBM compared to 43 percent for Xpert and 43 percent for culture. With composite standard, the researchers detected TBM in 22 of 129 participants. Xpert Ultra had higher sensitivity, 95 percent, than either Xpert (45 percent) or culture (45 percent) for definite tuberculous meningitis.

Of 21 participants that were identified as positive by Xpert Ultra, 13 of those were positive by culture, Xpert or both. Eight were identified positive exclusively by Xpert Ultra.

Dheda performed a similar study on HIV-infected patients with the GeneXpert platform, published in 2014 in *Scientific Reports*. As with his own study on the GeneXpert platform, Dheda worried about the sensitivity of the Xpert Ultra study.

For example, in the study, the authors took 6 ml of CSF from subjects to use for various purposes. As the amount of CSF for the assay increased, the Xpert Ultra's sensitivity increased as well. In the real world, however, that large of a sample would not be taken from a patient, Dheda said.

The abnormal volume is something that would need to validated, and the community must evaluate the practicality in the real world of taking that much CSF from a patient, he noted.

Another limitation Dheda found was the study's dichotomous categories of Xpert Ultra positive specimens. The study's results included semi-quantitative categories of trace; very low; low; moderate; and high. Of the 21 Xpert Ultra positive specimens, at least 16 (76 percent) were either trace or very low. Dheda expressed concern about the test's reproductivity, and whether Bahr and his team would find the same results if they repeated the test again.

"The trace, or barely positive samples are straddling the grey zone… a high number are near that cut point... which is concerning because the results could be quite stochastic," he said.

The study's authors noted that Xpert Ultra's combination of lower analytic limit of detection and ability to detect dead bacilli after starting tuberculosis therapy vastly improves sensitivity, compared with either culture or Xpert.

Looking forward, the researchers believe the assay should be evaluated in a larger study including HIV-negative individuals children, where postmortem evidence of tuberculosis can be included in a reference standard.

"This study is a step forward for TBM diagnosis," Bahr said, but cautioned that the Xpert Ultra is neither a panacea, nor a test that can be done and then relied on "absolutely. But it can be very helpful."

Dheda agreed that the study is a positive step for TBM detection worldwide. However, he believes that the study needs confirmation from additional reports to have a more precise estimate of sensitivities involved.

"Overall [the study] is a positive and encouraging finding, and it could mean that this ought to be the test of choice for TB meningitis, but that remains to be proven."

Last month, researchers determined that Xpert Ultra distinguishes itself from its predecessor through its ability to improve point-of-care detection of TB, as reported in a study in *mBio*.

Filed Under Infectious Disease | Molecular Diagnostics | PCR | HIV | meningitis | tuberculosis | nested PCR | Cepheid