Performance evaluation of the Xpert MTB/XDR assay

Anura David

ASLM webinar

15 July 2021
Disclosures

- Funding for this study was received from the Foundation of New Innovative Diagnostics (FIND)/KFW
- Cepheid provided the Xpert MTB/XDR cartridges for the study
Drug-resistant TB

• In 2019, ~500,000 individuals developed Rif-R TB, of which 78% developed MDR-TB
• The rapid diagnosis and appropriate treatment of drug-resistant TB (DR-TB) is therefore essential to prevent significant morbidity, mortality and further transmission of TB disease
• Available second-line diagnostics require laboratory infrastructure – pDST and Bruker-Hain MTBDRs/ LPA
• Xpert MTB/XDR assay is a lower complexity, automated molecular assay for broader resistance detection suitable for use at lower levels in the healthcare system

CE-IVD. In Vitro Diagnostic Medical Device. May not be available in all countries. Not available in the United States.
Xpert MTB/XDR Assay

- Results in <90 minutes
- Same easy-to-use process as Xpert MTB/RIF Ultra
- Performed on existing GeneXpert® platform equipped with 10-color modules
- On board internal controls: Sample Volume Adequacy (SVA), Probe Check Control (PCC), Sample Processing Control (SPC)
- Detects resistance to:
  - INH- katG, inhA pt, ahpC, fabG1
  - ETH – inhA promoter
  - FQs- gyrA, gyrB
  - SLID (AMK, KAN, CAP) - rrs, eis

10-color modules can also run any other Xpert test
• Phase II: Multicentre Clinical Study to Assess the Performance of the Xpert MTB/XDR Assay for INH- and Second-line Resistance Detection
• Sites
  o Mumbai, India: P.D. Hinduja Hospital
  o Delhi, India: National Institute of Tuberculosis and Respiratory Diseases
  o Chisinau, Moldova: Phthisiopneumology Institute "Chiril Draganiuc”
  o South Africa: University of the Witwatersrand, Johannesburg
• Primary Objectives: clinical diagnostic accuracy and operational characteristics of the Xpert MTB/XDR assay
• Secondary objectives: Assess additional Xpert MTB/XDR performance characteristics, including direct performance versus performance on cultured samples, performance between sites, by smear status, by gene target and compared to Hain MTBDRplus and MTBDRsl
**Inclusion Criteria**

- ≥ 18 years
- Symptoms suggesting pulmonary TB, i.e. persistent cough, and at least one DR-TB risk factor
- MTBC-positive and valid RIF-resistance profile by Xpert MTB/RIF Ultra
- Provision of informed consent
- Production of an adequate quantity (≥4mL) of sputum

# > 3ml of sputum is required for the trial. This can be achieved through an individual sputum or pooling of serially collected sputa, homogenized with glass beads.

*CE-IVD. In Vitro Diagnostic Medical Device. May not be available in all countries. Not available in the United States.
Participant cohort

- 710 participants were approached and enrolled at the four sites (Jul 2019 – Mar 2020)
- All participants were diagnosed with TB (as reported by the Xpert G4 or Xpert MTB/RIF Ultra assay) and all had a valid RIF result
- 611/710 had a MTBC-positive MGIT and were included in the analysis
- Reference standard = DST and/or WGS

<table>
<thead>
<tr>
<th></th>
<th>611</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics or clinical characteristics</td>
<td></td>
</tr>
<tr>
<td>Median age [min - max] (years)</td>
<td>37 [18, 77]</td>
</tr>
<tr>
<td>% Female sex [n/N]</td>
<td>35% [214/611]</td>
</tr>
<tr>
<td>% HIV positive [n/N]</td>
<td>16% [69/425]</td>
</tr>
<tr>
<td>% Xpert G4 or Ultra RIF-R [n/N]</td>
<td>81% [494/611]</td>
</tr>
<tr>
<td>% smear negative [n/N]</td>
<td>24% [146/609]</td>
</tr>
</tbody>
</table>

CE-IVD. In Vitro Diagnostic Medical Device. May not be available in all countries. Not available in the United States.
### Indeterminates

<table>
<thead>
<tr>
<th>Drug Resistance</th>
<th>%</th>
<th>n/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTB invalid</td>
<td>2.96</td>
<td>21/709</td>
</tr>
<tr>
<td>INH resistance</td>
<td>0.30</td>
<td>2/657</td>
</tr>
<tr>
<td>ETH resistance</td>
<td>0.15</td>
<td>1/657</td>
</tr>
<tr>
<td>FLQ resistance</td>
<td>1.37</td>
<td>9/657</td>
</tr>
<tr>
<td>AMK resistance</td>
<td>3.50</td>
<td>23/657</td>
</tr>
<tr>
<td>KAN resistance</td>
<td>3.20</td>
<td>21/657</td>
</tr>
<tr>
<td>CAP resistance</td>
<td>2.89</td>
<td>19/657</td>
</tr>
</tbody>
</table>

Xpert MTB/XDR invalid rate higher for smear negative samples than for smear positive samples (6.2% compared with 0.2%)
The composite reference standard was defined as "resistant" if either WGS or pDST was resistant, and defined as "susceptible" if both pDST and WGS were susceptible.
LPA and Xpert MTB/XDR compared to culture DST

The composite reference standard was defined as "resistant" if either WGS or pDST was resistant, and defined as "susceptible" if both pDST and WGS were susceptible.

<table>
<thead>
<tr>
<th>Resistance</th>
<th>LPA (Indirect)</th>
<th>XDR (Direct)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td></td>
<td>(%) 95% CI</td>
<td>(%) 95% CI</td>
</tr>
<tr>
<td>INH resistance</td>
<td>93.0 (90.0-95.0)</td>
<td>100 (94.0-100)</td>
</tr>
<tr>
<td>FLQ resistance</td>
<td>95.0 (91.0-97.0)</td>
<td>99.0 (97.0-100)</td>
</tr>
<tr>
<td>AMK resistance</td>
<td>73.0 (62.0-82.0)</td>
<td>100 (98.0-100)</td>
</tr>
<tr>
<td>KAN resistance</td>
<td>86.0 (81.0-90.0)</td>
<td>98.0 (96.0-99.0)</td>
</tr>
<tr>
<td>CAP resistance</td>
<td>61.0 (50.0-71.0)</td>
<td>100 (99.0-100)</td>
</tr>
</tbody>
</table>
Xpert MTB/XDR (Direct) compared to composite reference standard stratified by smear status

<table>
<thead>
<tr>
<th>Resistance</th>
<th>Smear positive</th>
<th>Smear negative</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity (%, 95% CI)</td>
<td>Sensitivity (%, 95% CI)</td>
<td>(%) 95% CI</td>
</tr>
<tr>
<td>INH resistance</td>
<td>94.3 (91.3-96.3)</td>
<td>94.1 (87.1-97.6)</td>
<td>100 (94.1-100)</td>
</tr>
<tr>
<td>ETH resistance</td>
<td>54.8 (48.5-60.9)</td>
<td>50.8 (38.2-63.3)</td>
<td>99.5 (97.0-100)</td>
</tr>
<tr>
<td>FLQ resistance</td>
<td>96.1 (91.7-98.3)</td>
<td>89.1 (77.1-95.5)</td>
<td>99.3 (97.3-99.9)</td>
</tr>
<tr>
<td>AMK resistance</td>
<td>76.1 (63.9-85.3)</td>
<td>53.8 (26.1-79.6)</td>
<td>99.5 (98.1-99.9)</td>
</tr>
<tr>
<td>KAN resistance</td>
<td>87.4 (81.4-91.8)</td>
<td>78.8 (60.6-90.4)</td>
<td>98.4 (96.0-99.4)</td>
</tr>
<tr>
<td>CAP resistance</td>
<td>60.8 (48.7-71.7)</td>
<td>54.5 (24.6-81.9)</td>
<td>99.8 (98.5-100)</td>
</tr>
</tbody>
</table>

The composite reference standard was defined as “resistant” if either WGS or pDST was resistant, and defined as “susceptible” if both pDST and WGS were susceptible.

CE-IVD. In Vitro Diagnostic Medical Device. May not be available in all countries. Not available in the United States.
Conclusions

• Similar performance demonstrated using Xpert MTB/XDR assay on direct sputum and MGIT
• Sensitivity >90% for INH and FLQ
• Specificity >98% for all drug targets
• Almost identical performance between LPAs and Xpert MTB/XDR assay
• Xpert MTB/XDR assay demonstrated better performance on smear positive specimens
Acknowledgements

**FIND**
- Adam Penn-Nicholson
- Sophia Georghiou
- Samuel Schumacher
- Sergio Carmona
- Morten Ruhwald
- Claudia Denkinger
- Aurélien Mace
- Stefano Ongarello
- Shubhada Shenai
- Shakir Reza
- Shweta Mall
- Megha Dhalla
- Sarabjit Chadha
- Sanjay Sarin

**University of the Witwatersrand**
- Lesley Scott
- Wendy Stevens
- Francesca Conradie
- Anura David
- Trish Kahamba
- Lyndel Singh
- Xabisa Makeleni

**Funder**
- KFW

**Support**
- ACOMED
- Medgenome
- Cepheid

**Moldova – Institute of Phthisioneumology**
- Dr. Valeriu Crudu
- Dr. Nelly Ciobanu

**India – NITRD**
- Dr. Vithal Prasad Myneedu
- Dr. Manpreet Bhalla
- Dr. Rohit Sarin

**India – PD Hinduja**
- Dr. Camilla Rodrigues
- Dr. Mubin Kazi