Treating Patients, Not Disease: People-Centered Approach

7th Annual TB Symposium
Ministry of Health of the Kyrgyz Republic
and Médecins Sans Frontières

1-2 March, 2018, BISHKEK, KYRGYZSTAN

TB Diagnostics
Kathleen England PhD MSc
TB Diagnostics Advisor
MSF Access Campaign
Currently WHO endorsed

Genotypic:
- GeneXpert MTB/RIF Ultra Assay
- LPA (HAIN/Nipro) for INH, RIF, FQ, and SLIs
- TB LAMP for MTB detection

Phenotypic
- Solid (LJ, 7H10, 7H11) and automated liquid-based culture methods for MTB detection and DST
- Microscopy (Light and LED)

Biomarker based
- TB LAM Ag (niche test for PLHIV)
- LTBI - IGRAs: QFT Gold (plus) / TSPOT TB

Others noncommercial considerations
- MODS, CRIs, NRA methods
In the Pipeline - FIND Diagnostics

Diversification of sputum-based testing and drug susceptibility testing (DST)

- Realtime MTB Rif/Inh (Abbott)
- FluoroType MDRTB (Hain Lifescience)
- BD MAX MDRTB (BD)
- QMAC QDST (QuantaMatrix)
- Cobas Tagman MDR TB (Roche)
- TB MultiTest (SelfDiagnostics)
- MGIT - Bedaquiline Delamanid (BD)
- Xpert XDR (Cepheid)
- TruArray MDRTB / XDRTB (Akonni)
- First sequencing solutions (Genoscreen, BMS, Longhorn)
- FluoroType XDR (Hain Lifescience)
- Q-POC TB/MDR TB (QuantuMDx)
- MtB Drug Resistance ID (Omnio)

† Enable TEST & TREAT
† Match the regimen pipeline

DISCLAIMER: Images & time estimates are to be taken as indicative only.
In the Pipeline - FIND Diagnostics

Non-sputum based tests for diagnosis or triage

Early identification of patients with TB or at high-risk of TB on easy to access samples ideally at level 0/1

Pediatric TB Disposable Squeeze Bottle for Stool Processing prior Xpert
(FIND, Elma Fdn & partners)

Active TB
- QIA-Predict (Qiagen)
- QIA-TB Signature (Qiagen)
- mRNA Signatures
  (Stanford, Zak et al.)
- T-cell Immune Profiling (BD)
- RTT TB (Lophius)
- Incipient TB Assay (Abbott)

Latent TB

Incipient TB tests (blood)
- Breath Tests and Skin Patches
  - breathtec/Technion
  - RBS
  - eNose

2017

Determine TB LAM Ag (urine) for HIV co-infected with low CD4 counts (Alere)

2018

Next-generation LAM POC assays (urine, blood)
- Fujifilm/FIND
- and others

Blood host marker POC tests
- TransDot signature (ScreenTB consortium)
- SomaLogic signature (SomaLogic, FIND)
- and others

2019

Computer-aided detection (X-ray)
- Delft
- Qure.ai

2020-2025

TB antigen POC assays (blood)
- Arizona State Univ.
- Tufts Univ.
- and others

cfDNA in blood or urine
- Standford Univ.
- Cornell Univ.
- Karius
- and others

DISCLAIMER: Images & time estimates are to be taken as indicative only.
Currently under WHO Evaluation 2018-2019

Molecular technologies for TB and drug resistance
• Fluorotype MTBDR, Hain Lifesciences, Germany
• M2000 RealTime MTB System, Abbott, USA
• BD Max MDR-TB, Becton Dickinson, USA
• GeneXpert Omni, Cepheid, USA

Radiology
• CAD4 TB X-ray technology

On the Market... or in use (not submitted to WHO for evaluation)
• ICubate System, ICubate, USA
• GeneChip TB drug resistance assay, CapitolBio, China
• EasyNat TB Diagnostics kit, Ustar Biotechnologies, China
• TrueLab/Truenat MTB, Molbio Diagnostics, India
• TB-TEST BioChip-EIMB, Russia
Cepheid MTB/RIF Ultra assay

- **WHO endorsed**: non-inferiority evaluation April, 2017
- **HBDC concession pricing ($9.98)** - limited procurement due to production scale and 12 month shelf-life.

- **Sensitivity/Specificity (Pulmonary TB)**
  - Overall 5% increase sensitivity (83 to 88%)
  - 3.2% decrease in specificity (detects dead bacilli)
  - SS+C+ = same sensitivity (98-100%)
  - SS - = Increased sensitivity of 17% (46% to 63%)
  - HIV+ = Increased sensitivity 12% (77% to 90%)
  - Detect RR = no change (95%)

- “**TRACE**” detection (<100 CFU/mL) may require follow-up testing depending on treatment history.
  - **RIF is indeterminate for all “TRACE” results.**
  - **Never treated before**: TRACE = positive for MTB, requires LPA or DST
  - **Previous treatment (<2yrs)**: Requires repeat test or culture/LPA or DST.

- **EPTB** - only one study with CSF from Uganda- 95% Sensitivity
Cepheid Xtend XDR Assay

- A prototype cartridge designed with performance data published in 2017
- FIND/WHO evaluations to begin in 2018 with hopeful release by end 2019.

<table>
<thead>
<tr>
<th></th>
<th>Xpert XDR Sensitivity (%)</th>
<th>Xpert XDR Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MGIT DST</td>
<td>Sequencing</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>83.3</td>
<td>98.1</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>88.4</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin 0.5µg</td>
<td>87.6</td>
<td>95.8</td>
</tr>
<tr>
<td>Moxifloxacin 2.0µg</td>
<td>96.2</td>
<td></td>
</tr>
<tr>
<td>Kanamycin</td>
<td>71.4</td>
<td>92.7</td>
</tr>
<tr>
<td>Amikacin</td>
<td>70.7</td>
<td>96.8</td>
</tr>
</tbody>
</table>

YL Xie et al. (2017) NEJM
S. Chakravorty et al (2016) JCM
Cepheid Xpert Omni Device

✧ **Delayed Launch:** end 2018 to 2019
✧ **New Price** $5315/unit - >80% increase, previously $2895
✧ **C360 cloud-based connectivity required for**
  - Routine software, systems and assay updates
  - Data transmission to monitor module / instrument performance.
  - Patient information transmitted but encrypted.
  - Remote areas must transport periodically to a wireless service area.
  - *OmniConnect* device available to link GxAlert, DataToCare, or other connectivity solution. (*Added cost*)

✧ **Omni specific cartridge with surcharge of $1.50**
  - cost of NFC chip to communicate via mobile device for assay function
  - to support cost for a new remote services model

✧ **Added costs** = Vodafone data plan, ~$500-600/mo.
✧ **Service Support** - requires data sharing agreement and new remote service model for troubleshooting and Omni swap.
✧ **Solar panels** available (added cost), battery lifespan 12hrs.
✧ **Feasibility in Remote settings:** not demonstrated yet. Factors related to temperature, humidity, dust, ruggedness, and durability are still unknown.
TB LAM RDT— and next generation test

New Tests in R&D: FUJIFILM, Biopromics, Omega Dx, NanoTechnologies

Alere TB LAM Ag
WHO endorsed Niche Test 2015

FUJIFILM “Sensitive LAM”

Sample: urine, sputum, serum

- Urine Rapid Diagnostic Test ($3.50/test)
- PLHIV, TB symptoms, severely ill, and with CD4 counts ≤ 100
- Sen/Spe (%) = 56/90
- LOD (0.5-1.0 ng/mL)
- HIV+ independent CD4, Sen/Spe (44/96)
- Currently in WHO Algorithms (HIV & TB)
- MSF evidence supports use in PLHIV, CD4≤200 & in outpatient settings.

- non Niche test
- All TB Presumptive
- Patient Monitoring?
- High Affinity MAbs
- LAM concentration device
- LOD (0.050 ng/mL)
- **Higher Sensitivity**
  >40% increase for HIV+ independent CD4 count.
- **Specificity** - 97%
- Studies in HIV- ongoing

https://www.ghitfund.org/impact/portfolio/awpdetail/detail/78
## Diagnostics for DRTB – high throughput technologies by 2019

<table>
<thead>
<tr>
<th>FluoroType MTBDR</th>
<th>m2000 MDRTB</th>
<th>BDMAX MDR</th>
<th>TrueLab/TrueNat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hain Lifesciences</td>
<td>Abbott</td>
<td>Becton Dickinson</td>
<td>Molbio</td>
</tr>
</tbody>
</table>

### Centralized - DNA Extraction/PCR-based (WHO Evaluation)

- **MTBDR (2 step)**  
  - (rpoB, inhA, katG)  
  - Sen (TB)  
  - S+C+(100) / S-C+(90)  
  - Spe (99)  
  - **LOD 15Cfu/mL**  
  - Sen/Spe (R)=(98/100)  
  - Sen/Spe (H)=(98/100)  
  - **LOD 22Cfu/mL**  
  - 12/96 samples, 3-5hr  

### Decentralized

- **MTBDR plus** (coming)  
  - (rrs, eis, gyrA, gyrB)  
  - Multi-disease testing  

### MTB (RR*) (2 step)

- SenSpe(TB)=93/100  
- SenSpe (R)= TBD  
- In FIND validation  
- Smear replacement  
- 1-4 samples/60min  
- **LOD 400Cfu/mL**  
- Portable/Recharg Printer/Charger  
- SMS/Connectivity  
- Multi-disease testing

### MDR-TB (2 step)

- (rpoB, inhA, katG)  
- **Sen (TB)**  
- S+C+(100) / S-C+(90)  
- Spe (99)  
- **LOD 12Cfu/mL**  
- **Sen (TB)**
  - S+C+(100) / S-C+(90)  
  - Spe (99)  
  - **LOD 12Cfu/mL**  
  - 24 Samples/ 2hrs  
  - LOD 10Cfu/mL  

- **Sen/Spe (TB) = (96/97)**  
- **LOD 10Cfu/mL**  
- **Sen/Spe (R)= (95/97)**  
- **Sen/Spe (H)= (96/97)**  

### MDR-TB (2 step)

- (rpoB, inhA, katG)  
- **Sen (TB)**
  - S+C+(100) / S-C+(90)  
  - Spe (99)  
  - **LOD 12Cfu/mL**  
  - 24 Samples/ 2hrs  
  - LOD 10Cfu/mL  
- **Sen/Spe (TB) = (96/97)**  
- **LOD 10Cfu/mL**  
- **Sen/Spe (R)= (95/97)**  
- **Sen/Spe (H)= (96/97)**  

### Multi-disease testing

- In Final Eval Studies  
- Plan to add FQ/SLIs  
- Multi-disease testing
Next Generation Sequencing – bench top testing available

Technologies in FIND Evaluation

- Molbio
- Genolution
- DiaSorin
- HAIN
- Oxford Nanopore
- Illumina MiniSeq/iSeq100
- ThermoFisher Ion Torrent Systems
- Qiagen GeneReader

Fully automated start to finish

Sierra Leone Lab – Ebola sequencing

- Mykrobe PedictorTB
- BioNumerics - Applied Math
- ReSeq - TB
- Hydrax BioScience

Illumina: MiniSeq and iSeq 100

Prediction Tool for Reporting Resistance Prediction Algorithm

TABLE 2: Overview of proposed confidence levels for grading mutations associated with phenotypic drug resistance.

<table>
<thead>
<tr>
<th>Year</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
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<tbody>
<tr>
<td>2017</td>
<td></td>
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<td>2018</td>
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<tr>
<td>2019</td>
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DNA Extraction (H2H Validation)

DR TB Assays (H2H Validation)

Pilot NGS Implementation (4 ref labs in India)

Clinical Studies of end-to-end solutions (~4 platforms)

WHO Endorsement? (IVD)

>12,000 Global Surveillance Strains in ReSeqWHO

ReSeqWHO Installed

ReSeqWHO Validated

Implementation?
Thank you...

...Questions