TB Diagnostics: Pipeline and Landscape

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Dx Program
PATH
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Global TB/HIV Meet
The UNITAID TB Dx Technology Landscapes

Seven reviews with specific focus on:
TB Dx pipeline
TB Dx global market
The TB Diagnostics Challenge

Multiple factors in concert:

1. Pathobiology: Relatively slow progression to active disease
2. Stigma
3. Lack of access to Dx and treatment
4. Misdiagnosis by clinicians
5. No highly predictive systemic antigens or antibodies
6. MTB is a ‘tough’ bug to lyse
7. Sputum is a challenging specimen type
8. Paucibacillary samples from PLHIV/pediatrics challenges Dx
9. Receiving WHO/GLI endorsement, PQ alone is not enough
The Distribution of TB Case Suspects Seeking Care

Resolution testing (current tests culture, DST, LPA and Xpert)

Passive case finding

Microscopy

Eiken LoopAMP

Detect and treat

Surveillance

Reference methods

Network supervision

~85% of patients seeking care at facilities with limited or no TB Dx test capacity

Adapted from: WHO. Diagnostics for Tuberculosis: Global Demand and Market Potential. 2006
Six ‘new’ products were reviewed and endorsed

<table>
<thead>
<tr>
<th>Assay</th>
<th>Facility level</th>
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<tbody>
<tr>
<td>Determine LAM RDT (Alere)</td>
<td>3 and 2</td>
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<tr>
<td>GenoType® MTBDRplusv2.0 (Hain)</td>
<td>3 and 2</td>
</tr>
<tr>
<td>NTM+MDRTB Detection Kit 2 (Nipro)</td>
<td>3 and 2</td>
</tr>
<tr>
<td>GenoType® MTBDRsl (Hain)</td>
<td>3 and 2</td>
</tr>
<tr>
<td>Loopamp MTBC assay (Eiken)</td>
<td>1!!!</td>
</tr>
<tr>
<td>GeneXpert Ultra (Cepheid)</td>
<td>3 and 2 (1?)</td>
</tr>
</tbody>
</table>
Green fill represents WHO recommended products * Eiken Loopamp was released in 2012 and endorsed in 2016
The Optimal Considerations...

3. Ref labs:
4 high throughput (HT) automated platforms
Reflexive DST assays for all PCR platforms
1 HT, partially integrated microarray (Dx + 1st line DST)

2. Intermediate labs:
6 companies developing 24 LPAs - Dx and 1st/2nd line DST
2 partially integrated microarrays - Dx and 1st line DST
1 open platform – Dx and 1st line DST
2 integrated tools - Dx and 1st/2nd line DST

1. Microscopy:
3 semi-automated or manual - Dx
2 integrated devices - Dx and 1st line DST

0. Health centers:
Nothing
3. Ref labs: WHO Endorsed/Guidelines
3 LPA products - Dx and/or 1\textsuperscript{st}/2\textsuperscript{nd} line DST
1 tool - Dx and 1\textsuperscript{st} DST (Xpert MTB/RIF/Ultra)

2. Intermediate labs: WHO Endorsed/Guidelines
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1. Microscopy center: WHO Endorsed/Guidelines
1 open platform (Eiken)

0. Health center: WHO Endorsed/Guidelines
Nothing

Most pending products had continuously revised release dates 2015, 2016, 2017, 2018, 2019......
What’s Happening?

Reference Laboratories at tier 3

Tools typically developed for high income country markets or volume (HIV VL), Never solely for TB Dx
Implementation of open assays is challenging (QA)
No product is yet WHO endorsed
Abbott, BD, Hain and Roche are in the FIND evaluation pipeline 2018/2019
Only Cepheid platform and assays are WHO endorsed
Integrated platforms did not enter (Enigma and NWGHF [Quidel])
Hain Fluorotype assays CE-IVD marked and scaling production
Xpert XDR-TB in late development/validation
Cepheid Xpert updates

MTB/RIF Ultra
1. Cartridge-based assay to replace the current MTB/RIF
2. Redesign of fluidic system, assays and spectral analyses
3. IS6110/1081, ‘sloppy’ molecular beacons for RifR (rpoB)
4. LOD of 15.6 cfu/mL as compared to 112.6 for MTB/RIF*
5. Increased sensitivity in Tb Dx for PLHIV
6. WHO endorsement/guidelines released in 2017
7. Same price as MTB/RIF ($9.98)

MTB/XDR reflex assay to MTB/RIF +ve
1. INH, FLQ and AMG
2. Larger probe size to tile larger target regions
3. Novel engineering (multiplexed PCR reactions, 2 nested and 1 hemi nested)
4. Asymmetric PCR with 10 color assay using SMB ¥
5. LOD of 300 cfu/mL

* Chakravorty et al. mBio 2017 Aug 29;8(4)
¥ Chakravorty et al. JCM. 2016 Dec 28;55(1):183-198
Cepheid GeneXpert updates 2...

Will the OMNI ever reach production???
First noted 2015: fully automated, robust, remote access, $2985 /unit

2018

MSF report: Jan, 2018, cost $5315/unit
Extra $1.50 per test for near field communication chip
Running cost estimated at $500-$600 per unit pa with Vodafone
Maintenance: approximately $1.50 /cartridge will be incurred
3 yr warranty included, extra warranty to 5 yr is $940/unit
Less if extra warranty bought upfront

And now....

Cepheid 19th July: GeneXpert Edge, a GX1 in smaller housing unit with UPS and tablet (and barcode scanner), release date/price TBD
NAATs for the Microscopy Center

2015:
- # of developers has decreased
- Release dates extended...
- 2015: 14 groups, ≥16 products
- 2016: 9 groups, 13 products
- 2018: 7 groups 12 products
Loopamp MTBC Assay Status and Pricing

WHO guidelines released in August 2016 – potential replacement test for SSM
Conditional recommendation and very low quality of evidence
PATH Tanzania validation  LAMP: sens/spec 67.4% and 97.5%
Front loaded SSM: sens/spec 71.43% and 95.47%
Negotiated pricing (FIND)

<table>
<thead>
<tr>
<th><strong>Loopamp™ MTB Detection Kit</strong> (2 x 48 tests, including positive and negative control = 84 TB tests)</th>
<th>$425 per kit</th>
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<tbody>
<tr>
<td><strong>Loopamp™ Pure DNA Extraction Kit</strong> (90 extractions)</td>
<td>$360 per kit</td>
</tr>
<tr>
<td><strong>Pipette-60 Set</strong> (1 pipette, 4 X 96 filter tips)</td>
<td>$53 per set</td>
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<tr>
<td><strong>HumaLoop T</strong></td>
<td>$2950</td>
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<tr>
<td><strong>UPS</strong></td>
<td>$480</td>
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~US$9.98/test

Xpert US$9.98
Molbio Trueprep, Truenat, and Truelab products

Rapid detection of MTB via a chip based real time PCR
CE-IVD marked, DCGI Approved
Undergoing RNTCP trial
Suite of kits, tools and equipment (battery powered/wireless enabled)
Key Challenges to Development

**Cost$:** TB Dx is a very hard sell to investors/company boards (value poorly defined)

**Barriers to market:** High income countries have no large market for TB testing, LMICs primary market but difficult to enter without lots of upfront investment

**Technology:** Dx tools are challenged by paucibacillary sputum (PLHIV/pediatrics)

**Performance:** Typically limited development data: Almost no peer reviewed performance data; paucity of test specimens increases risk of poor data

**Time:** ALL/most developers note overly optimistic market release dates, small developers challenged to scale for manufacturing

**WHO endorsement:** Cost, risk and time to get to dossier prepared/reviewed by GLI STAG and then guidelines for implementation

**Implementation:** NTPs need to know where to best place new technology, most NTPs wants to perform their own performance assessments prior to adoption

**Sustainability:** Majority of HBC market is supported by global donors
The Secret To Successful Products?

**Size** - Large Dx companies have expertise and financial muscle (Abbott, BD and Roche)

**Existing platforms on market** - Abbott, Hain, BD, Roche, Cepheid

**Early positioning in the TB Dx space** – Hain, Cepheid

**Exclusive access to innovative technologies** – e.g. Hain, LATE PCR/ “Lights on/lights off” or Cepheid, molecular ‘sloppy’ beacons

**Partnerships** – work with countries with highly proactive and engaged NTPS. FIND the only group in this PDP space for TB Dx.
Is there hope for new TB Dx Tools?

Are the ‘omics’ finally starting to deliver?...

Metabolomics (first on the block), still don’t know if they will work (Breath/urine tests)

Protein-based biomarkers to indicate severity of disease and culture conversion¹ ProteinLogic? mBio?

Transcriptomic analyses of cellular response to indicate active disease or progression to disease

- Down selection of RNAs for rapid NAATs, BioMérieux partnering to apply to BioFire FilmArray platform
- Other automated, multiplexed platforms may offer similar

‘Old’ biomarkers revisited with new tools?

Poor performance with LAM or CFP10/ESAT6 TB Dx

Affinity sequestration of LAM from urine increases sensitivity?\(^1\)
- Hydrogel containing copper complex reactive dye
- Competes to sequester LAM from urine associated proteins
- Increased LAM - allow detection of LAM in HIV-ve patients?

UNIMA Diagnostics (Mexico) Find™ TB + HIV diagnostic test
- 15 minute test measuring immunobead aggregation
- Phone app uses machine learning to improve performance
- Novel antibodies to 3 targets including CFP10 and ESAT6
- Unpublished clinical data, sens/spec >95% for both TB and HIV (n=328)

UNIMA FIND™ TB + HIV

Claims
1. High performance
2. Low cost
3. Training, 30 minutes
4. Finger stick sample
5. TB specific
6. Phone reader limits user error, data storage and data transmission

Field evaluations underway:
Zambia (PATH) and iLEAD partnership (South Africa, Senegal and Mozambique)
Questions?

Credit: Challenge TB

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