New TB diagnostics: landscape and pipeline

Catharina Boehme
8th December 2014
To reach global TB targets, we rely on novel diagnostics and testing strategies in both phases.

**TB deaths**
- Phase 1: + Universal health coverage
  - Reduction: -75%
- Phase 2: + Prevent reactivation
  - Reduction: -95%

**TB incidence**
- Early diagnosis + DST for ALL cases
  - Reduction: -50%
- Identifying those AT RISK among pool of infected
  - Reduction: -90%

Courtesy of Global TB Programme
Transmission model results that informed WHO TB strategy
Universal, early diagnosis and DST – where do we stand?

Facts:
- 9 million TB cases
- 1.5 million TB deaths
- 3 million undiagnosed
- Up to 30% of cases diagnosed never get treated

Facts:
- 480 000 with MDR
- 3.5% of new + 20.5% of previously treated TB cases
- 45% of those 300k detected are diagnosed

WHO Global TB report 2014

16 December 2014
## Advancements in TB diagnostics

<table>
<thead>
<tr>
<th>Year</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
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- Smear-positive TB case definition
- Liquid culture
- LPA
- LED-FM
- Automated NAAT (Xpert MTB/RIF)
- Xpert EPTB / children
- Number of smears
- Rapid speciation
- Front-loaded microscopy
- Negative rec: Serology
- MODS, CRI, NRA cond.

**Advancements in TB diagnostics**

- **2006**: Smear-positive TB case definition
- **2007**: Liquid culture
- **2008**: LPA
- **2009**: LED-FM
- **2010**: Automated NAAT (Xpert MTB/RIF)
- **2013**: Xpert EPTB / children
- **2014**: Number of smears, Rapid speciation, Front-loaded microscopy, MODS, CRI, NRA cond.
Can our new TB tests impact incidence and mortality? Yes, but -

The impact of novel tests for TB depends on the diagnostic cascade

Amanda Sun, Claudia Denkinger, David Dowdy

Diagnostic delays, reduced access and empirical treatment minimize potential impact
Limited impact of Xpert MTB/RIF as smear replacement test

Published and unpublished data from India, South Africa and Brazil show:

- Sustantially increased number of bacteriologically confirmed cases
- Does not necessarily result in increased case notifications (or patients on treatment)
- At least 1 in 10 confirmed TB patients not started on treatment
- Low coverage

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Insufficient Xpert coverage in 22 high burden countries
Limited fit of Xpert as smear replacement test – as defined in target product profiles

- Performance characteristics
  - Sensitivity/specificity for TB detection, treatment monitoring, DST
- Operational characteristics
  - Specimen type
  - Manual steps
  - **Infrastructure requirements** (e.g. power, temperature control)
  - Time to result
  - Requirements for reporting and **connectivity**
  - Importance of subgroups such as HIV-infected and children
- **Price targets**
Our 5-year vision for TB diagnosis

**Triage/case finding – first point of contact**

1. Triage test  
   - incl. for childhood TB & EDPT
2. Syndromic test (bac vs viral)

**Further work up & treatment – dedicated unit**

1. Highly sensitive TB confirmation with rapid DST for critical drugs
2. Treatment monitoring
3. TB infection with high risk of disease progression

**Surveillance, QA, training – specialized unit**

1. Real-time Surveillance
2. Comprehensive, rapid DST

**E-Health supported solutions**
# Global TB dx R&D pipeline (case detection/DST)

<table>
<thead>
<tr>
<th>Early development</th>
<th>Late or completed development</th>
<th>On pathway to WHO evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Molecular Detection/DST</strong></td>
<td><strong>Molecular Detection/DST</strong></td>
<td><strong>GenoTYPE MTBDRsl</strong> (Hain)</td>
</tr>
<tr>
<td>MDR-TB (Akkoni)</td>
<td>VereMTB (Veredus Laboratories)</td>
<td>LiPA MDR-TB (Nipro)</td>
</tr>
<tr>
<td>COBAS TaqMan MTB +DST(Roche)</td>
<td>LiPA Pyrazinamide (Nipro)</td>
<td>REBA MTB-Rifa (YD Diagnostics)</td>
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<tr>
<td>Late or completed development</td>
<td><strong>Culture-based technologies</strong></td>
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<tr>
<td>BNP Middlebrook (Nanologix)</td>
<td>Genedrive MTB (Epistem)</td>
<td>TB LAMP (Eiken)</td>
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<tr>
<td>Rapid colorimetric DST</td>
<td>Truelab/Truenat MTB (Molbio)</td>
<td><strong>Automated Microscopy &amp; Imaging</strong></td>
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<tr>
<td><strong>Volatile organic compounds</strong></td>
<td><strong>Automated Microscopy &amp; Imaging</strong></td>
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<tr>
<td>BreathLink (Menssana)</td>
<td><strong>Microimager</strong> (BD)</td>
<td><strong>Microimager</strong> (BD)</td>
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<tr>
<td>Prototype breathanalyzer (Next Dimensions)</td>
<td><strong>CAD4TB</strong> (Delft Imaging Systems)</td>
<td><strong>CAD4TB</strong> (Delft Imaging Systems)</td>
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<tr>
<td>TB Breathalyser (Rapid Biosensor Systems)</td>
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<td>Aeonose (The eNose Company)</td>
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<tr>
<td>Breath analysis instrument (Metabolonx)</td>
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<td>TBx (Applied Visual Sciences)</td>
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<td>Fluorescent microscopy (ID-FISH Tech.)</td>
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<td>Automatic TB Screener (Fluorobot)</td>
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<tr>
<td><strong>Low complexity assays</strong></td>
<td><strong>Moderate complexity assays</strong></td>
<td><strong>High complexity assays</strong></td>
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<tr>
<td><strong>Antigen &amp; Antibody detection</strong></td>
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<tr>
<td>LAM in sputum (Standard Diagnostics)</td>
<td>Alere Determine TB-LAM in urine (Alere)</td>
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<tr>
<td>Multiplex antibody array (mBio)</td>
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<tr>
<td><strong>Enzymatic detection/DST</strong></td>
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<tr>
<td>β-lactamase reporter (Global BioDiagnostics)</td>
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### DNA - the only solid biomarker for TB Dx

<table>
<thead>
<tr>
<th>High complexity assays</th>
<th>Moderate complexity assays</th>
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<tbody>
<tr>
<td>Hain GenoType MTBDRplus</td>
<td>Abbott TBMDx</td>
</tr>
<tr>
<td>Roche Cobas</td>
<td>Hain GenoType MTBDRsl</td>
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<tr>
<td>Zeesan MeltPro*</td>
<td>Nipro LiPA PZA &amp;</td>
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<tr>
<td>CapitalBio MTB-MDR</td>
<td>YD REBA MTB-XDR</td>
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<tr>
<td>Illumina Next-Generation Sequencing</td>
<td>Hain LATE PCR</td>
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<tr>
<td>BD BD Max</td>
<td>Lights on /Lights off MTB-PZA</td>
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<tr>
<td>Akkoni MDR-TB</td>
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<table>
<thead>
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<th>Moderate complexity assays</th>
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<tbody>
<tr>
<td>Cepheid Xpert® MTB/RIF</td>
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<tr>
<td>Eiken TBLAMP™</td>
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<tr>
<td>Veredus Laboratories VereMTB™</td>
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<tr>
<td>Enigma ML* MDR TB</td>
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<tr>
<td>Ustar MTB</td>
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<thead>
<tr>
<th>WHO-endorsed</th>
<th>Limited commercial availability</th>
<th>Expected completion of development</th>
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<tr>
<td>Limited commercial availability</td>
<td>2015</td>
<td>2016</td>
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<tr>
<td>Expected completion of development</td>
<td></td>
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</table>
R&D highlight 1: Taking molecular a step further

**Xpert® MTB/Rif Ultra** in late development, with the goal of closing the sensitivity gap with culture
- Sensitivity as low as 5 cfu/ml, depending on strain.
- Runs on existing systems
- Cost is the same at $9.98
- Anticipated release Q1 2016 (trials as of Q2 2015)

Rapid diagnosis of additional 30% Sm-Cul+ patients (or > in HIV+ and children); addressing overtreatment.

**Xpert® XDR** in development, which will detect resistance to INH, fluoroquinolones, and aminoglycosides
- Alpha study ongoing in 2 countries
- Runs on existing modules (10 color)
- Cepheid development and release plan is underway

MDR/XDR triaging in high DR settings; addressing INH concerns; preparedness for new FQ-based regimens.
R&D highlight 2:
Bringing molecular closer to patients

**Alere™ q TB** in late development, targeting microscopy centers
- Fully integrated.
- Time to result 20 min
- Runs on HIV VL systems
- Anticipated release & start of validation/impact trials Q4 2015

**Alere™ q DST** in development, which will detect resistance to RIF, INH, FQ, and potentially PZA
- Time to result 40 min (from DNA of TB assay)
- Resistance SNPs on microarray
R&D highlight 3: Making molecular local

**Molbio - Truenat; India.** In late development.
- Realtime-PCR
- A more automated TB assay developed, RIF integration planned.
- In first multi-center study now.

**Ustar – Easynat; China.** In development.
- Cross-priming amplification
- Started work on more automated version.

If successful, could save costs and ease access (shipment, import)
Beyond pulmonary TB

Policy update: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children

Xpert MTB/RIF implementation manual: technical and operational ‘how-to’; practical considerations

Recommendations for lymph node aspirates, tissue biopsy, cerebrospinal fluid

→ Invasive procedures still necessary!
Expanding utility of molecular tools

Improving detection of Extrapulmonary & Pediatric TB

TB detection using stool

TB detection using urine
Need for new tools spans the healthcare system, but concentrated at lower levels of the system.
Incremental improvements: Automating smear microscopy

- **Automated reading**
  - TBDx (Applied Visual Sciences)
  - CellScope TB Microscope (UCSF)
  - Fluorobot

- **Automated staining**
  - RALSTAINER (bioMérieux)
  - Aerospray TB (ELITechGroup)

- **Combined**
  - MIAFB2 (BD)
### LAM for TB Screening or Diagnosis

<table>
<thead>
<tr>
<th>Setting</th>
<th>Patients (%TB, #studies)</th>
<th>Pooled estimates: Grade 2 % (95% CI)</th>
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<tr>
<td></td>
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<td>Sensitivity</td>
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<tr>
<td>Inpatient</td>
<td>1805 (42%, 5)</td>
<td>48% (43-54)</td>
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<tr>
<td>Outpatient</td>
<td>1961 (24%, 5)</td>
<td>21% (15-29)</td>
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#### LAM among inpatients at Grade 2

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
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<tr>
<td>Unpublished 4</td>
<td>11</td>
<td>8</td>
<td>7</td>
<td>47</td>
<td>0.61 [0.36, 0.83]</td>
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<tr>
<td>Unpublished 6</td>
<td>53</td>
<td>3</td>
<td>83</td>
<td>274</td>
<td>0.39 [0.31, 0.48]</td>
<td>0.99 [0.97, 1.00]</td>
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<td>Nakiyangi 2014</td>
<td>114</td>
<td>19</td>
<td>132</td>
<td>287</td>
<td>0.46 [0.40, 0.53]</td>
<td>0.94 [0.90, 0.96]</td>
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<td>Peter 2012</td>
<td>58</td>
<td>31</td>
<td>58</td>
<td>94</td>
<td>0.50 [0.41, 0.59]</td>
<td>0.75 [0.67, 0.82]</td>
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<tr>
<td>Unpublished 3</td>
<td>130</td>
<td>26</td>
<td>119</td>
<td>251</td>
<td>0.52 [0.46, 0.59]</td>
<td>0.91 [0.87, 0.94]</td>
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#### LAM among outpatients at Grade 2

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<td>Unpublished 4</td>
<td>18</td>
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<td>19</td>
<td>393</td>
<td>0.49 [0.32, 0.66]</td>
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<td>322</td>
<td>0.18 [0.12, 0.26]</td>
<td>0.99 [0.98, 1.00]</td>
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<td>0.93 [0.90, 0.95]</td>
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<td>237</td>
<td>0.12 [0.04, 0.25]</td>
<td>1.00 [0.98, 1.00]</td>
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*Courtesy Maunank Shah and study PIs*
Various biomarker efforts towards a rapid diagnostic test

Level of certainty in Biomarker

Ease of translating onto a point of care platform

**Requirements:**
- **Systematic approaches**
- **Large well-characterized sample repositories**

### Biomarkers

- **VOC (breath)**
  - Belisle
  - Graham
  - Menssana
  - Next Dimensions
  - Rapid Biosensor Systems
  - The eNose Company
  - Metabolomx
  - K-Rith (urease)
  - Timmins (INH)

- **Antibodies (b)**
  - Anderson
  - Lowary
  - FIND
  - Dobos
  - Moritz
  - Feldheim
  - Campos
  - Ochsner
  - Kaufmann
  - Laal
  - Proteinlogic
  - FIND

- **Proteins (s, b, u)**
  - Feldheim

- **Metabolites (s, b, u)**
  - Feldheim

- **Sugars (s)**
  - Belisle

- **Enzymes (s, b, u)**
  - GBD (β-lactamase)

- **Nucleic Acids (u, b)**
  - LMU
  - Levin
  - Cirillo

- **Cellular stimulation (b)**
  - Geldmacher
  - Modlin
  - Lewinsohn

- **Mycolic acids/lipids (u)**
  - Belisle
  - Bangor U

- **microRNA (b, u)**
  - Cirillo
  - Zhou
  - Xu

- **Mycolic acids/lipids (s)**
  - Belisle

**s – sputum**
**u – urine**
**b – whole blood**
β-lactamase detection

Rapid point-of-care detection of the tuberculosis pathogen using a BlaC-specific fluorogenic probe

Hexin Xie¹, Joseph Mire², Ying Kong², MiHee Chang³, Hany A. Hassounah³, Chris N. Thornton⁴, James C. Sacchettini², Jeffrey D. Cirillo³ and Jianguhong Rao¹*

Feasibility study of early prototype reagent system in South Africa
Biomarker efforts towards a blood-based triaging test

**Schematic and representative image of MBio-FIND TB Serology Array.**

**ROC Curve: TB Host Response Signature in Serum**

<table>
<thead>
<tr>
<th>Sample Set (Serum)</th>
<th>Sens. / Spec.</th>
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<tbody>
<tr>
<td>Training</td>
<td>90% / 85%</td>
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<tr>
<td>HIV-negative</td>
<td>95% / 84%</td>
</tr>
<tr>
<td>HIV-positive</td>
<td>88% / 90%</td>
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<tr>
<td>smear-negative</td>
<td>100% / 90%</td>
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<tr>
<td>Test</td>
<td>89% / 88%</td>
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<tr>
<td>Verification (blinded)</td>
<td>80% / 84%</td>
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</tbody>
</table>

**9-Marker Model**
- Kallistatin
- Gelsolin
- TSP4
- Afamin
- BGH3
- C9
- Testican-2
- FCG3B
- DERM

**SOMAmer-based Detection of TB in Serum**

AUC = 0.94 (0.90, 0.96)

AUC = 0.92 (0.81, 0.96)

AUC = 0.88 (0.83, 0.92)
Novel strategies to reach patients as important as novel tools

- 40–60% of TB patients without reported symptoms – challenge for early detection
- Need for inclusive symptom screening / active screening + highly sensitive and widely available test.
Triaging at first point of contact

Fever, cough, weight loss

? Bacterial, viral, TB
? Severity

Targeted therapy

Reduction in antibiotic use and preservation of drugs

Integrated care

Example 1: First fever point-of-care tests

RPS Diagnostics obtains CE mark for test to differentiate viral and bacterial acute febrile respiratory infection based on Myxovirus Resistance Protein A (MxA) and C-reactive Protein (CRP)

Example 2: TB triaging
Combining new tools with a patient-centered approach

- The importance of integrated care for early diagnosis and diagnostic impact
- A holistic approach needs to include the private health sector

The right implementation strategy in scaling up Xpert in the Indian health care system

Pathways to TB treatment in India (> 2 providers prior to RNTCP)
Lessons learned from Xpert and Pima:
The need for solutions, not tools.

2010

Xpert
Launch

Policy & regulatory guidance
Policy endorsement at unprecedented speed (2 years after design lock / trial start)

2011

Quality assurance
Strong built-in controls
Calibration tool
Validation panels
Remote monitoring

Support & supply chain
Clear procurement system but long time to repair / replacement
Clear warranty conditions & coverage

Impact measurement
Strong trial data informed rapid policy (w/some impact data)
Early rollout not accompanied by data collection & feedback on implementation
Scarce impact data available; only from trials (not routine collection)

Connectivity & IT
Connectivity to lab management information systems
First independent IT tools to enable data transfer, mobile use
Chance to reach potential re: linkage to care & connectivity by 2015

Training & user manuals
1st implementation & basic training guide
More complete job aids & training package
Comprehensive online training

Key
Not available
Partially available but doesn’t fully meet need
Meets the need

2012

2013

2014

Being used in 108 high burden countries
Expanded guidance for pediatric & extrapulmonary TB

From tests to comprehensive diagnostic solutions

- Easy to use diagnostic
- Training & Advocacy
- Connectivity and IT
- Quality assurance
- Impact measurement
- Support and supply chain
- Policy & Regulatory guidance

26
Capitalizing on Connectivity

- Device Management
  - e.g., remote monitoring
- Global Diagnostics
  - Data Aggregator
- Connected 3rd party applications
  - Healthcare
    - e.g., electronic medical records and mobile alerts
  - Public Health
    - e.g., epidemiological and surveillance database
  - Health System Management
    - e.g., inventory management systems
  - Device Management and Quality Assurance
    - e.g., remote monitoring

Dx

Standardised interface for data upload & transfer

Digital & non-digital diagnostics
Getting to universal rapid diagnosis & DST: What will it take?

- **Novel tools implemented as comprehensive solutions**
  - Highly sensitive smear replacement test (by 2016);
  - Rapid, expanded DST (by 2017); Sequencing gold standard (by 2018).
  - TB, Fever and Cough triaging RDT (by 2018?);
  - Latent to active disease progression (by 2020?)

- **Novel testing strategies**
  - Implementation strategies targeted to include first points of contacts
  - Inclusive symptom screening and active screening

- **Strong, integrated lab and health systems**
  - With engagement of communities, and public/private care providers

- **Transformed diagnostic ecosystem**
  - Measure and communicate impact of dx
  - Foster and sustain willingness to invest / pay
  - Innovative partnerships across the diagnostic value chain
Towards a 90-90-90 TB target: 90% of vulnerable groups screened, 90% diagnosed, treated, & 90% cured

Requires: Selection and use of best-fit dx tools and testing strategies; and thus an active role in dx studies