Looking ahead: the new TB diagnostic pipeline

Annual GLI Meeting 2015

Catharina Boehme
To reach global targets, we rely on novel diagnostics and testing strategies in both phases.

The status:

- ~3 m undiagnosed TB cases and ~ 300 k undiagnosed MDR per year
- Only 70% of TB cases diagnosed get treated, and even less of the MDR cases

**TB deaths**

- Phase 1: + Universal health coverage
  - -75%

- Phase 2: + Prevent reactivation
  - -95%

**TB incidence**

- EARLY diagnosis +DST for ALL cases
  - -50%

- Identifying those AT RISK among pool of infected
  - -90%
Impact of new dx tools depends on health system strength & implementation strategies

Diagnostic delays, reduced access, test «issues» and empirical treatment reduce potential impact

Data for Xpert show:

- Sustantially increased number of bacteriologically confirmed cases, but not necessarily increased case notifications, patients on treatment or decreased mortality.

- In most settings, Xpert is not used as «POC» test, national algorithms are complex, empirical treatment common.

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

Salje PLOS Med 2014
5-year vision for TB diagnostic networks

Triage/case finding – first point of contact
1. Triage test
   • incl. for childhood TB & EDPT
2. Active case finding
   • Highly sensitive, portable
3. Syndromic test (Bact vs viral)

Further work up & treatment – dedicated unit
1. TB confirmation with rapid DST for critical drugs
   • Incl. for childhood TB & EPTB
   • Using platform synergies (e.g. HIV)
2. Treatment monitoring
3. Disease progression

Coordination, Surveillance, QA, M&E –
1. Real-time monitoring of network and integrated care
2. Comprehensive, rapid DST

E-Health supported solutions
Need for new tools spans the healthcare system, but concentrated at lower levels of the system.

- **Community health worker**
- **Health post**
- **Microscopy center**
- **District hospital**
- **Reference center**

**A** Passive & active case detection

**B** Rule out test

**D** Latent to active progression

**E** Drug susceptibility testing

**F** Treatment monitoring

**eHealth and connectivity solutions**

12 May 2015
Target Product Profiles

Prioritized TPPs:

- Point-of-care, non-sputum based test
- Point-of-care triage test
- Point-of-care sputum based test for microscopy replacement
- Point-of-care DST-microscopy center

Iterative process with input from many stakeholders

WHO Consensus Meeting

- Delphi process leading up to the meeting
- > 75% agreement amongst stakeholders

Ongoing: Latent to Active, Tx monitoring, connectivity standards

High-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting

http://apps.who.int/iris/bitstream/10665/135617/1/WHO_HTM_TB_2014.18_eng.pdf?ua=1

28–29 April 2014
Geneva, Switzerland
# Global TB Diagnostic Pipeline

<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>Culture-based technologies</strong></td>
<td><strong>Gastrointestinal (GI)ASSAY</strong></td>
</tr>
<tr>
<td>TruArray MDR-TB (Akkoni)</td>
<td>BNP Middlebrook (NanoLogix)</td>
<td>Gastrointestinal (GI)ASSAY</td>
</tr>
<tr>
<td>COBAS TaqMan MTB +DST(Roche)</td>
<td>Rapid colorimetric DST</td>
<td>(Standard Diagnostics)</td>
</tr>
<tr>
<td>Hydra 1K (insilixa)</td>
<td>TREK Sensitive MYCOTB (Trek)</td>
<td>Multiplex antibody array (mBio)</td>
</tr>
<tr>
<td>Mycobacterium Real-time MDR (CapitalBio)</td>
<td>Volatile organic compounds</td>
<td>Automated Microscopy &amp; Imaging</td>
</tr>
<tr>
<td><strong>TRC Rapid MTB (Tosoh)</strong></td>
<td>BreathLink (Menssana)</td>
<td>Microimager (BD)</td>
</tr>
<tr>
<td><strong>VereMTB (Veredus Laboratories)</strong></td>
<td>Prototype breathalyzer (Next Dimensions)</td>
<td>CAD4TB (Delft Imaging Systems)</td>
</tr>
<tr>
<td><strong>LIPA Pyrazinamide (Nipro)</strong></td>
<td>TB Breathalyser (Rapid Biosensor Systems)</td>
<td><strong>EPTB RDT</strong></td>
</tr>
<tr>
<td><strong>LATE-PCR Lights on / Lights off (Hain)</strong></td>
<td>Breath analysis instrument (Metabolomx)</td>
<td>Alere Determine TB-LAM in urine (Alere)</td>
</tr>
<tr>
<td><strong>TBMDx (Abbott)</strong></td>
<td><strong>Automated Microscopy &amp; Imaging</strong></td>
<td><strong>Enzymatic detection/DST</strong></td>
</tr>
<tr>
<td><strong>Meltpro (Zeesan)</strong></td>
<td><strong>Microimager (BD)</strong></td>
<td><strong>β-lactamase reporter (Global BioDiagnostics)</strong></td>
</tr>
<tr>
<td><strong>Mycobacteria RT PCR (CapitalBio)</strong></td>
<td><strong>CAD4TB (Delft Imaging Systems)</strong></td>
<td></td>
</tr>
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</table>
# Molecular pipeline

<table>
<thead>
<tr>
<th>High complexity assays</th>
<th>Moderate complexity assays</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hain GenoType MTBDRplus</td>
<td>Cepheid Xpert® MTB/RIF</td>
</tr>
<tr>
<td>Abbott TBMDx</td>
<td>iCubate</td>
</tr>
<tr>
<td>Roche Cobas</td>
<td>NanoBioSys LabChip G2-3</td>
</tr>
<tr>
<td>Zeesan MeltPro®</td>
<td>Eiken TBLAMP™</td>
</tr>
<tr>
<td>Hain GenoType MTBDRsl/</td>
<td>Veredus Laboratories VereMTB™</td>
</tr>
<tr>
<td>Nipro LIPA PZA &amp;</td>
<td>Cepheid Xpert® Ultra Xtend-XDR</td>
</tr>
<tr>
<td>CapitalBio MTB-MDR</td>
<td>Enigma ML® MDR TB</td>
</tr>
<tr>
<td>YD</td>
<td>Northwestern GHT/Quidel</td>
</tr>
<tr>
<td>Hain LATE PCR Lights on/Lights off MTB-PZA</td>
<td>Ustar MTB</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WHO-endorsed</th>
<th>Limited commercial availability</th>
<th>Expected completion of development</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2015</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2016</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2017+</td>
</tr>
</tbody>
</table>

- **Abbott TBMDx**: Limited commercial availability
- **Cepheid Xpert® MTB/RIF**: WHO-endorsed
- **Cepheid Xpert® Ultra Xtend-XDR**: WHO-endorsed
- **Enigma ML® MDR TB**: WHO-endorsed
- **Northwestern GHT/Quidel**: WHO-endorsed
- **Ustar MTB**: WHO-endorsed

**Note**: The image also includes a timeline for the expected completion of development, with the following markers:
- **2015**: WHO-endorsed, Limited commercial availability
- **2016**: WHO-endorsed, Limited commercial availability
- **2017+**: WHO-endorsed, Limited commercial availability
What needs do novel platforms address

New NAAT platforms

- Decentralization
- Improving time to diagnosis
- Improving MTB detection
- Higher throughput, multiplexing
- Extended, timely DST

Needs addressed

- Insilixa HYDRA
- GenePOC
- Roche
- Cepheid
- ABBOTT
- BD
- molbio
- QUANTUM MD
- epistem
- Alere
- USTYR
Molecular highlight 1: Taking molecular a step further

**Xpert® MTB/Rif Ultra** completed 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)
- Anticipated release Q1 2017

**MDR/XDR triaging in high DR settings; addressing INH concerns; preparedness for new FQ-based regimens**
Molecular 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 start of validation/impact trials Q1 2016

- **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
Molecular highlight 3: Making molecular local

- **Molbio - Truenat; India.** In late development.
  - Realtime-PCR
  - A more automated TB assay developed, RIF integration planned.
  - Improved assay under evaluation as of Q2 15

- **Ustar – Easynat; China.** In development.
  - Cross-priming amplification
  - Started work on more automated Version**, trials planned for 2016.

If successful, could save costs and ease access (shipment, import)
Molecular highlight 4: Expanding utility beyond sputum

Improving detection of Extrapulmonary & Pediatric TB

Xpert for MTB detection on stool

Trans-renal DNA detection
The next breakthrough in TB DST: Sequencing?

1. Introduce for real-time surveillance and fill knowledge gaps

2. Solve specimen processing & data interpretation

3. Miniaturize and bring closer to patient

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**Diagram:**

- **RDST Consortium**
  - **ReSeqTB**
    - Relational Sequencing TB Data Platform
  - **Academic Research Data**
  - **Government Research Data**
  - **Private Sector Research Data**
  - **Other High-Quality Research Data**
  - **Clinicians**
  - **Assay Developers**
  - **Researchers**

**Logos:**

- ion torrent
- illumina
- Qiagen
- Pacific Biosciences
Biomarker work – Detection and triage test

Level of certainty in Biomarker

Ease of translating onto a point of care platform

VOC (breath)
- Graham
- Mensanna
- 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

Enzymes (s, b, u)
- GBD (β-lactamase)

Sugars (s)
- Belisle

Cellular stimulation (b)
- Geldmacher
- Modlin
- Lewinsohn

Mycolic acids/lipids (u)
- Belisle

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

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

Whole Bug (s)
- Nucleic Acids (s)
- Fast followers

Mycolic acids/lipids (s)
- Belisle
- Bangor U

s – sputum
u – urine
b – whole blood
LAM for TB Screening or Diagnosis by setting
Culture reference standard (any site)

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

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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<tbody>
<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>
<td>0.85 [0.73, 0.94]</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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<tr>
<td>Nakiiyiingi 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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<tr>
<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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<tbody>
<tr>
<td>Unpublished 4</td>
<td>18</td>
<td>38</td>
<td>19</td>
<td>393</td>
<td>0.49 [0.32, 0.66]</td>
<td>0.91 [0.88, 0.94]</td>
</tr>
<tr>
<td>Unpublished 2</td>
<td>22</td>
<td>2</td>
<td>99</td>
<td>322</td>
<td>0.18 [0.12, 0.26]</td>
<td>0.99 [0.98, 1.00]</td>
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<tr>
<td>Unpublished 7</td>
<td>41</td>
<td>27</td>
<td>140</td>
<td>361</td>
<td>0.23 [0.17, 0.29]</td>
<td>0.93 [0.90, 0.95]</td>
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<tr>
<td>Unpublished 3</td>
<td>5</td>
<td>1</td>
<td>38</td>
<td>237</td>
<td>0.12 [0.04, 0.25]</td>
<td>1.00 [0.98, 1.00]</td>
</tr>
</tbody>
</table>

Courtesy Maunank Shah and study PIs
β-lactamase detection

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

Hexin Xie¹, Joseph Mire², Ying Kong³, MiHee Chang³, Hany A. Hassounah³, Chris N. Thornton⁴, James C. Sacchettini², Jeffrey D. Cirillo³ and Jianghong Rao¹*

Feasibility study of early prototype reagent system in South Africa: TPP not met.
Promising biomarker sets towards POC assay:  
(A) SomaLogic

<table>
<thead>
<tr>
<th>Biomarker discovery: Quantitative measurement of &gt;1,100 proteins in blood in hundreds of TB and non-TB samples by using SOMAmers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identified 9 promising host biomarkers (cytokines) that distinguish TB from non-TB population</td>
</tr>
<tr>
<td>9-marker model showed promising performance close to minimal targets as defined in TPPs in a blinded verification sample set (N=270) from FIND</td>
</tr>
<tr>
<td>Measuring antibody responses in the same assay could further increase performance</td>
</tr>
<tr>
<td>Potential to measure biomarkers on a simple, and patient near platform</td>
</tr>
</tbody>
</table>

**SomaLogic (Boulder, CO, USA)**

| Sensitivity: 85.8% |
| Specificity: 80.3% |

**Preliminary Data**

- **WHO negative recommendation** (2008) 19 commercial rapid diagnostic tests

**Hybridization slides**
- Agilent anti-sense probe array
- Fluorescent read-out (cyanine on 5’ end)
Promising biomarker sets towards POC assay: (A) ProteinLogic

ProteinLogic (Cambridge, UK)

- Measure patterns of soluble human cell surface CD antigens in blood that correlate with TB (ImmiPrint® technology)
- Identified TB associated soluble CD antigens (sCD’s)
- 15-marker model showed promising performance close to minimal targets as defined in TPPs in a blinded sample set (N=300) from FIND
- Potential to measure the biomarkers on a simple, and patient near platform

Sensitivity: 89%
Specificity: 58%

Preliminary Data
Incremental improvement on existing technologies, example smear microscopy

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

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

- **Combined**
  - MIAFB2 (BD)
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.
The need for novel testing strategies

Fever, cough, weight loss

? Bacterial, viral, TB
? Severity
? Resistance

Potential impact

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
Multiple challenges prevent TB diagnostics from having their intended impact in countries

**Incomplete solutions**

Tests launched without supporting elements, e.g.
- Tools and strategies for QA, support and supply chain, impact measurement, eHealth enablement and software, and user guides & training manuals

**Missing policy & implementation elements**

National TB programs & MoHs need to further strengthen planning and execution capacity, e.g.
- Strategic product selection / placement (incl. cross-cutting)
- Partner coordination and monitoring
- Regulatory, procurement, tax, insurance issues, Unique patient identifiers

**Underlying systems weaknesses**

Enable provision of effective, integrated care, e.g.
- Rapid specimen referral and result feedback
- Result feedback loop and linkage to care
- Clinician and patient demand
- Algorithm compliance
- QMS
Lessons learned from Xpert and Pima: The need for solutions, not tools.
From testing to providing comprehensive diagnostic solutions

Connectivity and IT

Training & Advocacy

Quality assurance

Support and supply chain

Impact measurement

Policy & Regulatory Guidance, product selection and implementation planning

Easy to use diagnostic
Capitalizing on Connectivity

- Device Management
- Quality Assurance

- 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

Digital & non-digital diagnostics

Standardised interface for data upload & transfer
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 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