Next Generation TB Diagnostics –
An Update from BMGF

Lee Pyne-Mercier

November 2012
Presentation Outline

- Foundation Strategic Context
- Next Generation TB Diagnostics Program
- TB Diagnostics Forum
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- TB Diagnostics Forum
## TB Strategy 2011-2016: Goal and vision

### Impact goal
Accelerate the reduction of global TB incidence

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>1 vaccine candidate in phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td>1 TB drug regimen in phase 3</td>
</tr>
</tbody>
</table>
| Diagnostics    | • 1 new TB biomarker identified
                | • 2 new molecular diagnostics endorsed by WHO STAG |

**Country-level Innovation in TB Control**
- Increase national TB budgets
- Accelerated uptake of innovative TB control
- New products with frugal engineering

**Global Access and Market Dynamics**
- Reduced costs of FDC and second-line drugs
- Accelerated uptake of innovation in target countries and globally

**Advocacy**
- Funding secured for one TB vaccine and one TB drug phase 3 clinical trial

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November 13, 2012

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Significant Progress To Date in TB Diagnostics; Challenges Remain

**FIGURE 8.1** The development pipeline for new TB diagnostics, July 2012

**REFERENCE LEVEL**
- New SS+ case definition 2-specimen approaches
- LED microscopy Same-day diagnosis
- Xpert MTB/RIF
- Manual NAAT
- Rapid colorimetric DST
- LPA for XDR-TB
- LPA for MDR-TB 2nd generation

**INTERMEDIATE LEVEL**
- VOC detection
- Enzymatic detection
- Ag and Ab detection
- NAAT 2nd generation

**PERIPHERAL LEVEL**
- Access after 5 years (60)
- 2007
- 2008
- 2009
- 2010
- 2011
- 2012
- 2013
- 2014
- 2015
- 2016

Technologies or methods endorsed by WHO
Technologies commercialized, not yet endorsed by WHO
Technologies at feasibility stage
Technologies at early stages of development

Abbreviations: **DST** Drug susceptibility test; **NAAT** Nucleic acid amplification test; **LTBI** Latent TB infection; **Ag** Antigen; **Ab** Antibody; **MODS** Microscopic observation drug-susceptibility; **NRA** Nitrate reductase assay; **CRI** Colorimetric redox indicator assay; **LED** Light-emitting diode; **LPA** Line probe assay; **VOC** Volatile organic compound.
Molecular diagnostics improve upon current tools, providing a bridge to true point-of-care Dx.

**Past and current**

- **Microscopy**
  - Very affordable
  - Poor sensitivity

- **Culture**
  - More expensive
  - Slow time to result

**Current and near term future**

- Genetic Xpert
- Next generation molecular Dx

**Molecular diagnostics**
- Highly sensitive and specific
- Rapid time to results
- Affordability and accessibility increasing over time

**Long term future (10-15 years+ ?)**

- **Expected health impact**
- True point-of-care Dx (based on biomarker TBD)
  - High performance
  - Very affordable
  - Accessible even to patients not reached by current Dx

**Focus of subsequent materials**
Fast-follower NAATs are rapidly entering the market

Loopamp® by Eiken, Japan

GeneDrive® by Epistem, UK

TrueLab® by Molbio, India

NATeasy® by Ustar, China
Potential visions for next generation of molecular Dx...

Key trade-off between affordability and access

<table>
<thead>
<tr>
<th>Affordability</th>
<th>Access</th>
<th>Illustrative</th>
<th>Next generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Low</td>
<td>Low, district-level</td>
<td>Similar performance to existing tech.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Target price: $4-6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Access constraints similar to Xpert</td>
</tr>
<tr>
<td>Low</td>
<td>Low</td>
<td>Xpert copycat</td>
<td>Similar performance to existing tech.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Target price: $8-10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Access constraints similar to Xpert</td>
</tr>
<tr>
<td>Low</td>
<td>High</td>
<td>Expensive, clinic-ready</td>
<td>Similar performance to existing tech.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Target price: $8-10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clinic-ready**</td>
</tr>
</tbody>
</table>

**e.g., Battery powered, heat stable, substantially lower cost instrument, etc.**
Simple and Affordable Molecular Testing for Tuberculosis

“To support the creation of a validated, low-cost, nucleic-acid assay for clinical TB detection on platforms capable of operation in rudimentary laboratories in low-resource settings. It is our intention for these assays to be created and validated for use within 24-36 months”
# Target Product Profile – Key Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Optimal</th>
<th>Minimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of consumables</td>
<td>&lt; $4</td>
<td>&lt; $8</td>
</tr>
<tr>
<td>Cost of instrument</td>
<td>&lt; $5,000</td>
<td>&lt; $10,000</td>
</tr>
<tr>
<td>Time to market</td>
<td>&lt; 24 mos</td>
<td>&lt; 36 mos</td>
</tr>
<tr>
<td>Specificity</td>
<td>&gt; 99%</td>
<td>&gt; 97%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>&gt; 98% smear-positive and 80% smear-negative patients</td>
<td>95% of smear-positive and 65% smear-negative patients</td>
</tr>
<tr>
<td>Sample Prep &amp; processing</td>
<td>Integrated</td>
<td>Minimal, &lt; 5 steps</td>
</tr>
<tr>
<td>Time to result</td>
<td>&lt; 1 hour</td>
<td>&lt; 2 hours</td>
</tr>
<tr>
<td>Sample type</td>
<td>Sputum</td>
<td>Sputum</td>
</tr>
<tr>
<td>Drug resistance screening</td>
<td>Detection of Rif, FQ, and INH resistance testing via a separate cartridge with additional consumable cost (Reflex Testing)</td>
<td>Rifampin drug resistance testing via a separate cartridge with additional consumable cost (Reflex Testing)</td>
</tr>
<tr>
<td>Training</td>
<td>&lt; .5 day</td>
<td>&lt; 1 day</td>
</tr>
</tbody>
</table>

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Problem Statement

- Progress is accelerating on drug regimens (REMox, PaMZ)
- Desire to save new drugs from resistance
- Historic underinvestment in TB R&D has led to significant unknowns, specifically related to DST for key regimen components
- Lack of coordination between researchers, drug developers, and the public health community that will be needed to achieve a common goal
Background and Purpose

- TB Diagnostics Forum established in 2012 in collaboration with NIH

- Overall purpose is to facilitate:
  - Communication and discussion of research priorities, research gap areas, and new relevant data
  - Coordination of research and research funding
  - Collaboration on select projects

- The Diagnostics Forum has identified rapid drug susceptibility testing as an initial topic of focus.
Proposed Structure

TB Diagnostics Research Forum Coordinating Committee
NIH, CDC, BMGF, WHO, EDCTP

Enabling Science Workgroup
Chair: David Sherman (Seattle Biomed)

Modeling Workgroup
Chair: David Dowdy (JHU)

Surveillance Workgroup
Chair: Bonnie Plikaytis (CDC)

Assay Development Workgroup
Chair: Mark Perkins (FIND)

Forum Coordinator

Program Management Support
Coordinated timeline – BMGF Activities

2012

Drug Development
- Bedaquiline

Next Generation TB Diagnostics
- Delaminid

TB Diagnostics Forum
- REMox

TB Biomarker Program
- Rapid DST Development/Adaptation
- Enhanced Drug Resistance Surveillance
- Modeling to Support Rapid DST Project
- Field Validation of Leads

Phase 1: Field Validation of Leads
- Next Generation Diagnostic Development

2013

2014

2015

2016

2017

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Grand Challenge: Biomarkers for the Diagnosis of TB

- $7.7M invested in 10 projects, 24 month grants
- **Program Goal:** support innovative research to facilitate development of a low-cost, simple-to-use tool that can quickly and accurately diagnose TB in developing countries
- **Investigators are evaluating both host and pathogen markers in highly characterized clinical samples through partnership with FIND**
- Concurrent development of TPPs for POC diagnostics to inform decisions

grandchallenges.org/biomarkers
Thank You