Target product profiles for next generation TB diagnostics

Claudia Denkinger, MD PhD MSc
Head of TB, FIND

29th October 2014
The Global TB Epidemic

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
- Only 8.5% new + 17% prev. treated are diagnosed

20 November 2014
WHO Global TB report 2014
Need for new diagnostics
What are product developers looking for?

TB Diagnostics: Top 10 FAQs By Test Developers

1. **TB BURDEN AND TREATMENT LANDSCAPE**
   - What is the global burden of TB (including latent TB, TB/HIV and MDR/XDR-TB) and what is the current and future TB treatment landscape? (Read more)

2. **CURRENT DIAGNOSTICS LANDSCAPE AND PIPELINE**
   - What is the current testing landscape for TB (including latent TB and DST), and what diagnostics are in the pipeline? What is the level of access to current TB diagnostics? (Read more)

3. **MARKET SIZE, POTENTIAL AND DYNAMICS**
   - What is the market size and potential for new TB diagnostics, and what are the market dynamics around TB diagnostics? (Read more)

4. **TARGET PRODUCT PROFILES**
   - What are the unmet diagnostic needs and target product profiles (TPPs) of greatest relevance? (Read more)

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Pai IJTL 2013
Dolinger FIND internal data
What are target product profiles?

- Define the medical/public health need (goal of test; target population; setting of intended use; user)
- Make the need transparent to test developers by defining features and characteristics of the desired test
  - Performance characteristics
  - Operational characteristics
  - Desired price
- Outline features that would provide a competitive advantage
- Communication tool with investors and stakeholders
- Tool for tracking results
Prioritization exercise

Tuberculosis diagnostics: which target product profiles should be prioritised?

Sandra V. Kik¹,2, Claudia M. Denkinger¹,2,3, Martina Casenghi⁴, Caroline Vadnais¹,2 and Madhukar Pai¹,2
¹McGill International TB Centre, McGill University, Montreal, Canada. ²Dept of Epidemiology and Biostatistics, McGill University, Montreal, Canada. ³Division of Infectious Disease, Beth Israel Deaconess Medical Center, Boston, MA, USA. ⁴Médecins Sans Frontières Access Campaign, Geneva, Switzerland.

ERJ Express. Published on April 2, 2014 as doi: 10.1183/09031936.00027714
# Test needs considered

## TRIAGE, RULE OUT AND SYSTEMATIC SCREENING
- Triage test for those seeking care
- An HIV/ART clinic-based test to rule out active TB
- Systematic screening test for active case finding

## RAPID TB DIAGNOSIS (WITH OPTIONAL DRUG SUSCEPTIBILITY TESTING)
- Rapid, sputum-based, cartridge-based, molecular test for microscopy centers (with the option of add-on DST cartridge)
- Rapid biomarker-based instrument-free test for non-sputum samples (which can also detect childhood and extrapulmonary TB)
- Multiplexed test for TB and other infectious diseases

## NEXT-GENERATION DRUG SUSCEPTIBILITY TEST
- Centralized, high-throughput, drug susceptibility test (incorporating new drugs to support the roll out of new TB Rx regimens post 2014)

## TREATMENT MONITORING TEST
- Treatment monitoring test (test for cure)

## PREDICTIVE TEST FOR LATENT TB INFECTION
- Predictive test for latent TB infection at high risk of active TB
### Prioritization

**POC Triage/rule-out test**

**POC Sputum-based, smear replacement**

**POC Biomarker-based, non-sputum**

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**Kik S et al. ERJ 2014**
POC testing

Goal-oriented definition:

“Testing that will result in a clear, actionable, management decision (e.g. referral, initiation of confirmatory test, start of treatment), within the same clinical encounter (e.g. day).”
TPP development

- 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 drug susceptibility tests (microscopy center)

- Iterative process with input from many stakeholders

- Consensus Meeting on high-priority TPPs convened in April 2014 by WHO
  - Delphi-like process leading up to the meeting
  - > 75% agreement amongst stakeholders across defined characteristics
The TPPs

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

28–29 April 2014
Geneva, Switzerland

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

<table>
<thead>
<tr>
<th></th>
<th>Optimal</th>
<th>Minimal</th>
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<tbody>
<tr>
<td><strong>Clinical purpose</strong></td>
<td>A highly sensitive and specific, rapid, biomarker-based test that can diagnose pulmonary TB (PTB) and ideally also extrapulmonary TB (EPTB) using non-sputum samples (e.g., urine, blood, oral mucosal transudates, saliva, exhaled air) with the purpose of initiating TB treatment within the same clinical encounter (or same day).</td>
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<tr>
<td><strong>Target population</strong></td>
<td>Countries with medium to high TB prevalence. Target groups are adults + children (incl HIV) with suspected active TB; either PTB or EPTB</td>
<td></td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>Health posts without attached laboratories (a level lower than MCs)</td>
<td>Primary health clinics (with attached laboratories); Peripheral MCs</td>
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<tr>
<td><strong>User</strong></td>
<td>Health care workers with minimal training</td>
<td>Trained microscopy technicians</td>
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The concept of triage testing

Further testing
High Sensitivity
Lower specificity

Ruled OUT
<table>
<thead>
<tr>
<th><strong>Triage test</strong></th>
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<td><strong>Clinical purpose</strong></td>
<td>A highly sensitive test used at the first encounter to the health care system to identify, among patients with symptoms or risk factors of active TB, including HIV coinfected patients, those who do not have TB and those in need of referral for further confirmatory testing.</td>
</tr>
<tr>
<td><strong>Target population</strong></td>
<td>Countries with medium to high TB prevalence (WHO Categories). Adults and children.</td>
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<tr>
<td><strong>Setting</strong></td>
<td>Community/village level</td>
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<tr>
<td><strong>User</strong></td>
<td>Minimally trained community health workers and informal providers</td>
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Smear-replacement tests

- Increased portability, ruggedness, performance, and DST portfolio

<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>Cepheid Xpert® MTB/RIF</td>
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<tr>
<td>Roche Cobas</td>
<td>iCubate</td>
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<tr>
<td>Abbott TBMdx</td>
<td>Eiken TBLAMP™</td>
</tr>
<tr>
<td>Hain Genotype MTBDRplus</td>
<td>Veredus Laboratories VereMTB™</td>
</tr>
<tr>
<td>Hain Genotype MTBDRplus</td>
<td>NanoBioSys LabChip G2-3</td>
</tr>
<tr>
<td>Veredus Laboratories VereMTB™</td>
<td>Cepheid Xpert® Ultra Xpress-XDR</td>
</tr>
<tr>
<td>YD REBA MTB-XDR REBA MTB-Rifa</td>
<td>Northwestern GHT/Quidel</td>
</tr>
<tr>
<td>Hain LATE PCR Lights on Lights off MTB-PZA</td>
<td>Ustar MTB</td>
</tr>
<tr>
<td>Illumina Next-Generation Sequencing</td>
<td>Akkoni MDR-TB</td>
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<thead>
<tr>
<th>2015</th>
<th>2016</th>
<th>2017</th>
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<tr>
<td>WHO-endorsed</td>
<td>Limited commercial availability</td>
<td>In development</td>
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Date: 20 November 2014
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<tr>
<td>A highly sensitive and specific test for sputum-based pulmonary TB detection (NAAT or other) at the level of a microscopy center with the purpose of supporting initiation of TB therapy within the same clinical encounter (or same day) with a higher sensitivity of smear microscopy.</td>
<td></td>
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</tr>
<tr>
<td><strong>Target population</strong></td>
<td>Countries with medium to high TB prevalence (WHO Categories). Target groups are all patients suspected of having pulmonary TB and able to produce sputum.</td>
<td></td>
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<tr>
<td><strong>Setting</strong></td>
<td>Microscopy center level (primary health centers with attached peripheral laboratories)</td>
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<tr>
<td><strong>User</strong></td>
<td>Microscopy center technicians</td>
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## Drug-susceptibility tests

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<td><strong>Clinical purpose</strong></td>
<td>A highly sensitive and specific test for the rapid detection of drug resistance to inform decision-making concerning optimal first line therapy (HRZE, REMox, vs. PaMZ), possibly presence of additional second line drug resistance and need for further testing.</td>
<td></td>
</tr>
<tr>
<td><strong>Target population</strong></td>
<td>Countries with medium to high TB prevalence (WHO Categories). Target groups are all patients suspected of having TB with a special focus on those at high risk of morbidity and mortality from drug-resistant TB such as people living with HIV, and those at high risk of having MDR-TB</td>
<td></td>
</tr>
<tr>
<td><strong>Drugs</strong></td>
<td>RIF &gt; FQ (incl. Mox)&gt; INH = PZA &gt; AG/CAP</td>
<td></td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>Microscopy center level</td>
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Interplay of novel diagnostic tests

Status quo:
- Smear microscopy
- Xpert
- Very little Culture
- Even less DST
POTENTIAL MARKET FOR PRIORITY TPPS
PARTNERS: MCGILL, FIND, UNITAID, NDWG & NTP IN COUNTRIES

POTENTIAL IMPACT OF PRIORITY TPPS
PARTNERS: HOPKINS, AIGHD, LSHTM, HARVARD, TB-MAC, MCGILL, FIND
Thank you - Questions

**McGill**
- Sandra Kik
- Madhu Pai

**FIND**
- Mark Perkins
- Catharina Boehme
- David Dolinger

**Others**
- CPTR working group
- WHO team
- Martina Casenghi – MSF
- Carol Jefferson
- Janet Ginnard - UNITAID

**BMGF team**
- Jim Gallarda
- Michael Kimerling
- Jennifer Gardiner

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[Bill & Melinda Gates Foundation logo]
Additional slides
Target product profile attributes

• Scope
  • The clinical purpose of the test (e.g. triage)
  • Target population (children, adults, community or HIV-clinic)
  • Intended level of implementation in the health care system and user

• Performance characteristics
  • Sensitivity/specificity for TB detection
  • Treatment monitoring
  • DST

• Operational characteristics
  • Sputum type
  • Manual steps
  • Infrastructure requirements (e.g. power, temperature control)
  • Time to result (how important is same-day results?)
  • Requirements for reporting and connectivity
  • Importance of subgroups such as HIV-infected and children

• Price targets