The Biomarker Pipeline for Active TB detection

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The problem: Many biomarker studies, limited impact

- Numerous reports on biomarkers from exploratory studies
- Often based on few, poorly characterized samples
- Limited independent confirmation and prospective validation
- Little translation into clinically useful tools
- Limited knowledge and data sharing
- Failure to articulate the intended use case

A TB Biomarker Database
to accelerate the translation of biomarkers into products

What data?

Quality Filter

How?

Why?
The intended use cases

TPP1: A non-sputum based TB diagnostic test for the purpose of initiating treatment

OR

TPP2: A triage test using a non-sputum sample that identifies patients for confirmatory testing

on-going systematic search!

Latent to Active Progression  Active  Treatment Monitoring
### «Active TB detection»: Relevant high-priority TPPs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TPP1: Non-sputum based detection test</th>
<th>TPP2: Triage test (Rule-out)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Goal</strong></td>
<td>● Biomarker based test</td>
<td>● identify patients with any symptoms of or risk factors for active (pulmonary) TB</td>
</tr>
<tr>
<td></td>
<td>● non-sputum samples</td>
<td>● rule-out disease or refer to confirmatory testing</td>
</tr>
<tr>
<td></td>
<td>● for the purpose of initiating treatment</td>
<td></td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>&gt;80% overall</td>
<td>&gt;95% overall</td>
</tr>
<tr>
<td></td>
<td>≥98% SS+</td>
<td>&gt;90% overall</td>
</tr>
<tr>
<td></td>
<td>≥68% S-C+</td>
<td></td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>≥98%</td>
<td>&gt;80%</td>
</tr>
<tr>
<td><strong>Time-to-result</strong></td>
<td>&lt;20 mins</td>
<td>&lt;5 mins</td>
</tr>
<tr>
<td></td>
<td>&lt;60 mins</td>
<td>&lt;30 mins</td>
</tr>
<tr>
<td><strong>Price</strong></td>
<td>&lt;US$ 4</td>
<td>Not needed</td>
</tr>
<tr>
<td></td>
<td>&lt;US$6</td>
<td>Small, portable, or handheld, &lt;1 kg</td>
</tr>
<tr>
<td><strong>Instrument</strong></td>
<td>Not needed</td>
<td>Not needed</td>
</tr>
<tr>
<td></td>
<td>Small, portable, or handheld, &lt;1 kg</td>
<td>Small, portable, or handheld, &lt;1 kg</td>
</tr>
<tr>
<td><strong>Manual preparation of samples</strong></td>
<td>Integrated or no manual preparation</td>
<td>Integrated or no manual preparation</td>
</tr>
<tr>
<td></td>
<td>Limited number of steps, no precise measuring</td>
<td>only 2 steps</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>Health post without lab and higher levels</td>
<td>Community or village level or higher levels</td>
</tr>
<tr>
<td></td>
<td>Primary health-care clinics with lab or microscopy center or higher</td>
<td>Health post or primary health-care clinics or higher</td>
</tr>
</tbody>
</table>
Performance targets

**TPP 1:** Rapid biomarker-based non-sputum-based test for detecting TB

**TPP 2:** Triage test (Rule-out)

Optimal targets ★
Minimal targets ★★

«Fill» the database with published evidence

**Approach**

- Systematic literature search to synthesize biomarker knowledge
- Search for all «target conditions»: risk of progression, detection of active TB, treatment monitoring
- Full-text extraction for «detection of active TB»

**Goals**

- Show the status of the TB biomarker pipeline
- Identify the most promising biomarkers and biomarker classes for POC test development
- Data input for the database

**Included studies**

- Studies reporting on diagnostic performance of «non-DNA» biomarkers
- Studies ≥30 participants or human samples
- Published 2010 - 2015
Included studies

5549 records identified through database searching + 8 from other sources

3417 records after duplicates removed

2253 excluded on the basis of title or abstract
- 1611 target condition
- 125 animal
- 161 language
- 91 index test
- 265 review

1164 full-text articles screened

876 excluded on the basis of title or abstract
- 56 target condition
- 3 animal
- 3 language
- 546 index test
- 10 no performance data
- 50 size ≤30 samples/participants
- 208 other

288 studies included describing 413 biomarkers or signatures

preliminary unpublished
<table>
<thead>
<tr>
<th>Biomarkers or Biomarker Signatures</th>
<th>Host n=373</th>
<th>Protein biomarkers n=245</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>antibody</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cytokines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>protein peak</td>
</tr>
<tr>
<td></td>
<td></td>
<td>enzymes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cell surface protein</td>
</tr>
<tr>
<td></td>
<td></td>
<td>glycoprotein</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lectin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>transmembrane protein</td>
</tr>
<tr>
<td>Transcriptional biomarkers n=35</td>
<td></td>
<td>microRNA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mRNA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hematological markers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>metabolomic biomarkers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>other</td>
</tr>
<tr>
<td>Pathogen n=40</td>
<td></td>
<td>Protein biomarkers n=12</td>
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<tr>
<td></td>
<td></td>
<td>antigens</td>
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<td></td>
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<td>transcriptional biomarkers</td>
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<tr>
<td></td>
<td></td>
<td>mycolic acid</td>
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<tr>
<td></td>
<td></td>
<td>lipid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VOC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>other</td>
</tr>
</tbody>
</table>

Not for on-line publication
The biomarker pipeline for active TB

Level of Evidence

<table>
<thead>
<tr>
<th>DISCOVERY</th>
<th>EXPLORATORY STUDY</th>
<th>PROSPECTIVE COHORT</th>
<th>META-ANALYSIS WHO REVIEW</th>
</tr>
</thead>
<tbody>
<tr>
<td>only statistical significance</td>
<td>case control design</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Quality of Evidence

- REFERENCE STD CULTURE BASED?:
  - 67%
  - 78%
  - 84%

- CONTROL GROUP Other Resp. Dis.?:
  - 18%
  - 18%
  - 77%

- CONSECUTIVE SAMPLING?:
  - 17%
  - 13%
  - 26%

- BLINDING?:
  - 15%
  - 24%
  - 49%

- STUDY SIZE ≥100 ?
  - 18%
  - 53%
  - 42%

preliminary unpublished
Blood biomarker entries with culture based reference std.

Not for on-line publication
Blood biomarker entries with control group other respiratory disease (ORD)

Not for on-line publication
Blood biomarker entries with control group other respiratory disease (ORD)

- Tendency towards biomarker signatures
- Host markers (cytokines, mRNA, «host proteins»)
- Studies are relatively small
- Study bias?

70% Retrospective timing, 58% Case control, 50% no blinding, etc.
Example for high quality biomarker evidence: Host signature

Diagnostic performance of a seven-marker serum protein biosignature for the diagnosis of active TB disease in African primary healthcare clinic attendees with signs and symptoms suggestive of TB

- n=716 (five African countries)
- Prospective cohort
- Adults with symptoms
- Sensitivity 94%; Specificity 73% (test set)
Next steps

- Development of the TB Biomarker Database
- Development of a consensus-based biomarker evaluation and grading framework

NDWG Biomarker Task Force
Thank you!

Emily MacLean
Sophie Huddart
Madhukar Pai

Claudia M. Denkinger
Seda Yerlikaya

NDWG Biomarker Task Force