TPP for test that predicts progression to active TB

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Head of TB Programme at FIND

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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
Diagnostic cascade – the patient perspective

First symptoms

Community health worker/Health post/Primary health care

Referral/persistent symptoms

POC test for diagnosis
POC Triage test

Test that predicts progression from TBI

Second test/results

Expanded DST for patients suffering from resistant TB

POC test for diagnosis
POC Triage test

Smear replacement test

DST for regimen selection

Expanded DST for patients suffering from resistant TB

Treatment monitoring test

Test of cure
Process for TPP development

Step 1: Drafted TPP by FIND and reviewed with experts

Step 2: Meeting May 2015 with experts organized by NDWG, WHO and FIND > revised document

Step 3: Survey with a larger stakeholder group also leveraging the WHO LTBI taskforce

Step 4: Final review in stakeholder meeting prior to finalization
Tests we have available

- IGRAs, skin tests (TST, C-Tb, Diaskintest)

- Available data suggest that the majority (>95%) of those with a positive IGRA or TST result (one time testing) will never develop TB (IRR of ~2 over TST or IGRA negative patients)

- Lack the capacity to differentiate between recent and remote infection

- Not useful in monitoring response or cure with preventive therapy for LTBI
What are we looking for in LTBI tests?

- **Individual patient diagnosis**
  - A test that diagnosis infection with better predictive value of who will progress to active disease (but differentiates from active TB)
  - A test of cure that allows to say who received sufficient therapy/predicts relapse at the end of therapy
  - A test that is able to detect re-exposure after treatment was taken

- **Epidemiology/ Research**
  - A test for surveillance of who is infected and can inform burden of disease in the absence of therapy
  - Identify recent transmission
Test for TB infection

Pulmonary vs Extrapulmonary

- Identifies TBI that never progresses
- Identifies infection that progresses
- Detects cure/predicts relapse/useful in re-exposure

- Clinical disease
- Bacterial replication maintained at a subclinical level by the immune system
- Infection controlled with some bacteria persisting in non-replicating form
- Infection eliminated in association with T cell priming
- Infection eliminated without priming antigen-specific T cells

Barry Nature Reviews 2009
What are we looking for in LTBI tests?

### Individual patient diagnosis
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### Epidemiology/Research
- A test for surveillance of who is infected and can inform burden of disease in the absence of therapy
- Identify recent transmission
Definitions – clinical and research

**TB infection:**
- Any person with a positive test for TB infection (TST≥5mm, positive IGRA according to manufacturer’s instructions)
- Without microbiological, radiological, or clinical evidence of active TB.

**Subclinical TB disease (for research purposes)**
- Asymptomatic patients with evidence of TB on radiographic and/or microbiological examination or with development of TB within 2 months of initial evaluation.
- Two forms of subclinical TB are conceivable:
  - disease is early and still contained (mostly immunocompetent patients) or
  - disease is early but not contained however the patient is unable to mount an inflammatory response that would result in symptoms (mainly immunocompromised patients).
- A subset of patients with subclinical disease (primarily immunocompetent patients) will not progress to active disease.

**TB disease:**
- Symptomatic patients
- With compatible clinical and/or radiology and/or histology for TB and a positive microbiological test and started TB treatment (confirmed TB),
- or with compatible clinical and/or radiology and/or histology for TB and started TB treatment (clinical TB).
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Scope of the test

**Who do we want to test?**
- People at risk of TBI and at risk for progression
- People where active TB has been ruled out

**Use cases:**
- High-prevalence settings in patients with high risk of progression to active TB (e.g. HIV, recent exposure)
- Low-medium prevalence settings aiming for elimination

**Do we need a point-of-care test?**
- No immediate clinical decision necessary
## Scope of Test

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Optimal</th>
<th>Minimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goal of test/Intended use</td>
<td>Biomarker-based test that can be used to <strong>predict risk of progression</strong> to active TB from TB infection (TBI) within the next 2 years, with the ability to <strong>rule out active TB</strong>. Ideally the test result should <strong>decrease or revert to negative</strong> with treatment and thus allow an assessment of treatment success or cure and consequentially also reinfection.</td>
<td>Biomarker-based test that can be used to predict risk of progression to active TB from TB infection within the next 2 years. As this test may also be positive in patients with active TB, identification of these individuals needs to be done by a highly sensitive test</td>
</tr>
<tr>
<td>Target user of the test</td>
<td>Health care workers with no or minimal laboratory training e.g. nurses</td>
<td>Health care workers with laboratory training e.g. skilled laboratory technicians</td>
</tr>
<tr>
<td>Setting</td>
<td>Health post</td>
<td>Referral facilities with some laboratory facilities</td>
</tr>
</tbody>
</table>
### Diagnostic performance – How good is good enough?

<table>
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<tr>
<th>Characteristic</th>
<th>Optimal</th>
<th>Minimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic sensitivity for progression to active TB</td>
<td>≥90% sensitivity</td>
<td>≥75% sensitivity</td>
</tr>
<tr>
<td>Diagnostic specificity for risk of progression to active TB</td>
<td>≥90% sensitivity</td>
<td>≥75% specificity</td>
</tr>
<tr>
<td>Diagnostic specificity for TBI (able to differentiate from active TB)</td>
<td>&gt;97%</td>
<td>NA (expected to be positive in active TB)</td>
</tr>
</tbody>
</table>
2-step approach to determining performance targets

Premise: risk/benefit-profile is key, thus PPV and NNT useful metrics for the determination of performance targets

- PPV captures patient perspective (If test+, how likely am I to have disease?)
- NNT captures clinician/PH perspective (If treating all test+, how many do I need to treat to prevent one case?)

[Of course PPV and NNT are closely linked to one another]

Step 1. Clarify what values of PPV and NNT are currently found acceptable to patients/clinicians/policy makers
- Based on tests and groups for whom IPT is currently recommended by WHO
- Estimate PPV/NNT in those groups

Step 2. Assess what combinations of sensitivity/specificity are compatible with acceptable values of PPV and NNT
- Look at contours of PPV/NNT across combinations of Se/Sp
- Investigate differences between key subgroups
‘Number Needed to Treat’ according to Sens/Spec for risk of progression

2-year cumulative incidence: 2%
Effectiveness of IPT: 50%

TST/IGRA estimates based on WHO review
‘Positive Predictive Value’ according to Sens/Spec for risk of progression

TST/IGRA estimates based on WHO review
Reproducibility

- If quantitative outcomes of a test are measurable
- Reproducibility: Inter-assay CV =< 10.0% at high and low extremes of the assay

Reproducibility of Interferon Gamma (IFN-γ) Release Assays
A Systematic Review

Saloua Tagmouti¹, Madeline Slater², Andrea Benedetti³, Andrea Benedetti⁴, Sandra V. Kik³,⁴, Niaz Banaei⁵, Adithya Cattamanchi⁶, John Metcalfe⁶, David Dowdy⁷, Richard van Zyl Smit⁸, Nandini Dendukuri⁹, Madhukar Pai³,⁴, and Claudia Denkinger³,¹⁰
Can we aim for a test with better predictive value in a first step (at the cost of IGRAs currently) and then improve complexity at a later step?
## Selected operational characteristics

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<tr>
<th>Characteristic</th>
<th>Optimal</th>
<th>Minimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of steps to be performed by operator</td>
<td>&lt; 2, no timed steps</td>
<td>&lt; 10, 1-2 timed steps</td>
</tr>
<tr>
<td>Volume measurements</td>
<td>None</td>
<td>Measuring device provided with kit</td>
</tr>
<tr>
<td>Sample preparation</td>
<td>None or fully integrated</td>
<td>Allows for centrifugation/ incubation</td>
</tr>
<tr>
<td>Time to results</td>
<td>&lt; 24 hours</td>
<td>2-5 days</td>
</tr>
<tr>
<td>Operating Temperature</td>
<td>Between 5 and 50°C, 90% humidity</td>
<td>Between 5 and 30°C, 70% humidity</td>
</tr>
<tr>
<td>Reagents</td>
<td>Self-contained within test kit</td>
<td>Up to 2 external reagent, reconstitution not required</td>
</tr>
<tr>
<td>Instrumentation</td>
<td>No instrument</td>
<td>Preferably instrument free. If instrument: Small, portable or hand-held instrument (&lt;1kg) that can operate on battery or solar in places with interrupted power supply</td>
</tr>
<tr>
<td>Internal Quality control</td>
<td>Included positive control</td>
<td></td>
</tr>
<tr>
<td>Power requirements</td>
<td>Ideally instrument free test; all equipment with rechargeable battery lasting up to 8 hours</td>
<td>110-220 V AC current; UPS for power failures</td>
</tr>
<tr>
<td>Electronics and software</td>
<td>None</td>
<td>Integrated</td>
</tr>
<tr>
<td>Training</td>
<td>&lt;1 day dedicated training for non-laboratory trained health personnel</td>
<td>3-7 days dedicated training for a laboratory trained health personnel</td>
</tr>
</tbody>
</table>
What can a test cost?

- Considering performance characteristics of the test
- Considering package of test and treat (% completion; success rates of therapy)
- Consider how often a test needs to be performed
- Cost-effectiveness studies: several have demonstrated cost-effectiveness for IGRAs but variable quality and input parameters

How Methodologic Differences Affect Results of Economic Analyses: A Systematic Review of Interferon Gamma Release Assays for the Diagnosis of LTBI

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Affordability considering priority setting in countries
thank you/mercì/danke/gracias/obrigado

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