Triage Testing for TB
McGill Advanced TB Dx Course 2018

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Harvard Medical School
10.4 million people FELL ILL FROM TB
That's 28,500 people every day

6.1 million people had ACCESS TO QUALITY TB CARE

4.3 million people MISSED OUT

WHO Global TB Report 2017
Pathy Nature 2015
Mind the Gap:
TB Cascade of Care in India

Prevalent cases: 2,700,000
Reached TB diagnostic centers: 1,938,027 (72%)
Diagnosed with TB: 1,629,906 (60%)
Registered for treatment: 1,417,838 (53%)
Completed treatment: 1,221,764 (45%)
Recurrence-free survival: 1,049,237 (39%)

760,000 (25%) patients never seek government TB care
520,000 (20%) seek government care but are never started on treatment

Diagnostic delays experienced by PTB patients in India

Sreemareddy IJTL 2014
Diagnostic Gap – what about Xpert?

- WHO stated Xpert may be used as initial test (2016 update)
- 52% of 29 HBCs have adopted Xpert for all
- Only 50% of HBCs providing Xpert to ‘high risk’ have widely implemented it
- Xpert often centralised
- Limited impact

PERCENTAGE OF PEOPLE WITH TB DIAGNOSED AND NOTIFIED TO WHO IN OUT OF STEP COUNTRIES (2015) *

<table>
<thead>
<tr>
<th>50-74%</th>
<th>25-49%</th>
<th>&lt;25%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armenia</td>
<td>Brazil</td>
<td>Nigeria</td>
</tr>
<tr>
<td>China</td>
<td>Georgia</td>
<td>Indonesia</td>
</tr>
<tr>
<td>Russia</td>
<td>Mozambique</td>
<td></td>
</tr>
</tbody>
</table>

MSF Out of Step Report 2017
WHO Xpert policy statement 2016
## Target Product Profiles (TPPs)

<table>
<thead>
<tr>
<th>Target product profiles for potential new TB diagnostic tests</th>
<th>Prioritisation by key stakeholders</th>
<th>Impact</th>
<th>Market</th>
<th>Implementation and scalability</th>
<th>Score</th>
<th>Priority rank</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients and community advocates</td>
<td>National TB programmes</td>
<td>Field practitioners</td>
<td>Research</td>
<td>Potential to reduce TB incidence</td>
<td>Potential to reduce TB morbidity and mortality</td>
</tr>
<tr>
<td>Triage, rule out and systematic screening test</td>
<td>High</td>
<td>High</td>
<td>Medium</td>
<td>High</td>
<td>Medium</td>
<td>High</td>
</tr>
<tr>
<td>A Triage test for those seeking care</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>B A HIV/ART clinic-based test to rule out active TB</td>
<td>Medium-high</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Medium</td>
<td>High</td>
</tr>
<tr>
<td>C Systematic screening test for active case finding</td>
<td>High</td>
<td>High</td>
<td>Medium-high</td>
<td>Medium</td>
<td>High</td>
<td>Medium</td>
</tr>
<tr>
<td>Treatment monitoring test</td>
<td>High</td>
<td>High</td>
<td>Medium</td>
<td>Medium</td>
<td>Low</td>
<td>Medium</td>
</tr>
<tr>
<td>H Treatment monitoring test (test for cure)</td>
<td>High</td>
<td>High</td>
<td>Medium</td>
<td>Medium</td>
<td>Low</td>
<td>Medium</td>
</tr>
<tr>
<td>Predictive test for latent TB infection</td>
<td>High</td>
<td>High</td>
<td>Medium</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>I Predictive test for Latent TB infection at high risk of active TB</td>
<td>High</td>
<td>High</td>
<td>Medium</td>
<td>High</td>
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</tbody>
</table>
Potential value of a Triage or Rule Out TB Test

• Transmission is not from TB patients on effective treatment but rather from those with unsuspected TB
• A triage test for TB could have a large global market and a high impact potential to reduce TB
• Decision analysis modeling demonstrated that a TB triage test with equal sensitivity to Xpert and 75% specificity at a cost of $5 could reduce diagnostic costs by ~40% if Xpert was only performed in patients with a positive triage test
• Goal – enhance case finding and ↑ Xpert affordability
Symptom screening

- WHO recommends three options: cough >2 weeks vs. any symptom vs. CXR followed by diagnostic test algorithm depending on availability of smear/Xpert/CXR
- Sensitivity variable: 25-50% for prolonged cough vs. 77-84% for any symptom
- Specificity may drop from ~92-96% for prolonged cough to 67-74% for any TB symptom
- Clinic-based exit screening: 20-50% with identified TB symptoms undergo sputum-based TB testing

References:
- Van’t Hoog BMC ID 2014
- Chihota PLoS One 2015
- Claasens IJTLD 2013
- Roy JAIDS 2016
- Kweza IJTLD 2018
Is cough the optimal screening strategy? How does this vary by setting?

- 10,901 patients screened at a tertiary hospital in Lima
  - Cough > 2 weeks: 36 (0.3%) [any cough: 250 (2.2%)]
  - Smear+ PTB: 16 (44.4%), 5 of whom had new Dx
- 8,028 patients screened at PHCs
  - Cough or resp symptoms: 259 (3.2%)
  - Smear + PTB: 11 (4.2%)

- 19,000 patients screened: 16 previously cases of previously undiagnosed TB detected
  - need to understand local epi to adapt screening

FAST, unpublished data
Frequency of cough varies across studies

- Rapid literature review: 297 abstracts, 52 full-texts, extracted from 17 papers
- Total patients screened: 31,267 (median, wide range)

- Any cough 13% (mean, range 2-90%)
- Prolonged cough 3% (median 1-35%)
- Patients with cough dx with TB: 9% (range 2-24%)

➢ Cough prevalence/epidemiology is highly variable

FAST, unpublished data
Triage Test: Definition, Characteristics

- To test people with TB symptoms to determine who requires confirmatory or follow on TB diagnostic testing (for triage test-positive patients) versus investigation of non-TB aetiologies (for triage test-negative patients)
- Can be used as part of PCF versus ACF
- Needs high NPV (rule out)
- Optimal use in adults and children with symptoms and signs of any form of active TB (minimal for active PTB)
- Ideally non-sputum based, scalable, affordable
- Different use case to screening test
Triage Test 
Performance Criteria

• Optimal sensitivity >95%
• Minimal sensitivity >90%
• Optimal specificity >80%
• Minimal specificity >70%
Triage Test: Role

- Facilitate earlier diagnosis by increasing the number of patients with TB symptoms who undergo TB testing
- Improve PPV of follow-up testing
- Reduce the patient and health system costs by decreasing the number of necessary follow-up tests, which will typically involve more expensive molecular diagnostics such as Xpert

- Primarily for use at lower levels of healthcare system
- PPV will vary according to prevalence
Triage Test: Clinical Pathway

Patient being evaluated for TB symptoms (PCF vs. ACF)

Patients reporting one or more TB symptoms (cough, haemoptysis, fever, night sweats or weight loss) vs. patients with cough > 2 weeks undertake triage test

Patients with + triage test undergo or are referred for confirmatory test (typically Xpert)

- If + confirmatory test, patients should be started on therapy unless further drug susceptibility testing is required e.g. if Xpert RIF-resistant.
- If - confirmatory test, evaluation for other causes of symptoms should be pursued
Location, Location, Location: where are TB services in HBCs?

### Table: Availability of tuberculosis diagnostic and treatment services

<table>
<thead>
<tr>
<th>Country</th>
<th>Triage (CXR)</th>
<th>Sputum smears</th>
<th>DST (Xpert, LPA, culture)</th>
<th>LTBI testing</th>
<th>DST TB Rx</th>
<th>MDR-TB Rx initiation</th>
<th>MDR-TB Rx continuation</th>
<th>LTBI Rx</th>
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<tbody>
<tr>
<td><strong>Upper middle income</strong></td>
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<td>Angola</td>
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<td>South Africa</td>
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<td>Thailand</td>
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<td><strong>Lower middle income</strong></td>
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<td>Papua New Guinea</td>
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<td><strong>Low income</strong></td>
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<td>DR Congo</td>
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<td>Ethiopia</td>
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<td>Mozambique</td>
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</tbody>
</table>

**Figure 1:** Availability of tuberculosis diagnostic and treatment services across various health-care levels in 14 highest burden countries

CXR = chest radiography. LTBI = latent tuberculosis infection. DS = drug sensitive. DST = drug sensitivity testing. MDR-TB = multidrug-resistant TB. L0 = care by community or village health workers or at health posts. L1 = microscopy centres or primary health centres. L2 = district hospitals or community health centres. L3 = reference or tertiary hospitals. TB = tuberculosis.

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Huddart Lancet Global Health 2016
Triage Test: Clinical populations/settings

- Key initial study population for the evaluation of triage tests will be adults with symptoms of PTB (need for reference standard which is challenging in children)
- Populations of interest: paucibacillary/smear-negative TB, extrapulmonary TB (test would need to be non-sputum based) and paediatric TB
- Patient enrolment & testing should ideally be performed in the primary settings of intended use i.e. L0-L2
- N.B. prevalence at L0 lower -> need higher specificity
- TT may be based on host markers which may vary
Triage Test: Evaluation

- Ideally culture as reference standard, consider Xpert
- For impact (vs. DTA) studies, results of triage testing followed by confirmatory testing e.g. with Xpert should be compared to confirmatory testing alone or other algorithms
- Triage tests may detect early or subclinical TB, which may be culture negative -> needs adequate follow up
- Should consider using clinical or composite reference standard or latent class analysis
- Other comparators e.g. human readers for CXR? CRP?
Triage Test: Other considerations

• Sample type- ideally non sputum based
• Specimen flow- ideally integrated sample preparation, no precise timing required, disposable, low maintenance
• Evaluation on banked specimens may aid development but needs to demonstrate pre-analytic stability

• Test development may involve machine learning e.g. CAD versus ROC curve analysis of biomarker signatures e.g. breath testing
Triage Test: Limitations

• Reliant on symptom screening
• Test performance limitations – false negatives that may still warrant confirmatory testing or empiric therapy, false positives result in high volume of confirmatory tests needed
• Implementation is critical – no test is a magic bullet and impact relies on functional systems of care i.e. linkage to confirmatory testing -> results -> Rx initiation
• Importance of implementation studies to evaluate process indicators and other benefits (costs, access)
TB Diagnostic Pipeline

Impact
- Public health impact
- Individual impact

Pending biomarker work
- Active case detection
- Syndromic test
- Latent to active test

Active development work
- Triage test
- Passive case detection
- Drug susceptibility testing

Transformational
Critical
Moderate
Low

Likelihood of FIND's success
- Technical feasibility
- Availability of funding
- Fit with FIND capabilities/strategy
Triage test questions?

- Current tests e.g. CXR -> ↑sensitivity but ↓specificity
- Where in the testing pathway should triage test be placed?
  - Triage at community health post level vs. PHCs?
  - Triage for patients in healthcare facilities?
  - Screening for asymptomatic patients e.g. PLHIV?
- Who is the target user? CHWs, nurses, doctors?
- What sort of tests can be used in different settings e.g. widespread applicability of CAD4TB?
- What should follow up strategy be? How to ensure?
rnathavi@bidmc.harvard.edu
Twitter: @ruvandhi

NIH/NIAID K23 AI132648 01/A1
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Optimal requirements</th>
<th>Minimal requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scope</td>
<td>To develop a test that can be used during a patient's first encounter with the health-care system to identify patients with any symptoms of or risk factors for active TB, including patients coinfected with HIV, those who do not have TB and those who need referral for further confirmatory testing.</td>
<td>To develop a test that can be used during a patient's first encounter with the health-care system to identify patients with any symptoms of or risk factors for active pulmonary TB, including patients coinfected with HIV, those who do not have TB and those who need referral for further confirmatory testing.</td>
</tr>
<tr>
<td>Goal</td>
<td>Adults and children with signs and symptoms of active TB at any site in countries with a medium prevalence to a high prevalence of TB as defined by WHO*.</td>
<td>Adults and children with signs and symptoms of active pulmonary TB in countries with a medium prevalence to a high prevalence of TB as defined by WHO*.</td>
</tr>
<tr>
<td>Target population</td>
<td>Community health workers and informal providers who have had a minimum of training.</td>
<td>Health workers trained to the level of auxiliary nurses.</td>
</tr>
<tr>
<td>Target user of the test b</td>
<td>Community level or village level or higher levels of the health-care system.</td>
<td>Health posts and primary-care clinics or higher levels of the health-care system.</td>
</tr>
<tr>
<td>Setting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostic sensitivity c</td>
<td>Overall sensitivity should be &gt; 95% when compared with the confirmatory test for pulmonary TB no lower range of sensitivity was defined for extrapulmonary TB.</td>
<td>Overall sensitivity should be &gt; 90% compared with the confirmatory test for pulmonary TB.</td>
</tr>
<tr>
<td>Diagnostic specificity c</td>
<td>Specificity should be &gt; 80% compared with the confirmatory test</td>
<td>Specificity should be &gt; 70% compared with the confirmatory test</td>
</tr>
<tr>
<td>Operational characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample type</td>
<td>Non-sputum samples (such as urine, oral mucosal transudates, saliva, exhaled air or blood from a finger-stick)</td>
<td>Sputum; non-sputum samples are preferred (such as urine, oral mucosal transudates, saliva, exhaled air, or blood from a finger-stick; imaging technology)</td>
</tr>
<tr>
<td><strong>Manual preparation of samples (steps needed after obtaining sample)</strong></td>
<td>Sample preparation should be integrated or manual preparation should not be required (excluding waste disposal); precise timing and measuring should not be required</td>
<td>2 steps (excluding waste disposal); precise timing and measuring should not be required</td>
</tr>
<tr>
<td>---</td>
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</tr>
<tr>
<td><strong>Time to result</strong></td>
<td>&lt; 5 minutes</td>
<td>&lt; 30 minutes</td>
</tr>
<tr>
<td><strong>Instrument and power requirement</strong></td>
<td>None</td>
<td>Small, portable or handheld device (weighting &lt; 1 kg); should have an option for battery power or solar power</td>
</tr>
<tr>
<td><strong>Maintenance and calibration</strong></td>
<td>Disposable, no maintenance required</td>
<td>Preventative maintenance should not be needed until after 1 year or 1000 samples; only simple tools and minimal expertise should be required; an alert to indicate when maintenance is needed should be included; the device should be able to be calibrated remotely, should calibrate itself, or no calibration should be required</td>
</tr>
<tr>
<td><strong>Operating temperature and humidity level</strong></td>
<td>Between +5 °C and +50 °C with 90% humidity</td>
<td>Between +5 °C and +40 °C with 70% humidity</td>
</tr>
<tr>
<td><strong>Result capturing, documentation and data display</strong></td>
<td>An instrument-free test with visual readout and with the ability to save results using a separate, attachable reader</td>
<td>The test menu must be simple to navigate; the instrument should have an integrated LCD screen, a simple keypad or touch screen, and the ability to save results using either the instrument or a separate reader</td>
</tr>
<tr>
<td><strong>Internal quality control</strong></td>
<td>Internal controls should be included for processing the sample and detecting TB</td>
<td>Internal control included only for processing the sample</td>
</tr>
<tr>
<td><strong>Pricing</strong></td>
<td>Price of individual test* (costs of reagents and consumables only; after scale-up; ex-works)</td>
<td>&lt; US$ 1.00</td>
</tr>
</tbody>
</table>