We need better tools & we need to better use existing tools!

Number of TB cases notified vs estimated (millions)

- 30% of patients remain undiagnosed or unreported

Number of MDR/RR-TB cases detected vs estimated (thousands)

- 40% of MDR/RR-TB patients remain undiagnosed or unreported
Which TB diagnostics do we need?
Priorities defined in TPPs, aligning product specifications with patient & user needs

1. Triage tests
2. Non-sputum (biomarker) based Dx tests
3. Smear-replacement tests
4. Drug susceptibility tests
Rigorous evaluation is critical — but how?

JID supplement: “Generating high-quality evidence for policy on WHO high-priority TPPs for TB diagnostics”

- Developed with WHO and >50 TB diagnostics researchers
- Lays out study design considerations separately for each TPP

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</table>
### Early development

- **Molecular – detection/DST**
  - Hydra 1K (InnoLife)
  - LifeArc/Univ. St Andrews – Molecular Bacterial Load Assay
  - PNAClamp (Panagene)
  - End-to-end targeted sequencing for DR-TB (Veila)
  - Targeted sequencing for DR-TB (Clamedi)

- **Culture-based – detection/DST**
  - BNP Middlebrook (NanoLogix)
  - MYCOLOR TK BNP (Salubris)
  - Phage-based tests

- **Cellular response/transcriptomic – detection/latent and latent-to-active progression**
  - Abbott – Incipient TB Assay
  - Becton-Dickinson – T-cell Immune Profiling
  - Qiagen – Q-FIT-Predict
  - Qiagen – QIA-TB Signature
  - Biomérieux/Bioaster – Host signature
  - LG Chem - Advansure™ i3 TB-IGRA

- **Digital diagnostics & AI-based tools**
  - Digital stethoscopes
  - POC Ultrasound
  - CDS tools for TB

### Late or completed development

- **Molecular – detection/DST**
  - AccuPower TBA/MDR RT PCR (Bioneer)
  - FluorType XDR (Hain)
  - TruArray MDR-TB (Akkon)
  - Metrino (Qeesan)
  - Mycobacteria RT PCR (CapitalBio)
  - VireMTB (Vereas Laboratories)
  - Anyplex series (Seegene, Korea)
  - Targeted sequencing for DR-TB (Genoscreen, ABL)

- **Culture-based – detection/DST**
  - MGIT Bedaquiline (BD)
  - QMAB DST (QuantaMatrix)

- **Cellular response/transcriptomic – detection/latent and latent-to-active progression**
  - TAM-TB (Beckman Coulter)
  - RTT TB (Lophius Biosciences)
  - C-Tb skin test (Serum Institute India)
  - SD Biosensor – Standar E/F feron test
  - LG Chem – Avenure TB-IGRA
  - Qiangen – QFT Access
  - Boditech - iChroma IGRA-Tb
  - rBiopharm – IR-10 IGRA

### On pathway to WHO evaluation

- **Molecular – detection/DST**
  - RealTime MTB RIF/INH (Abbott)
  - BD MAX MDR-TB (Becton-Dickinson)
  - FluorType MTBDR (Hain)

- **Culture-based – detection/DST**
  - Sensititre MYCOTB AST Plate (Thermo Fisher)

- **Cellular response/transcriptomic – detection/latent and latent-to-active progression**
  - Quantiferon Access (QIAGEN)

- **Digital diagnostics & AI-based tools**
  - CAD4TB (Delft Imaging Systems)
  - qXR (Qure.ai)
  - Lunit (Fujifilm)

### Digital diagnostics & AI-based tools

- **Breath/VOC biomarker – detection**
  - TB Breathalyser (Rapid Biosensor Systems)
  - Aeonose (The eNose Company)

- **Antigen, antibody and biomarker – detection**
  - C-reactive protein
  - SILVAMP TB LAM (Fujifilm)
TB diagnostics recommended by WHO over the past decade

- **2007**: MTB rapid speciation (TAUNS, SD/Alere)
- **2008**: TB MDR-TB MGIT liquid culture (BD)
- **2009**: 1st line drugs LPA – TB (1st gen) (Hain Lifescience)
- **2010**: TB iLED fluorescent microscope (ZEISS)
- **2014**: MTB/RIF (GenoXpert; Cepheid)
- **2015**: 1st line drugs LPA – TB (2nd gen) (Hain Lifescience; NIPRO Corporation)
- **2016**: 2nd line drugs LPA – TB (Hain Lifescience)
- **2017**: TB LAM RDT (Alere)
- **2018**: MTB/RIF Ultra (GenoXpert; Cepheid)
- **2019**: TrueNat TB & RIF (Molbio)

To be reviewed in December
In 2020: 18 products may be sufficiently advanced to get reviewed by WHO

Centralized molecular TB tests/DST

- BD Max MDR-TB (BD)
- Cobas® MTB-RIF/INH (Roche)
- FluoroType MTBDR (Hain-Bruker)
- RealTime MTB RIF/INH (Abbott)
- Genoscholar PZA-TB (Nipro)

Culture-based DST

- MGIT Bedaquiline (BD)
- Sensititre™ MYCOTB AST Plate (Thermo Fisher)

POC molecular tests

- Omni (Cepheid)
- XDR TB (Cepheid)

POC LAM test

- SILVAMP TB LAM (Fujifilm)

POC LAM test

- CAD4TB (Delft Imaging Systems)
- qXR (Qure.ai)
- Lunit Insight CXR (Fujifilm)

Stool processing solutions

- FIND & partners
- TB-Speed
- Simple One-Step (KNVC)

New IGRAs/skin tests

- QFT-Access
- Diaskintest
- Generium
### Which TB diagnostics do we need?
Priorities defined in TPPs, aligning product specifications with patient & user needs

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To accelerate progress in ending the global tuberculosis epidemic, the first UN High-Level Meeting on tuberculosis, held in 2018, resolved to close the case detection gap by 2022. However, diagnosing an additional 4 million cases of tuberculosis annually, on top of what is currently being detected, requires the immediate and expanded scale-up of systematic tuberculosis screening, followed by confirmatory testing for all individuals who screen positive. Although new confirmatory tests that are substantially more sensitive than smear microscopy are available (eg, Xpert and Xpert Ultra MTB/RIF), annual reductions in tuberculosis incidence (1.5% per year) are individuals with tuberculosis in most settings. As a public health strategy, the purpose of screening for tuberculosis (and other infectious diseases with long incubation periods, including HIV and hepatitis C) is to detect infectious cases before symptoms develop, thereby curbing transmission and improving patient outcomes. However, using any symptom to select individuals for confirmatory testing means that tuberculosis cases will only be diagnosed well after most transmissions have already occurred; such a strategy is now considered unacceptable for HIV, and the same expectations should apply for tuberculosis.
Why do we need better tools for triage/screening?

Data from prevalence surveys in 26 countries

- Myanmar
- Mongolia
- Cambodia
- Thailand
- Philippines a
- Eryngales
- Zimbabwe
- Viet Nam
- Rwanda
- China
- Ukraine
- Kenya
- Zambia
- Peru
- Lao PDR
- Uganda
- Uganda
- DPR Korea
- Ethiopia
- Indonesia
- Gambia
- Russia
- Pakistan
- Rwanda
- Indonesia
- Philippines b
- Zimbabwe
- Bangladesh
- Philippines a
- Thailand
- Cambodia
- Mongolia
- Myanmar

Unpublished data removed

Percentage of TB cases screening symptom-negative

30%  40%  50%  60%  70%  80%

Many patients with TB don’t report TB symptoms

Many patients that report TB symptoms don’t receive TB testing

Data from systematic review of SP studies & exit interviews

Courtesy Global TB Programme, World Health Organization

Divala et al, manuscript in preparation
Chest X-Ray & Computer Assisted Diagnosis
Enabling improved screening & triage today

CAD software products

ECAD-TB to support WHO review

Portable CXR products

- 5,000 images from 8 countries
- Comparative assessment of tools & versions
- Assessment across use cases: triage/screening

Comparative assessment ongoing to support WHO review in early 2020

Qin et al. 2019

Standardized panel of DICOM files

Symptomatic screening

Immigration screening

Prevalence surveys
Host protein signatures
Promising developments but major challenges remaining

**FIND triage project**

- **Initial biomarker discovery efforts** identified 7 promising host-biomarkers
  - De Groote et al., JCM 2017

- **2-marker signatures**
- **n=461, 3 countries**

**ScreenTB project (Gerhard Walzl’s group)**

- **Initially: 7-marker signature Luminex-based assay**
- **Now: focus on 3-marker signature POC**

**Challenge:** finding universal signature and cut-off & implement as simple test at low cost
Host RNA signatures
Extensive work in basic science starting to yield first products

RNA signature discovery

FIND validation study: ‘3-gene Xpert Prototype’ cartridge from Cepheid*

- Evaluation of performance among people living with HIV
- Biobanked blood samples (PAXgene)
- 201 patients, 67 MTB culture-positive
- Sens 91%, Spec 86% (vs Xpert)

Sweeney et al, Lancet Respiratory Medicine 2016

Digital diagnostics and AI-based tools
Early promise for extremely low-cost, easy to use triage/screening tools

The potential of digital diagnostics

- Very limited evidence on performance for TB
- Highly active field
- Marginal cost ~$0
  - High potential to be low cost tools
- Potential for self-testing

Handheld digital ultrasound

Digital stethoscopes

Cough apps

Clinical decision support tools & AI-based algorithms

Source: https://medicalfuturist.com/fda-approvals-for-algorithms-in-medicine
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Non-sputum Diagnostics: what do we have?

**Serological tests**

“… it is strongly recommended that these tests not be used for the diagnosis of pulmonary and extra-pulmonary TB.”

**Skin tests & IGRAs**

“Neither IGRAs nor the TST should be used for the diagnosis of active TB disease.”

**Alere urine LAM**

2015 policy: Recommended for PLHIV that are very ill…

2019 update: broadened indication
Fujifilm SILVAMP TB LAM
First of a new generation of highly sensitive urine LAM assays

Designed for the POC in LMIC’s where patients seek care
Urine-based, rapid time-to-result, instrument-free and safe

Enhanced sensitivity to detect TB in all HIV+
Around 30% increased sensitivity over existing POC LAM assay

Additional emerging data
- Data on in- and out-patients presented at WHO in May
- Additional promising data to be published
  - Children
  - Extrapulmonary TB
  - HIV-negative TB
  - Mortality

Additional studies
- FIND multicenter prospective study
- Studies via RFP & other partners

Will support WHO review in 2020
Comparative performance of Fuji LAM and Alere LAM in PLHIV
Meta-analysis of 1,600 patients

- CD4-cell dependency... but sensitivity 40-60% even at high CD4-counts and HIV-negative TB patients
- No substantial difference between in- and outpatients
- LAM likely present in all TB patients (requires ↑ sensitivity)
Next generation LAM test – how will we get there?

Next Generation LAM assay
Ultra sensitive (<10 pg/mL) to detect LAM in all TB patients
Regardless of HIV status

- Improved reagents (antibodies, antigens)
- Pre-analytical Sample Preparation
- Innovative Assay Design
Molecular diagnostic testing from stool for Pediatric TB
Improving Pediatric TB diagnosis through use of more accessible samples

### The problem

- In 2017, ~1 million children with TB
- 234,000 children died of TB (incl. 40,000 children with HIV).
- Lack of **effective** diagnostic tests that can be performed on **easily accessible** samples
- Lack of availability of quality TB diagnosis in primary care and private sector

### Stool processing solutions

<table>
<thead>
<tr>
<th>Stool processing kit</th>
<th>FIND &amp; partners</th>
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<td><strong>Stool processing</strong>kit</td>
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<td><strong>Optimized Sucrose Flotation</strong></td>
<td>TB-Speed</td>
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<td><strong>Simple One-Step</strong></td>
<td>KNCV</td>
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</tbody>
</table>

### Head-to-head comparison of 3 stool processing methods

### Ongoing studies

- Uganda, South Africa, India, Zambia

### Endpoints

- Clinical performance combined with Ultra
- Acceptability & feasibility
- Preliminary costing data

Multicenter studies ongoing to support WHO review in 2020
New biomarkers & approaches to TB testing for triage and diagnosis

**Host RNA**

- Genome-wide expression for diagnosis of pulmonary tuberculosis: a multicohort analysis
  - Berry et al., Nature 2010
  - Sweeney et al., Lancet Respiratory Medicine 2016

**Cell-free DNA / liquid biopsy**

- Toward the Development of a Circulating Free DNA-Based In Vitro Diagnostic Test for Infectious Diseases: a Review of Evidence for Tuberculosis
  - Fernandez-Carballo et al., JCM 2019

- 15 studies
- sensitivities 29% to 79%
- specificities 67% to 100%

**Breath tests & skin patches**

- Turner et al., Nature Reviews Microbiology 2004
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Priorities defined in TPPs, aligning product specifications with patient & user needs

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Sputum-based diagnostics & DST: What do we have?

**Microscopy**

**LPAs**

**MGIT**

**GeneXpert**

**LAMP**
Centralized molecular diagnostics
High-throughput & efficiency

- Enable
  - high-throughput testing
  - upfront INH testing
  - multi-disease testing

- Comparative analytical study
  - Sensitivity similar to Xpert
  - Resistance detection similar to LPA

Abbott
- Abbott m2000sp
- Abbott m2000rt

Hain
- GenoXtract®96
- FluoroCycler® 96

BD
- BD MAX™

Roche
- Roche: cobas® 6800 System

Bioneer
- Bioneer: ExiStation™ Universal MDx System

Abbott, BD, Roche, Bioneer

XDR assay in development
Sequencing
Optimizing individualized care for DR-TB

FIND next-generation sequencing (NGS) strategy 2019–2022 (funded by Unitaid)

Goal 1: Establish rapid, culture-free, end-to-end targeted NGS (tNGS) solutions for DR-TB diagnosis and surveillance
Goal 2: Empower LMICs to utilize sequencing for clinical decision making and expand NGS capacity to areas beyond TB

### Phenotypic DST vs. tNGS DST

<table>
<thead>
<tr>
<th>Phenotypic DST</th>
<th>tNGS DST</th>
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<tbody>
<tr>
<td>Culture</td>
<td>6–9 weeks</td>
</tr>
<tr>
<td>2–3 days</td>
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<table>
<thead>
<tr>
<th>Rapid</th>
<th>Huge potential for automation</th>
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<tbody>
<tr>
<td>Minimal biosafety hazards</td>
<td>Benchtop workflow</td>
</tr>
<tr>
<td>Rapidly decreasing costs</td>
<td>Designed for national/global networking</td>
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</table>

**Optimize & validate end-to-end tNGS workflows**

**Targeted NGS solutions for DR-TB diagnosis**

**Enable standardized analysis and reporting**

**Seed local capacity**

**Support policy & guidelines**

**WHO TB Knowledgebase**

DISCLAIMER: Images & time estimates are to be taken as indicative only.
## POC molecular diagnostics
Bringing solutions closer to patients

### MOLBIO Trueprep + Truelab + Truenat
- First POC molecular diagnostic on the market
- MTB, MTB+, RIF chips already in use in India
- FIND studies on Molbio ongoing
- Work on additional assays / validation ongoing

### OMNI & XDR cartridge
- Integrated processing from sample to result
- Small, portable, in-built connectivity
- Proven cartridge technology
- FIND studies on Omni starting in 2019
- FIND trial of XDR cartridge ongoing

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**Beyond 2019/20**

- **Bioneer**
- **QuantuMDx**
- **BLINK**
- **Ontera**

---

WHO review of interim data in December 2019

WHO review of Omni and XDR cartridge planned for 2020
Multicentre study of Truenat assays (MTB, MTB Plus, MTB RIF Dx)
- India, Peru, Ethiopia, PNG
- 17 microscopy centres, 7 Reference labs
- 1,882 patients

Results from interim analysis
- 490 participants
- Similar performance to Xpert

First results from interim analysis of Molbio solution
Conclusions

- **Major diagnostic gaps remain**

- **Many new tools will become available within the next year**
  - Critical to make use of what we have now!
  - Establishment of 'Essential Diagnostics List' will help

- **Exciting new developments on the horizon**
  - New tools urgently needed & would allow us to re-imagine TB diagnosis & care
  - Collaboration & strong partnerships critical to ensure that opportunities become new realities
Thank you to the many partners and donors who make the work of FIND possible!

Thank you to the team!

Morten Ruhwald
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Swapna Uplekar
Tim Rodwell
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Sandra Kik
Tobias Broger
Claudia Denkinger
Romain Wyss
Karishma Saran
Sarah-Jane Loveday