TB DIAGNOSTICS PIPELINE
- Leveraging Covid-19 innovations

Adam Penn-Nicholson
Deputy Director of TB programme
FIND, the global alliance for diagnostics
Covid impacts further emphasize the urgent need for simpler tools to enable PHC and community-based screening and testing. 

- **18% (1.3M!)** fewer people were notified in 2020 compared to 2019.
- The hardest hit countries are among the highest absolute TB incidence...India, Indonesia, China, Bangladesh, Nigeria, Pakistan...

Testing remains the weakest link in the cascade of care:
- Of annual 10M cases, 4.1M remain undiagnosed.
- 1 in 3 TB patients are bacterially confirmed.
- 1 in 5 TB patients are diagnosed with a WHO recommended mDx.
- 1 in 3 with DR-TB are tested and put on relevant treatment.

Diagnostic gaps in TB have many root causes:
- Existing tools are not fit for purpose.
- 70% of patients initiate care at the community and PHC where there is no capacity to diagnose TB.
- Symptom screen miss 50% of TB cases in communities.
- Reliance on sputum makes diagnosis difficult and selects patients with advanced disease.

The pandemic has opened new opportunities:
- Bringing diagnostics closer to the patients.
- Diverse MDx portfolio, the end of one-size-fits-all.
- Leveraging investments in DX infrastructure, digital and connectivity.
- New tools for a comprehensive response with TBI test-and-treat strategies, scTB and personalized medicine in TB.

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3 WHO Global TB report 2021
2 StopTB modelling
3 WHO Global TB report 2021
4 Pai M et al, Nat.Microb. 2017
5 Francella et al, CID, 2021 DOI: 10.1093/cid/ciaa1402
OUR MISSION

FIND, the global alliance for diagnostics, seeks to ensure equitable access to reliable diagnosis around the world.

◆ We connect countries and communities, funders, decision-makers, healthcare providers and developers to spur diagnostic innovation and make testing an integral part of sustainable, resilient health systems.
HOW WILL WE DELIVER ON THIS VISION?
Onsite Xpert testing and access to same day treatment initiation leads to 56% increase in treatment start (measured a day 14) (Xpel study, Katamba, Cattamanchi et al in press).
The platforms with the highest demonstrated sensitivity are PCR-based amplification.
5 of the platforms are disposable
GROWING LANDSCAPE AND PIPELINE OF ‘LOW COMPLEXITY AUTOMATED NAATS’
NEAR POC MDX

SD BIOSENSOR, STANDARD M10

- MTB assay
  - TB, RIF, INH
  - Result in 60 mins

BIONEER, IRON-qPCR

- MTB assay
  - TB, RIF, INH, FQ, SLID
  - Result in 30 mins

MOLBIO, TRUENAT

- New Ultima, INH and FQ chips
- Combined TB and Covid-19 assay
- Clinical trials start 2022
tNGS - THE PATH TO EXTENSIVE GENOTYPIC RESISTANCE DETECTION DIRECT FROM SPUTUM
END-TO-END TARGETED NGS SOLUTIONS

Schematic representation of NGS end-to-end solution

DNA extraction → Library preparation → Targeted sequencing → Data analysis

WHO TB Knowledgebase & Mutations Catalogue
Endorsed commercial tNGS solutions for global access
Evaluation of end-to-end tNGS solutions

Implementation models and guidance
Knowledge sharing, advocacy & global procurement listing

Catalogue of mutations by country and their associations with drug resistance

Policy review planned Q4 2022
ADVERTISE MAJOR ACCESS BARRIERS
LEAD STRATEGIES PURSUED

Tongue swabs

Simple sample prep

Fast MDx backend

Bioaerosols

Blood

Urine LAM

AN ALTERNATIVE TO SPUTUM -
Some unknowns remain
- The optimal swab?
- How to sample prep.?
- The optimal backend?
- Stability and optimal transport media...or dry?
- Simultaneous SARS-CoV2 testing?

**Non-Sputum Based Sampling with Swabs**
**Tongue Swabs is a Potentially Disruptive Strategy to Replace Sputum**

<table>
<thead>
<tr>
<th>Country</th>
<th>MRS+</th>
<th>MRS-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peru</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>South Africa</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Uganda</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Vietnam</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (N=30)</th>
<th>Specificity (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tongue</td>
<td>87%</td>
<td>100%</td>
</tr>
<tr>
<td>Cheek and gums</td>
<td>69%</td>
<td>100%</td>
</tr>
<tr>
<td>Nostrils</td>
<td>55%</td>
<td>100%</td>
</tr>
<tr>
<td>Tongue, cheek and gum</td>
<td>67%</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Sensitivity (N=30)**
- Tongue: 87%
- Cheek and gums: 69%
- Nostrils: 55%
- Tongue, cheek and gum: 67%

**Specificity (n=30)**
- Tongue: 100%
- Cheek and gums: 100%
- Nostrils: 100%
- Tongue, cheek and gum: 100%

**Sensitivity**
- Tongue Swab Ultra, Method 2 (N=183)
- Sputum Xpert: 77.8 (64.4-88.0)
- Microbiologic reference standard*: 73.4 (59.1-83.3)

**Specificity**
- Tongue Swab Ultra, Method 2 (N=183)
- Sputum Xpert: 100 (97.2-100)
- Microbiologic reference standard*: 100 (96.9-100)

**Adama et al JCM 2022**

**FEND-TB consortium, in preparation**

**R2D2 TB Network**

**FEND-TB**

**SWABS IN ACTIVE CASE FINDING PILOT**
**ANALYZING SWABS IN REAL TIME IN THE COMMUNITY, POOLING SWABS FROM HOUSEHOLD**

Andrew Medina-Marino and Bernard Fourie, in preparation
Sample Collection & Lysis
Insert Strip & Add Sample
Amplification 15 minutes
Analysis and Report

Total Test Time: ~20 Minutes

LumiraDx Smart Connectivity
- Step-by-step test instructions on screen
- Digital display of results and reporting
- Data analytics and decision support
- Seamless, secure connectivity to the cloud and health IT systems
- Platform launch 2018, in 2021 5k instruments installed in Africa, 20k globally
- TB assay enter policy trial Q1 2023

Proprietary process subject to LumiraDx IP protection. Project subject to further development and regulatory approval.
IS THIS PRACTICAL?
FIND and the University of Leicester have developed the concept into a scalable product for tidal breath sampling (30min) and TB detection.

Clinical performance for TB detection is currently being evaluated in FEND-TB – results by Dec 2022.

Once clinical evidence is available, production will be scaled up and face masks will be made available for clinical use via an RFP process.

https://www.fend-tb.org/
NON-SPUTUM-BASED TESTING USING BLOOD?
BLOOD-BASED DX

STUDY OVERVIEW
- Gambia, Vietnam, Uganda and South Africa
- 75 Xpert positive, 120 negative
- 200ul fingerstick blood

FINDINGS
- AUC 0.94
- Sensitivity 87%
- Specificity 94%

Source: Sutherland et al CID 2022

MRNA TRANSCRIPTOMETICS

CFDNA AND CRISPR

CRISPR detection of circulating cell-free Mycobacterium tuberculosis DNA in adults and children, including children with HIV: a molecular diagnostics study

https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(22)00087-8/fulltext

Serum based cfDNA with CRISPR:
100% sensitivity for detection of confirmed TB and 85% for unconfirmed TB in paediatric HIV+ cohort
UNITAID – KICKSTARTING 3 NEW CLASSES OF GAME-CHANGING TECHNOLOGIES

3rd Gen. LAM

Ultra sensitive urine LAM for fast and simple diagnosis of TB at point of care

POC MDx

Point of care molecular TB detection from non-sputum samples

Near POC MDx

Uptake of affordable and faster MDx platforms for TB detection and broader DST
DETERMINE TB LAM Ag and Fujifilm SILVAMP TB LAM

PLHIV (5 cohorts, n=1595)

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FujiLAM</td>
<td>70.7 [59.0 – 80.8]</td>
<td>90.9 [87.2 – 93.7]</td>
</tr>
<tr>
<td>AlereLAM</td>
<td>34.9 [19.5 – 50.9]</td>
<td>95.3 [92.2 – 97.7]</td>
</tr>
</tbody>
</table>

HIV uninfected patients (n=372)

<table>
<thead>
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<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FujiLAM</td>
<td>53.2% (43.9 to 62.2)</td>
<td>98.9% (96.7 to 99.6)</td>
</tr>
<tr>
<td>AlereLAM</td>
<td>10.8% (6.3 to 18.0)</td>
<td>92.3% (88.5 to 95.0)</td>
</tr>
</tbody>
</table>

PATHWAYS TO 3RD GENERATION LAM TESTS

3rd Generation LAM assay
Ultra sensitive (<10 pg/mL) to detect LAM in all TB patients

Pre-analytical
Improved reagents

Pre-analytical
Sample Preparation

Innovative
Assay Design
**CAD/CXR – AUTOMATED CHEST X-RAY INTERPRETATION WITH AI SOFTWARE AND PORTABLE AND SAFER INSTRUMENTS**

**Input:**
Digital AP CXR

**Output:**
Abnormality score

- **A fast-moving field**
  - CXR remains the most sensitive screening and triage tool for TB
  - CXR is underutilized due to global shortage of radiologists, infrastructure and logistical restraints
  - Portable x-ray instruments are now on the market and WHO endorsed
  - 8 CE marked CAD products in 2022 (only 3 in 2019)

www.ai4hlth.org

Available for download on www.finddx.org

Portable x-ray instruments takes CXR to where no x-ray has gone before!
CAD AIs FOR TB
A FAST-MOVING FIELD

- 2017 - 1 product
- 2020 - WHO evidence review of 3 CE marked products
- 2021 - WHO policy issued
- 2022 - >17 products

- Frequent version upgrades and new features added
- New area for policy makers and regulators

www.ai4hlth.org
- Product description and comparison
- Certification status
- Data sharing and privacy
- Pricing
12 CAD solutions compared H2H

Study Overview
- X-ray’s collected from community ACF in Vietnam (one site)
- 1,032 participants
- 133 TB (Xpert MTB/RIF)
- Compared to human radiologist
  - Expert (>30 yrs experience)
  - Intermediate (5yrs experience)

Findings
- AUCs 0.82-0.50
- 6 CADs on-par with Expert reader (Qure.ai, Delft, DeepTek, Lunit, JF Helatcare, Oxipit)
- 3 CADs superior to Intermediate Reader (Qure.ai, Delft, Lunit)

Codlin et al, Scientific reports 2021.
OTHER FAST MOVERS IN AI4TB

AI enabled POCUS

AI enabled dStethoscopes

AI enabled cough apps

You download the app, cough into it and receive a diagnosis within minutes. Too good to be true? Maybe not.
**SPECIFIC SKIN TESTS: THE ‘IGRA IN THE SKIN’**

- **ESAT-6**
- **CFP-10**

- Safety profile on par with PPD
- IGRA like specificity in BCG vaccinated
- High agreement with IGRA and correlation with exposure in contacts
CONNECTING THE CENTURY OLD SKIN TEST

SMART PATCH AND COMPANION APP FOR CY-TB

SmartCut™ Flap
Designed for accurate injecting and providing observation window

Guldemarks
Allows accurate measurements and reduce operator error

Color Calibrator
Allows accurate image processing in different skin tones and light conditions

QR Code
Ensures genuine Product and links observation with Uuid

Mylab C-Tb SmartPatch®
Mylab TBConnect App
Serum C-Tb Test
Pen / syringe and Intradermal adapter

STEP 1
Inject the Mylab C-Tb SmartPatch in an area of preferred skin

STEP 2
Remove the circular SmartPatch that is applied skin for injection

STEP 3
Prepare the site for injection

STEP 4
Scan and capture the second image after 24-48 hours to measure the inflammation

Mylab
Discovery solutions
Translating Discovery to Delivery
TAKE HOME MESSAGES

- TB remains the top infectious disease killer; C-19 impacts will take decades to recover from
- Diagnostic gap in TB is a disaster...but
- ...unprecedented opportunities coming through COVID-19 and we need to build on the momentum before the window of opportunity closes
- New instruments and alternative sampling strategies are showing promise to bring the diagnostics close to the patients
  - Therr may be a trade off in accuracy but with increased access the impact still is to be evaluated
- Plenty of new diagnostics and shorter regimens for TBI
ACKNOWLEDGMENTS

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We also thank the many partners and other donors who make the work of FIND possible.
OVERALL PROJECT OBJECTIVES

- To accelerate the introduction of new TB tests through generating the high-quality evidence required to change global policy, the main barrier for transformative change in-country.

- To mitigate existing diagnostic barriers with sputum-based TB testing, bringing testing platforms closer to the patient and reducing the cost and complexity of existing centralized molecular platforms.

The DriveDx4TB project has four main pillars, which include:

1. Technology selection, feasibility assessment and co-development of products from three technology classes to reach design lock
2. Technology evaluation and policy trialling
3. Market preparation and readiness (outputs by product class)
4. Country-level advocacy and early-adoption

Grant under negotiation with Unitaid and subject to funding approval by Unitaid
CREATING SYNERGIES – PATHWAY FOR SCALE-UP OF INNOVATIVE DX

1. Identification of manufacturers
2. EOI and RFP
3. Co-development
4. Operational research
5. Validation and accuracy trialling
6. Market shaping/Access
7. In-country validation, EQA
8. Implementation Research
9. Country scale-up

Partners:
- Unitaid
- BMGF
- SMART4TB
- CDC
- Right fund
FIND ACTIVITIES TO INFORM POLICY DEVELOPMENT AND OPERATIONAL RESEARCH

Accuracy trialling (3-4 countries)
Costing analysis
Usability assessment
Alignment GTB & PQ evidence requirements
Operational Research
Algorithm development
Country selection
Patient important outcomes
In-country formative pilots
Strong recommendations
Country scale-up
FIND Diagnosis for all

CE markings
ERPD submissions
Ongoing interim analysis
MapErics University

World Health Organization
WHO PREQUALIFICATION TEAM DIAGNOSTICS
World Health Organization

Conditional recommendations