TB DIAGNOSTICS PIPELINE
(THE GLOBAL PERSPECTIVE)
– what to expect in the future

Morten Ruhwald, MD, PhD
Director of TB programme
FIND, the global alliance for diagnostics
Geneva, Switzerland
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 and personalized medicine in TB

12 Months of COVID-19 Eliminated 12 Years of Progress in the Global Fight Against Tuberculosis

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, Philippines, China, Bangladesh, Pakistan

Global notified new TB

Covid impact on TB mortality....and incidence (2020-2025)

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1 WHO global TB report 2021
2 StopTB modelling
3 WHO Global TB report 2021
4 Pai M et al, Nat.Microb. 2017
THEME 1 - NEW OPPORTUNITIES FOR SPUTUM BASED DX/DST
GROWING LANDSCAPE AND PIPELINE OF ‘LOW COMPLEXITY AUTOMATED NAATS’

STATUS ON mWRD

**CEPHEID**

- **Ultra**
  - TB/RIF

- **Xpert MTB/XDR + 10 color**
  - INH/FQ/SLIDs

**MOLBIO**

- **True prep + Truenat**
  - MTB + RIF

- INH/FQ/BDQ/TB Ultima + TB/Covid-19 in trial
**SD BIOSENSOR, STANDARD M10**

**Assay menu**
- SARS-CoV-2
- FLU/SARS-CoV-2
- MTB and MTB/NTM
- Arbovirus
- STD
- HIV
- Hepatitis
- HAI

- LAMP and RT-qPCR
- Up to 12 targets including IC
- Touch screen and connectivity
- Scalable configuration, 1-8 random access modules
- MTB assay
  - TB (IS6110, IS1081), RIF(rpoB), INH (katG, inhA)
  - Result in 60 mins
  - CE-MARK TB assay 2022/3

**BIONEER, IRON-qPCR**

**Assay menu**
- SARS-CoV-2
- MTB
- AMR (17 target genes/organisms)
- TSU (scrub typhus)
- STD/HPV
- Resp. Virus panel (6 pathogens)
- Malaria

- RT-qPCR
- Maximum 48 targets
- Touch screen and connectivity
- 2 random access modules
- MTB assay
  - TB, RIF, INH, FQ, SLID
  - Result in 30 mins
  - CE-MARK and policy trialing 2022, policy 2023
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

Policy review planned Q4 2022
THEME 2 – BRINGING DX CLOSER TO THE PATIENTS
BRINGING DX CLOSER TO THE PATIENT

XPEL TRIAL – ON-SITE MOLECULAR DETECTION AND STREAMLINED WORKFLOWS
INCREASE TREATMENT INITIATION 56%
LEAD STRATEGIES PURSUED

- Tongue swab
- Simple sample prep
- Simple MDx backend
- Bioaerosol sampling
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>Test Positive</th>
<th>Number Determinate</th>
<th>Sensitivity (%)</th>
<th>Wilson's 95% CI (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Airway Swab 1 (tongue)</td>
<td>25</td>
<td>29</td>
<td>86.7</td>
<td>(70, 94.8)</td>
</tr>
<tr>
<td>Upper Airway Swab 2 (cheeks and gums)</td>
<td>20</td>
<td>29</td>
<td>69</td>
<td>(50.8, 82.8)</td>
</tr>
<tr>
<td>Upper Airway Swab 3 (nostrils)</td>
<td>16</td>
<td>29</td>
<td>55.2</td>
<td>(37.6, 71.7)</td>
</tr>
<tr>
<td>Upper Airway Swab 4 (tongue, cheeks, and gums)</td>
<td>19</td>
<td>28</td>
<td>67.2</td>
<td>(48.7, 81.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Test Negative</th>
<th>Number Determinate</th>
<th>Specificity (%)</th>
<th>Wilson's 95% CI (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Airway Swab 1 (tongue)</td>
<td>30</td>
<td>30</td>
<td>100</td>
<td>(88.6, 100)</td>
</tr>
<tr>
<td>Upper Airway Swab 2 (cheeks and gums)</td>
<td>30</td>
<td>30</td>
<td>100</td>
<td>(88.6, 100)</td>
</tr>
<tr>
<td>Upper Airway Swab 3 (nostrils)</td>
<td>30</td>
<td>30</td>
<td>100</td>
<td>(88.6, 100)</td>
</tr>
<tr>
<td>Upper Airway Swab 4 (tongue, cheeks, and gums)</td>
<td>30</td>
<td>30</td>
<td>100</td>
<td>(88.6, 100)</td>
</tr>
</tbody>
</table>

**Table 5. Semiquantitative results**

<table>
<thead>
<tr>
<th>Tongue swab Xpert Ultra Method 2 (N=183)</th>
<th>Trace+ for all</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum Xpert</td>
<td>Microbiologic reference standard*</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td><strong>Specificity</strong></td>
</tr>
<tr>
<td>77.8 (64.4-88.0)</td>
<td>100 (97.2-100)</td>
</tr>
<tr>
<td>73.4 (59.1-83.3)</td>
<td>100 (96.9-100)</td>
</tr>
</tbody>
</table>

FEND-TB consortium, in prep.
Adama A et al. medRxiv https://doi.org/10.1101/2022.02.17.22271147
Total Test Time: ~20 Minutes

- 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 expected 2022/23

Proprietary process subject to LumiraDx IP protection. Project subject to further development and regulatory approval.
The platforms with the highest demonstrated sensitivity are PCR-based amplification.

5 of the platforms are disposable.
mWRDs, moderate complexity NAATs

READY TO LEVERAGE COVID-19 INVESTMENTS, MULTI-PATHOGENIZE MDX SERVICES (AND MIX-AND-MATCH WITH NON-SPUTUM BASED SAMPLING STRATEGIES?)

- **Enable**
  - Sputum based
  - high-throughput testing
  - upfront INH testing
  - multi-disease testing

- **Performance**
  - Sensitivity similar to Xpert
  - Resistance detection similar to LPA

- **Abbott**
  - Abbott m2000sp
  - Abbott m2000rt

- **Hain**
  - GenoXtract®96
  - FluoroCycler® 96
  - Fluorotype XDR - in trial

- **BD**
  - BD MAX™

- **Roche**
  - Roche: cobas® 8800/6800 System

- **Bioneer**
  - Bioneer: ExiStation™ Universal MDx System
HIGH THROUGHPUT SIMULTANEOUS TESTING

Up to 384 specimens in one 8-hour shift
Assay tape, 5,888 samples per run

Bar codes from beginning to end, links sample to result and back to patient

Automated swab handling, and sample prep.

Nexar reel based high throughput PCR system. Up to 100,000 samples per day

Source:
https://www.medrxiv.org/content/10.1101/2020.10.09.20210302v2
NON SPUTUM BASED SAMPLING WITH BIOAEROSOLS
BIOAEROSOL CAPTURE CONCEPTS

A silicon sieve...  ...capturing particles on impaction

[Images of different components and setups related to aerosol capture concepts]
BIOAEROSOLS
ACCEPTABLE SENSITIVITY FOR TB DIAGNOSIS AND POTENTIAL FOR CONTACT TRACING

Williams et al. Lancet RM, 2020

Pretoria, n=24 micr. conf. in-patients
- 16 Rx naïve
- 6 Rx <24h
- 2 Rx >24h

Mask and sputum every 3h
Total: 192 sampling time points

43 sputum and mask collected at the same time

<table>
<thead>
<tr>
<th>Sputum</th>
<th>+</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>31</td>
<td>7</td>
</tr>
<tr>
<td>-</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

36 7 43

N=46 TB pts.
- Low/no aerosolizers
- (<20k copies, n=27)
- High aerosolizers
- (>20k copies, n=19)

N=181 household contacts tested for TB infection (QFT) at baseline and after 6m

Williams et al medrxiv, 2021.
See also Jones-Lopez EC ARJCCM 2013
### ALERE LAM (and the much anticipated) Fujifilm SILVAMP TB LAM

#### PLHIV (5 cohorts, n=1595)

<table>
<thead>
<tr>
<th></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>
<tr>
<th></th>
<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>

**Source:** Broger et al. J Clin Invest 2020; Broger et al, PLOS Med 2020
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
NON-SPUTUM-BASED TESTING USING BLOOD?
FIRST RESULTS OF TRANSCRIPTOMICS BASED DX FROM FINGER STICK BLOOD

Study Overview
- Enrolment at local health clinics in Gambia, Vietnam, Uganda and South Africa
- 195 patients with signs/symptoms of TB, 75 Xpert positive, 120 negative
- 200ul fingerstick blood

Findings
- AUC 0.94
- Sensitivity 87%
- Specificity 94%
- No significant difference in performance across sites

Source: Sutherland et al CID 2022
CXR REMAINS THE MOST SENSITIVE TOOL TO DETECT LUNG TB

COMPUTER AIDED DETECTION (CAD) SOFTWARE INTERPRET DIGITAL CXR IMAGES AND PROVIDES AN ABNORMALITY SCORE

Input: Digital AP CXR

AI algorithm

Output: Abnormality score & overlay

91% TB
THE GLOBAL SHORTAGE IN RADIOLOGISTS

Number of radiologists per million inhabitants

- >100.0
- 50.0-100.0
- 25.0-49.9
- 10.0-24.9
- 0.0-9.9
- Data not available
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

WHO consolidated guidelines on tuberculosis
Module 2: Screening
Systematic screening for tuberculosis disease

www.ai4hlth.org
**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.
ULTRA-PORTABLE DIGITAL X-RAY SYSTEMS
TO GO WHERE NO X-RAY HAS GONE BEFORE


Aspen Europa, Aspen Imaging, US
MINE, ALNU, KR
REiLI, Lunit INSIGHT, KR
Delft Ultra; Delft NL
Xair, FUJIFILM, JP
FujiFilm, JP
Delft Light; Delft NL

Available for download on www.finddx.org
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.
BORSTEL IS A KEY PARTNER FOR EVIDENCE GENERATION FOR GLOBAL POLICY

Five of 15 WHO guidelines since 2010
ON A PERSONAL NOTE

2006

500 TB cases / yr

New colleagues and collaborations
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
- New instruments and sampling strategies are showing promise to bring the diagnostics close to the patients
  - trade off in accuracy for yield is expected and impact is unknown
- We are entering a new era in sequencing and bioinformatics – with Borstel continuing to lead the way forward!
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Anna Mantsoki
Aurelien Mace
Tatiana Letsko
Karishma Saran
Sarah-Jane Loveday

Contact: morten.ruhwald@finddx.org

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