



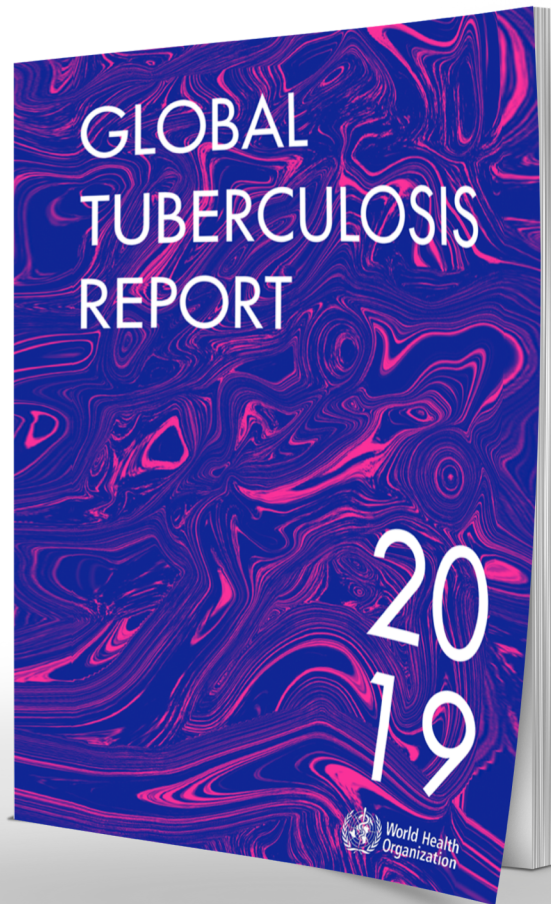
## **TB Diagnostics pipeline: needs & solutions**

Samuel Schumacher, Deputy Head TB

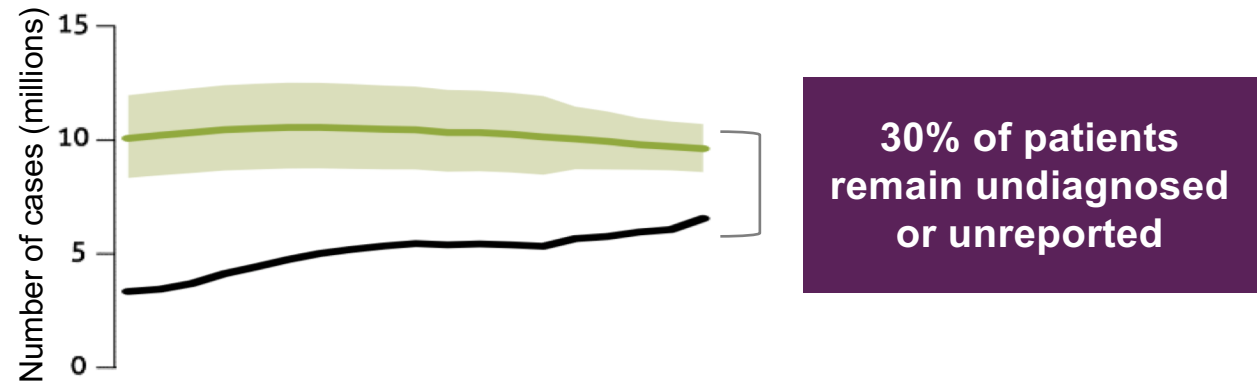
FIND & NDWG joint symposium, 50<sup>th</sup> Union World Conference, 30 October 2019

[www.finddx.org](http://www.finddx.org)

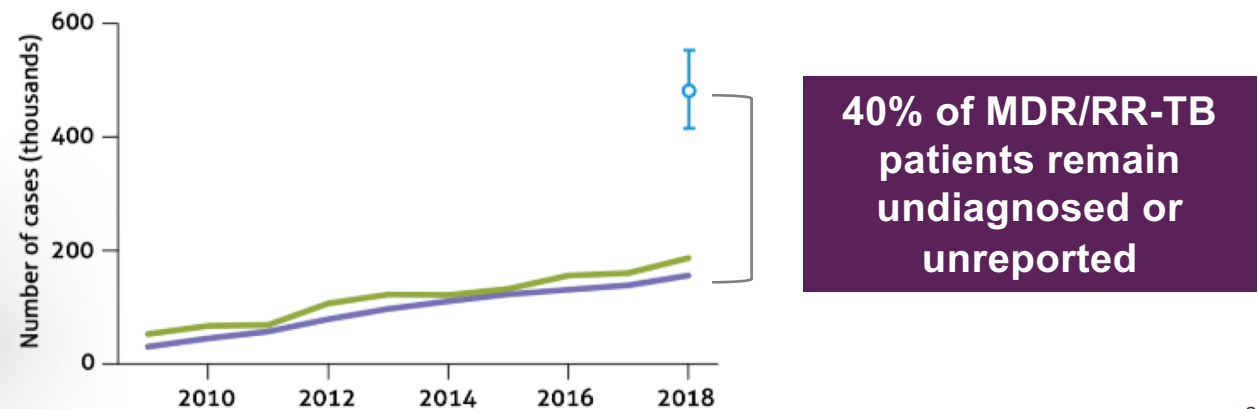
We need better tools & we need to better use existing tools!



Number of TB cases notified vs estimated (millions)



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

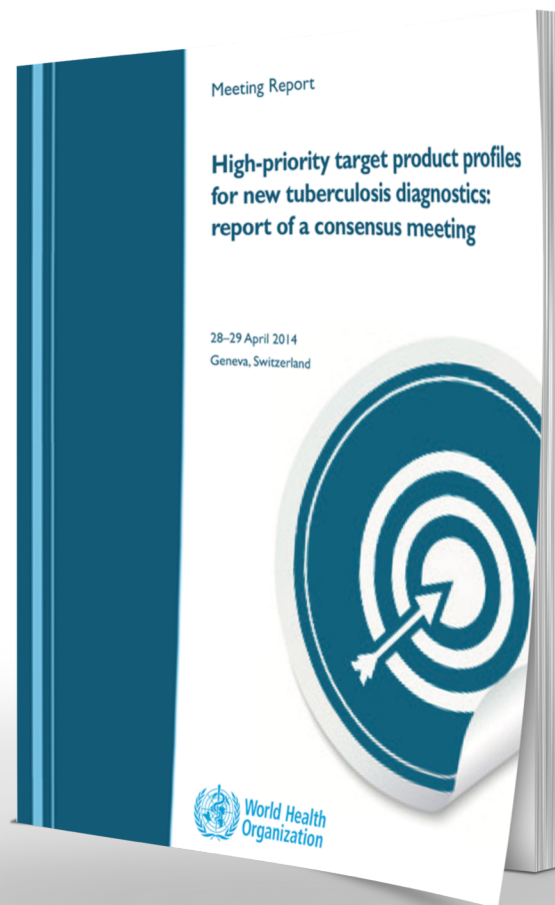






## Which TB diagnostics do we need?

Priorities defined in TPPs, aligning product specifications with patient & user needs



**1** Triage tests

**2** Non-sputum (biomarker) based Dx tests

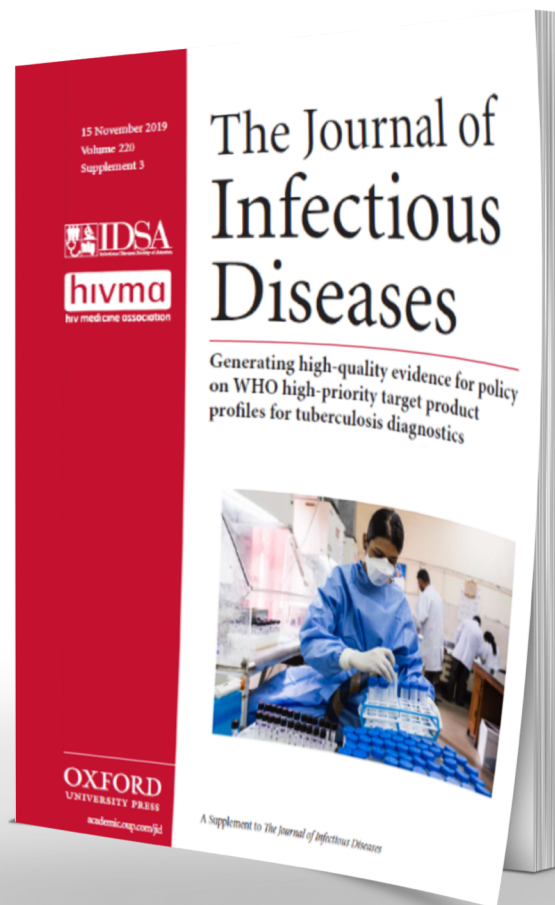
**3** Smear-replacement tests

**4** Drug susceptibility tests

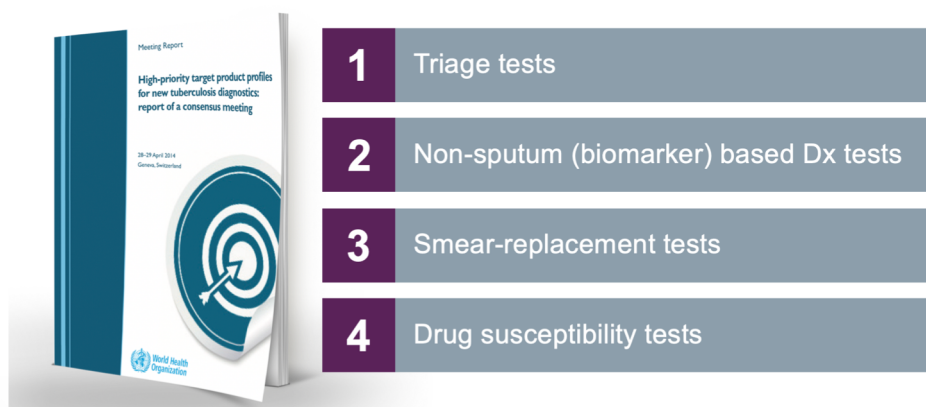


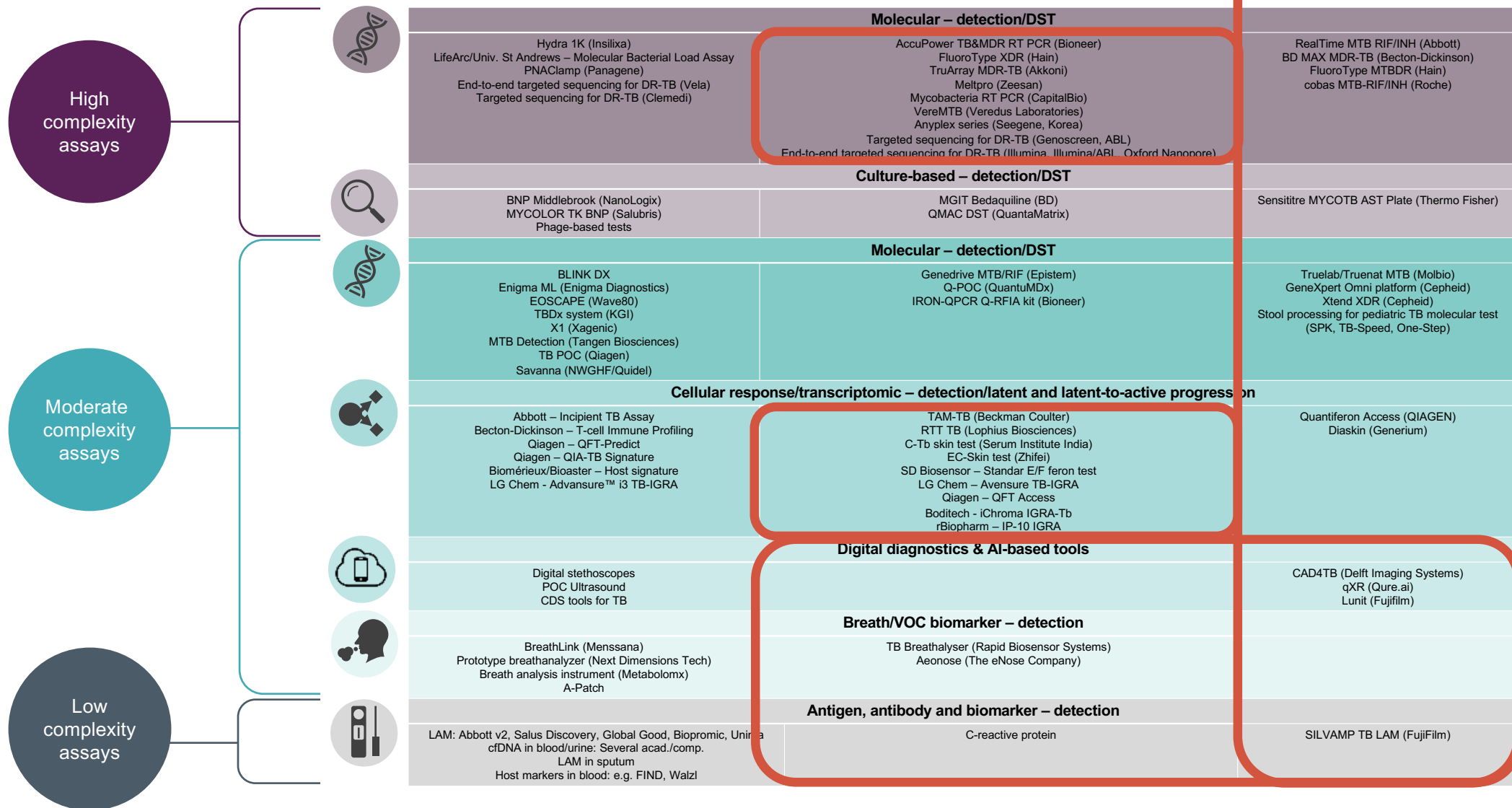
## Rigorous evaluation is critical – but how?

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



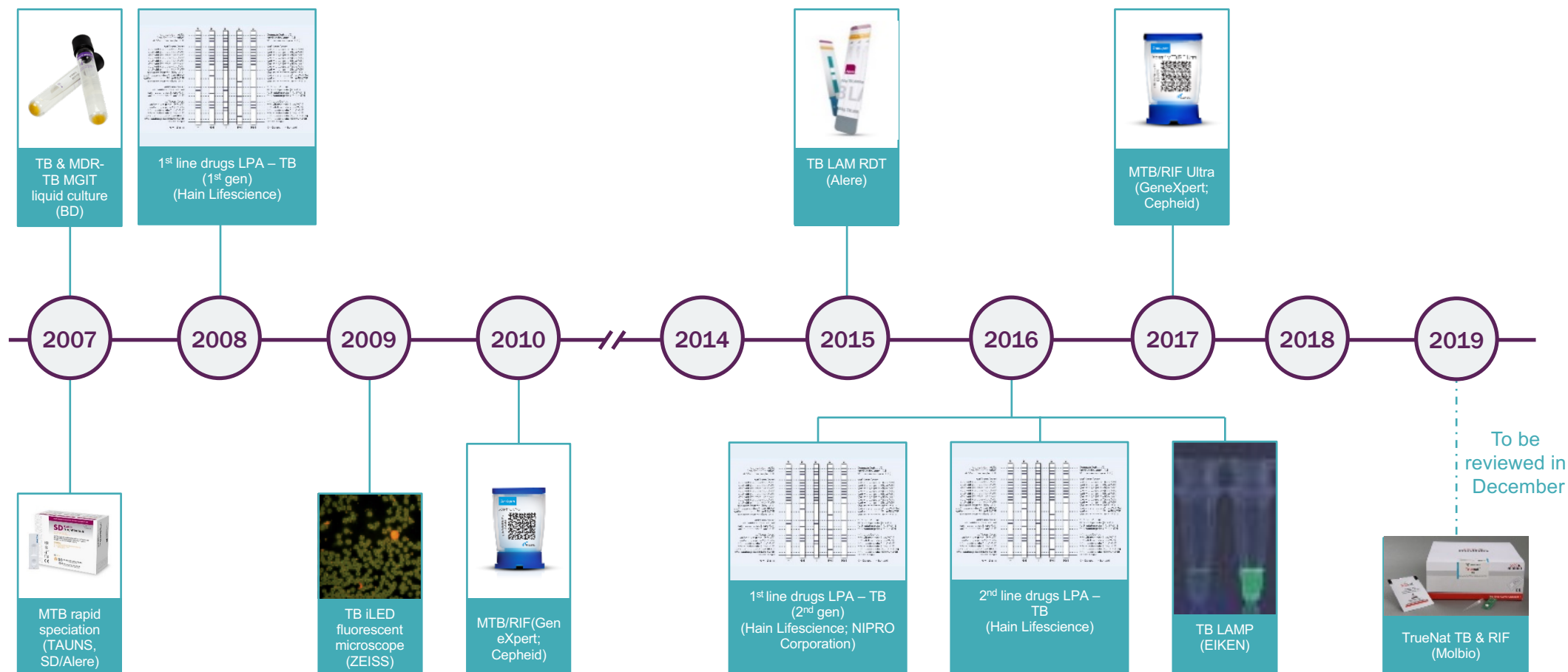
- Developed with WHO and >50 TB diagnostics researchers
- Lays out study design considerations separately for each TPP







## TB diagnostics recommended by WHO over the past decade

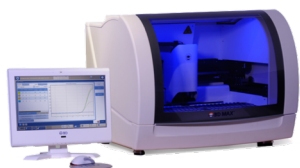






**In 2020: 18 products may be sufficiently advanced to get reviewed by WHO**

## 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)

## Stool processing solutions



**Stool processing solutions**  
(FIND & partners)

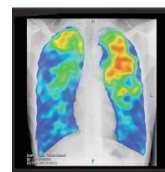


**Optimized Sucrose Flotation**  
(TB-Speed)

**Simple One-Step**  
(KNVC)



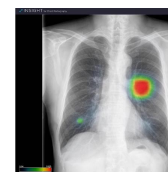
## CAD solutions



**CAD4TB**  
(Delft Imaging Systems)



**qXR**  
(Qure.ai)



**Lunit Insight CXR**  
(Fujifilm)

## New IGRAs/skin tests



**QFT-Access**  
**QIAGEN**

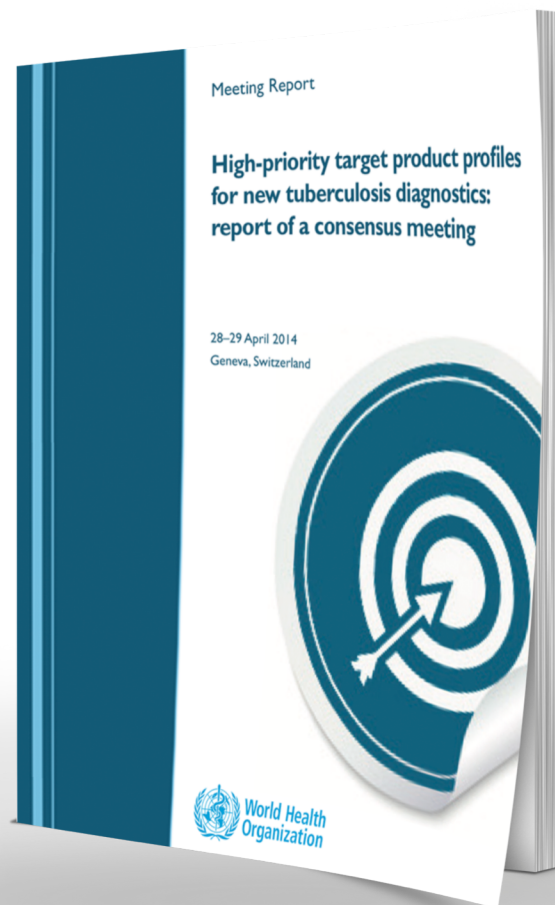


**Diaskintest**  
**Generium**



## Which TB diagnostics do we need?

Priorities defined in TPPs, aligning product specifications with patient & user needs



**1** Triage tests

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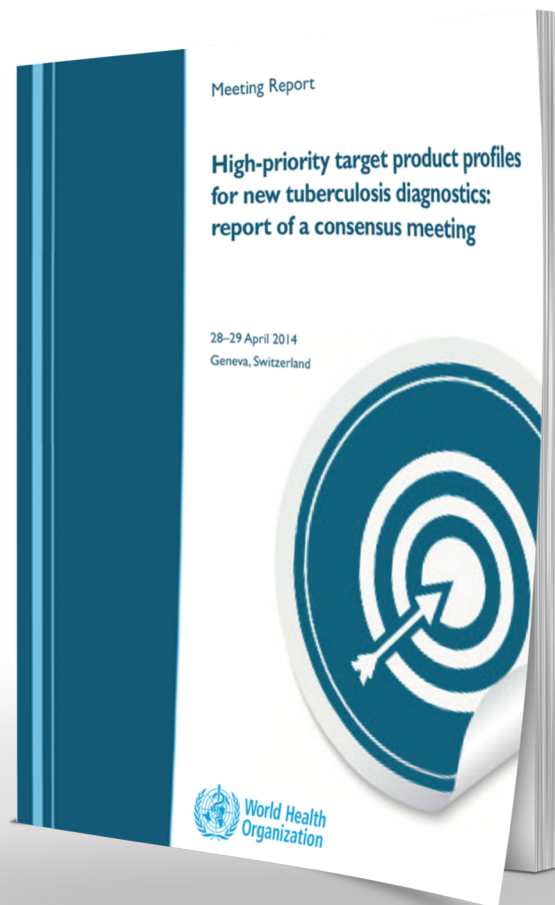
**3** Smear-replacement tests

**4** Drug susceptibility tests



## Which TB diagnostics do we need?

Priorities defined in TPPs, aligning product specifications with patient & user needs



**1** Triage tests

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**3** Smear-replacement tests

**4** Drug susceptibility tests



## Time to move beyond symptoms as the triage/screening tool for TB

### Comment



### Screening for tuberculosis: time to move beyond symptoms



Sebastian Kaulitzki/Science Photo Library

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.<sup>1</sup> 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),<sup>2</sup> annual reductions in tuberculosis incidence (1.5% per year) are

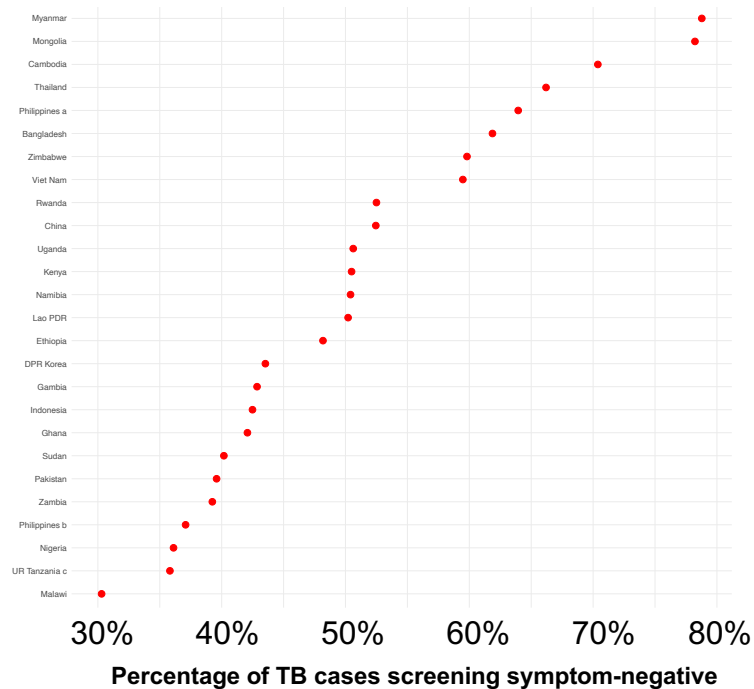
individuals with tuberculosis in most settings.<sup>6</sup> As a public health strategy, the purpose of screening for tuberculosis (and other infectious diseases with long incubation periods, including HIV and hepatitis C) is to detect infectious cases before symptoms develop, thereby curbing transmission 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



**Many patients with TB  
don't report TB symptoms**

Courtesy Global TB Programme, World Health Organization

### Data from systematic review of SP studies & exit interviews

Unpublished data removed

**Many patients that report TB symptoms  
don't receive TB testing**

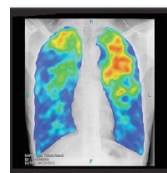
Divala et al, manuscript in preparation



# Chest X-Ray & Computer Assisted Diagnosis

## Enabling improved screening & triage today

### CAD software products



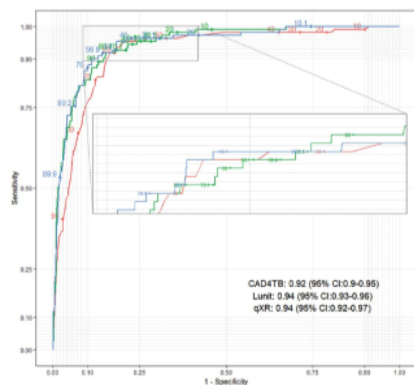
**CAD4TB**  
(Delft Imaging Systems)



**qXR**  
(Qure.ai)

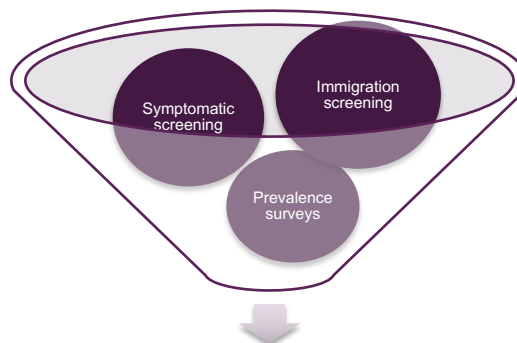


**Lunit Insight CXR**  
(Fujifilm)



Qin et al. 2019

### ECAD-TB to support WHO review



Standardized panel of DICOM files

- 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

### Portable CXR products



**DELFT**  
IMAGING SYSTEMS



**MINXRAY**



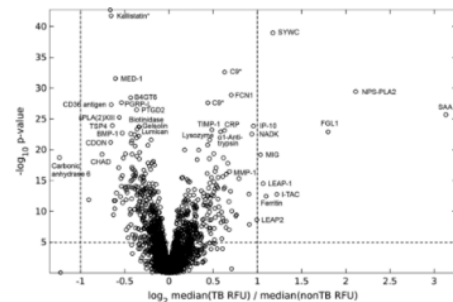
**FUJIFILM**



# Host protein signatures

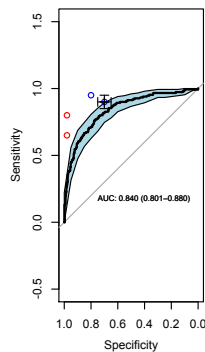
Promising developments but major challenges remaining

## 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**



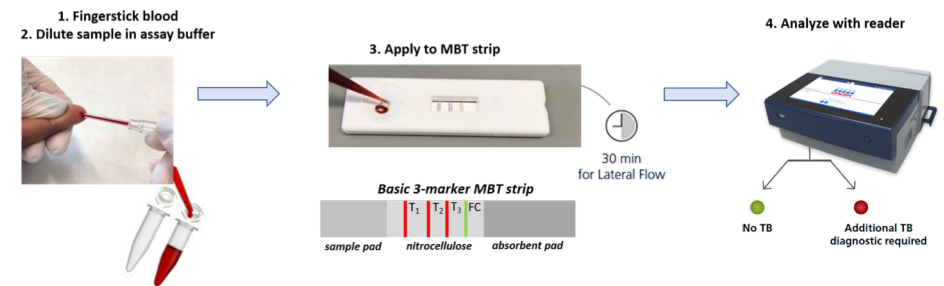
A reader

A kit for a rapid test

## ScreenTB project (Gerhard Walzl's group)



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



Courtesy Gerhard Walzl

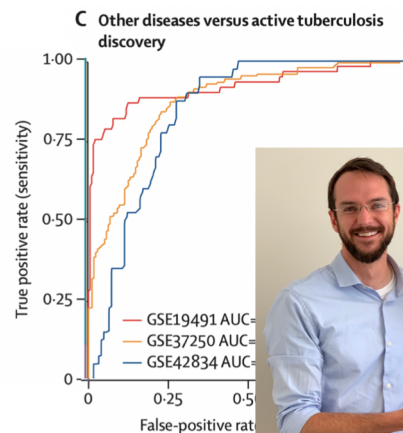
**Challenge: finding universal signature and cut-off & implement as simple test at low cost**



# Host RNA signatures

Extensive work in basic science starting to yield first products

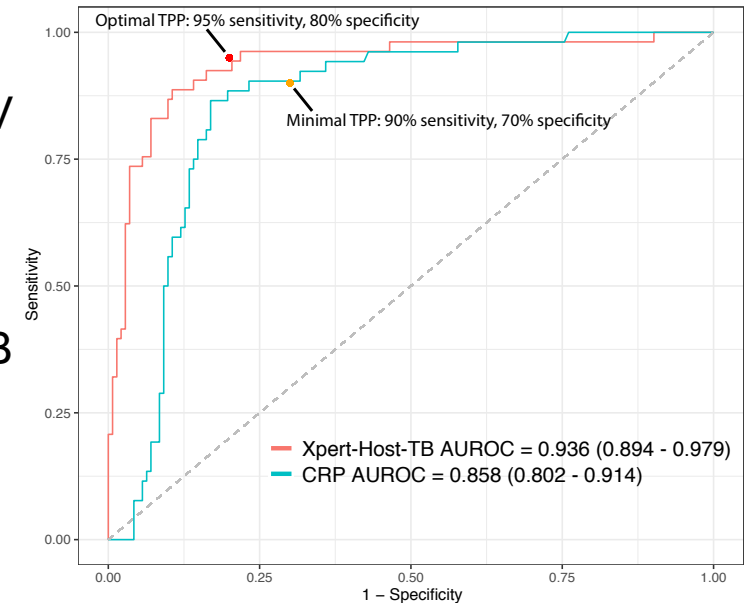
## RNA signature discovery



Sweeney et al, Lancet Respiratory Medicine 2016

## FIND validation study: '3-gene Xpert Prototype' cartridge from Cepheid\*

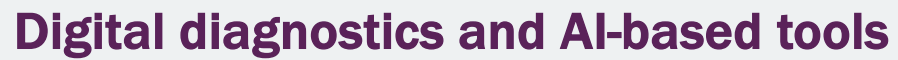
- Evaluation of performance among people living with HIV
- Biobanked blood samples (PAXgene)
- 201 patients, 67 MTB culture-positive
- Sens 91%, Spec 86% (vs Xpert)



Manuscript in preparation

\*Product in development. Not for use in diagnostic procedures. Not reviewed by any regulatory body.





## The potential of digital diagnostics

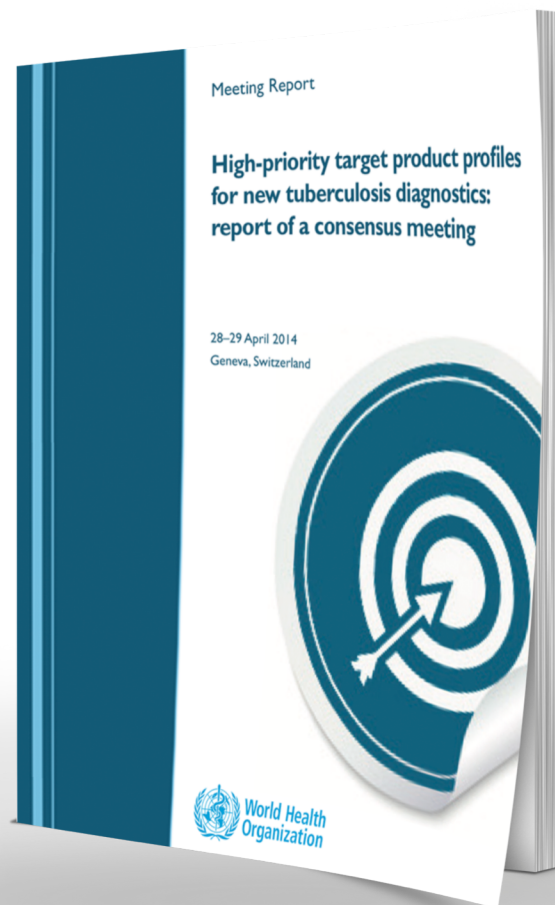
- ## Handheld digital ultrasound





## 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

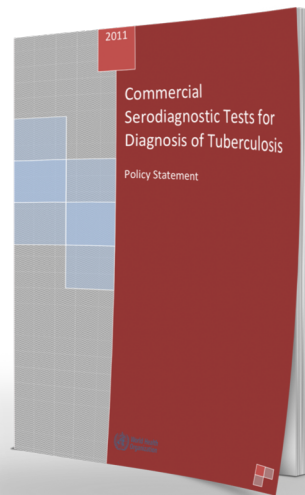
4

Drug susceptibility tests



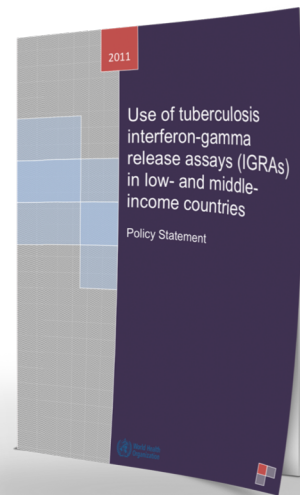
## Non-sputum Diagnostics: what do we have?

### Serological tests



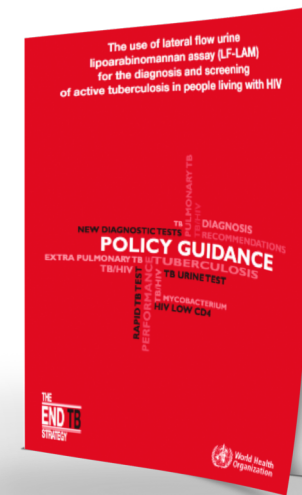
“... it is strongly recommended that these tests not be used for the diagnosis of pulmonary and extra-pulmonary TB.”

### 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

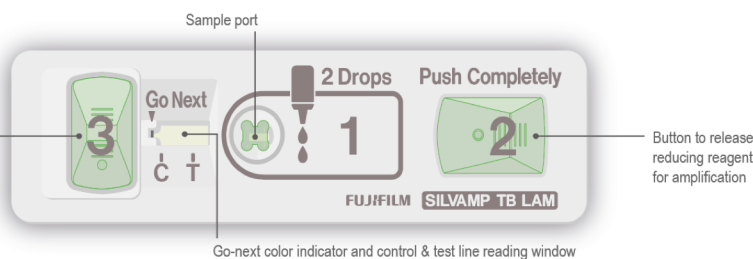


## Fujifilm SILVAMP TB LAM

First of a new generation of highly sensitive urine LAM assays

TB Test Device

Button to release silver ion reagent for amplification



**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

### Novel lipoarabinomannan point-of-care tuberculosis test for people with HIV: a diagnostic accuracy study

Tabias Broger\*, Bianca Sassen\*, Eiloise du Toit, Andrew D Kerkhoff, Charlotte Schutz, Elena Ivanova Reipold, Amy Ward, David A Barr, Aurélien Macé, Andre Trollip, Rosie Burton, Stefano Ongarello, Abraham Pinter, Todd L Lowary, Catharina Boehme, Mark P Nicol, Graeme Meintjes†, Claudia M Denkinger†



## 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

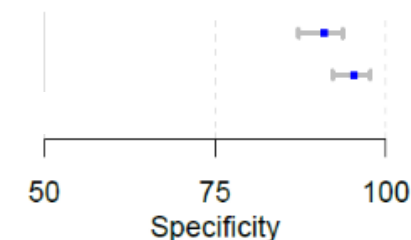
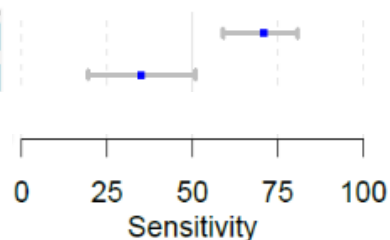




# Comparative performance of Fuji LAM and Alere LAM in PLHIV

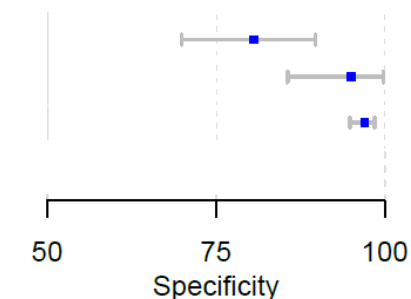
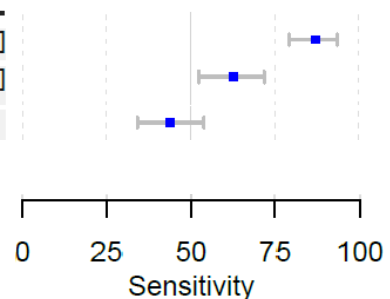
Meta-analysis of 1,600 patients

|          | N    | TP  | FP | FN  | TN  | Sn   | [95% CI]      | Sp   | [95% CI]      |
|----------|------|-----|----|-----|-----|------|---------------|------|---------------|
| FujiLAM  | 1595 | 541 | 76 | 183 | 795 | 70.7 | [59.0 – 80.8] | 90.9 | [87.2 – 93.7] |
| AlereLAM | 1595 | 307 | 41 | 417 | 830 | 34.9 | [19.5 – 50.9] | 95.3 | [92.2 – 97.7] |



Stratification by CD4 count

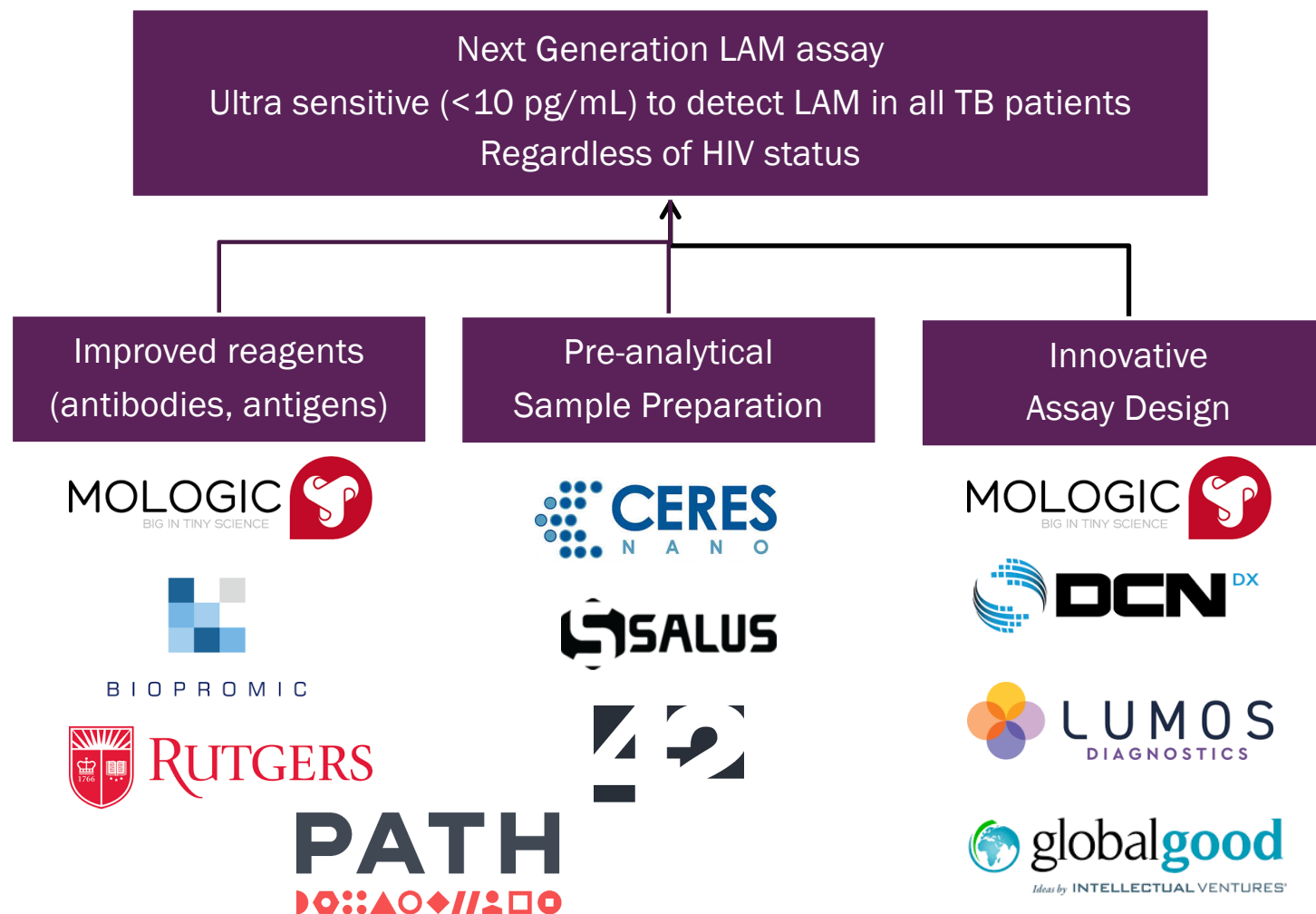
|             | N   | TP  | FP | FN | TN  | Sn   | [95% CI]      | Sp   | [95% CI]      |
|-------------|-----|-----|----|----|-----|------|---------------|------|---------------|
| MRS         |     |     |    |    |     |      |               |      |               |
| CD4 0-100   | 677 | 379 | 52 | 53 | 193 | 87.1 | [79.3 – 93.6] | 80.5 | [69.8 – 89.7] |
| CD4 101-200 | 319 | 100 | 10 | 57 | 152 | 62.7 | [52.4 – 71.9] | 95.0 | [85.6 – 99.8] |
| CD4 >200    | 581 | 56  | 13 | 71 | 441 | 43.9 | [34.3 – 53.9] | 97.0 | [94.9 – 98.5] |



- 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?





## 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

Walters JCM 2018  
Marcy CID 2016

### Stool processing solutions

**Stool processing kit**  
(FIND & partners)



**Optimized Sucrose Flotation**  
(TB-Speed)



**Simple One-Step**  
(KNCV)



### Stool processing solutions

- 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



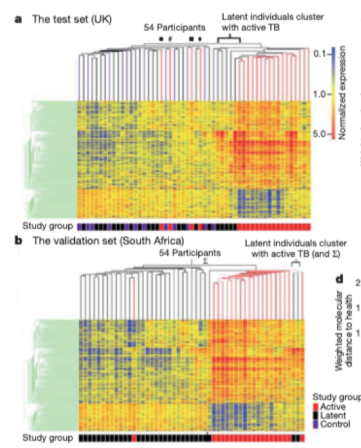
# New biomarkers & approaches to TB testing for triage and diagnosis

## Host RNA

Articles

### Genome-wide expression for diagnosis of pulmonary tuberculosis: a multicohort analysis

Timothy E Sweeney, Lindsay Browne, Cristina M Tate, Puneeth Khatri



Berry et al, Nature 2010  
Sweeney et al, Lancet Respiratory Medicine 2016

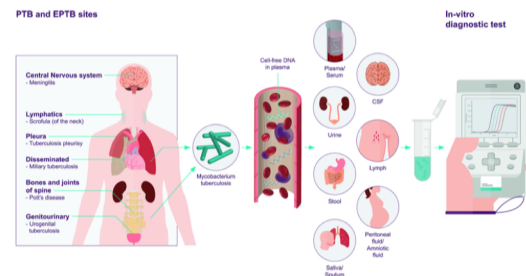
## Cell-free DNA / liquid biopsy

Journal of Clinical Microbiology®

MINIREVIEW

### Toward the Development of a Circulating Free DNA-Based In Vitro Diagnostic Test for Infectious Diseases: a Review of Evidence for Tuberculosis

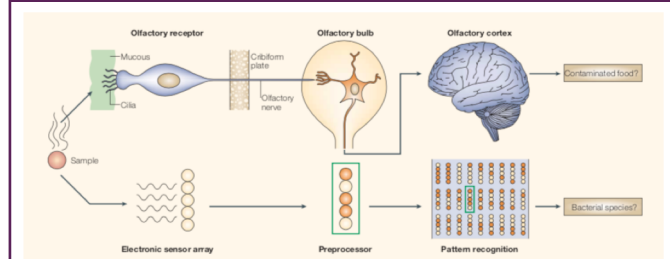
B. Leticia Fernández-Carballo,\* Tobias Broger,\* Romain Wyss,\* Niaz Banaei,\* Claudia M. Denlinger\*



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

Fernandez-Carballo et al., JCM 2019

## Breath tests & skin patches

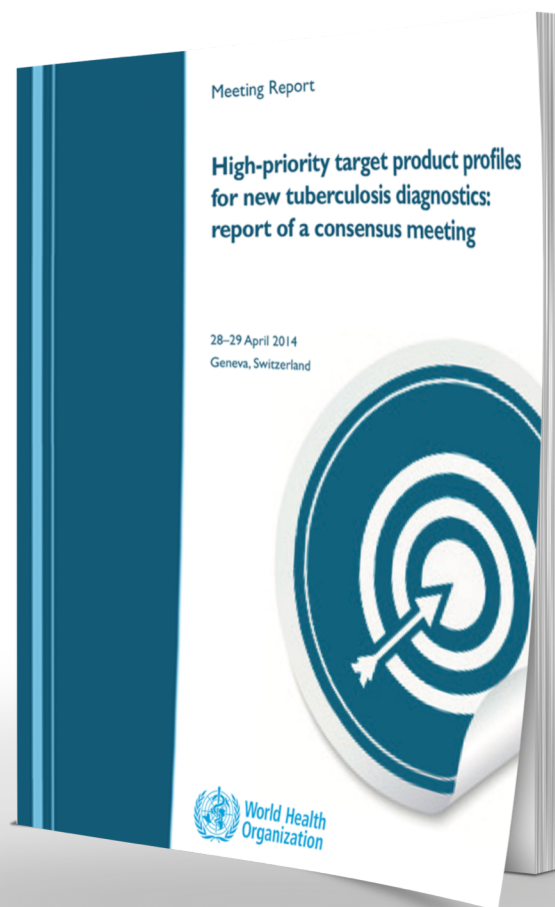


Turner et al., Nature Reviews Microbiology 2004



## 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



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

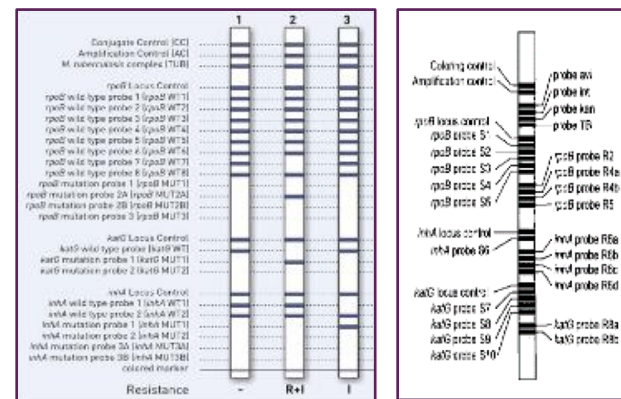
## Microscopy



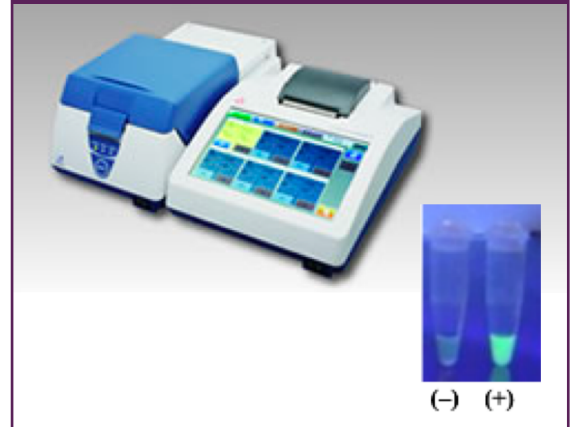
## MGIT



## LPAs



## LAMP



## GeneXpert







## 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

XDR assay in development

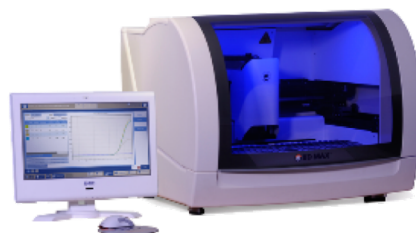


GenoXtract®96



FluoroCycler® 96

#### BD



BD MAX™

#### Roche



Roche: cobas® 6800 System

#### Bioneer

XDR assay in development



Bioneer: ExiStation™ Universal MDx System



# Sequencing

## Optimizing individualized care for DR-TB

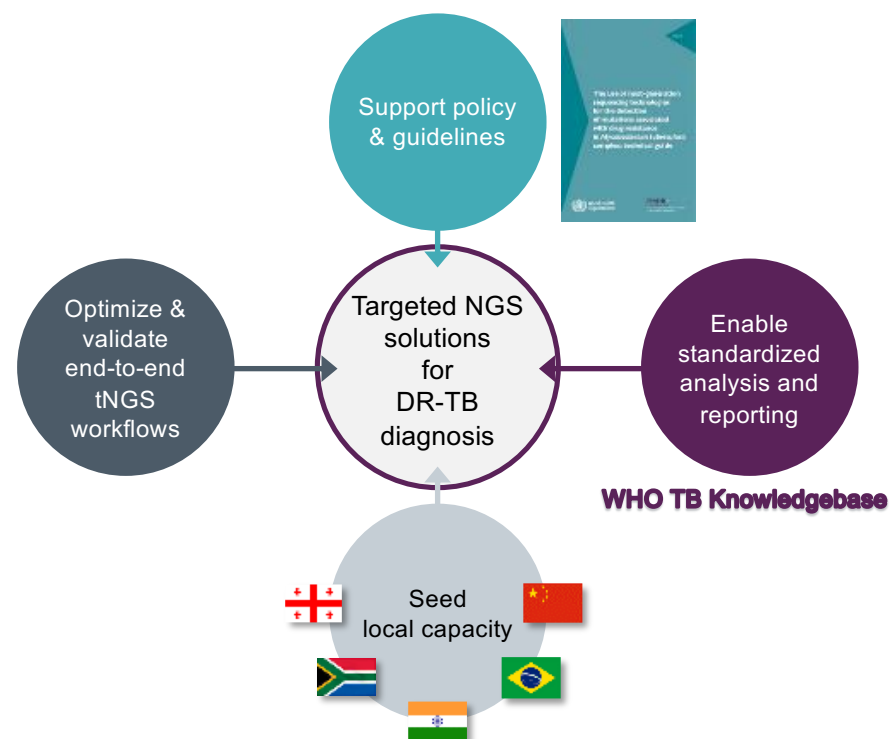
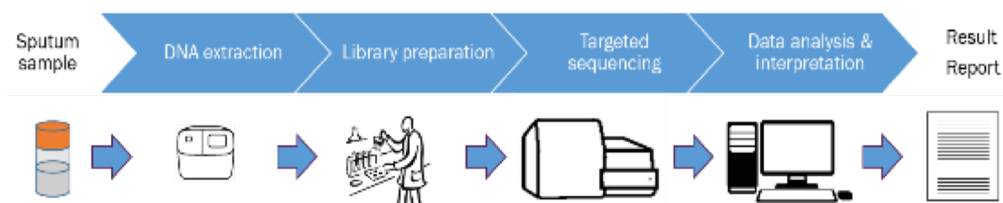


### FIND next-generation sequencing (NGS) strategy 2019–2022 (funded by Unitaidd)

- 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



|                           |   |
|---------------------------|---|
| Rapid                     | Huge potential for automation           |
| Minimal biosafety hazards | Benchtop workflow                       |
| Rapidly decreasing costs  | Designed for national/global networking |



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

WHO review of interim data in December 2019

### 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



WHO review of Omni and XDR cartridge planned for 2020

### Beyond 2019/20



Bioneer



QuantuMDx



BLINK



Ontera





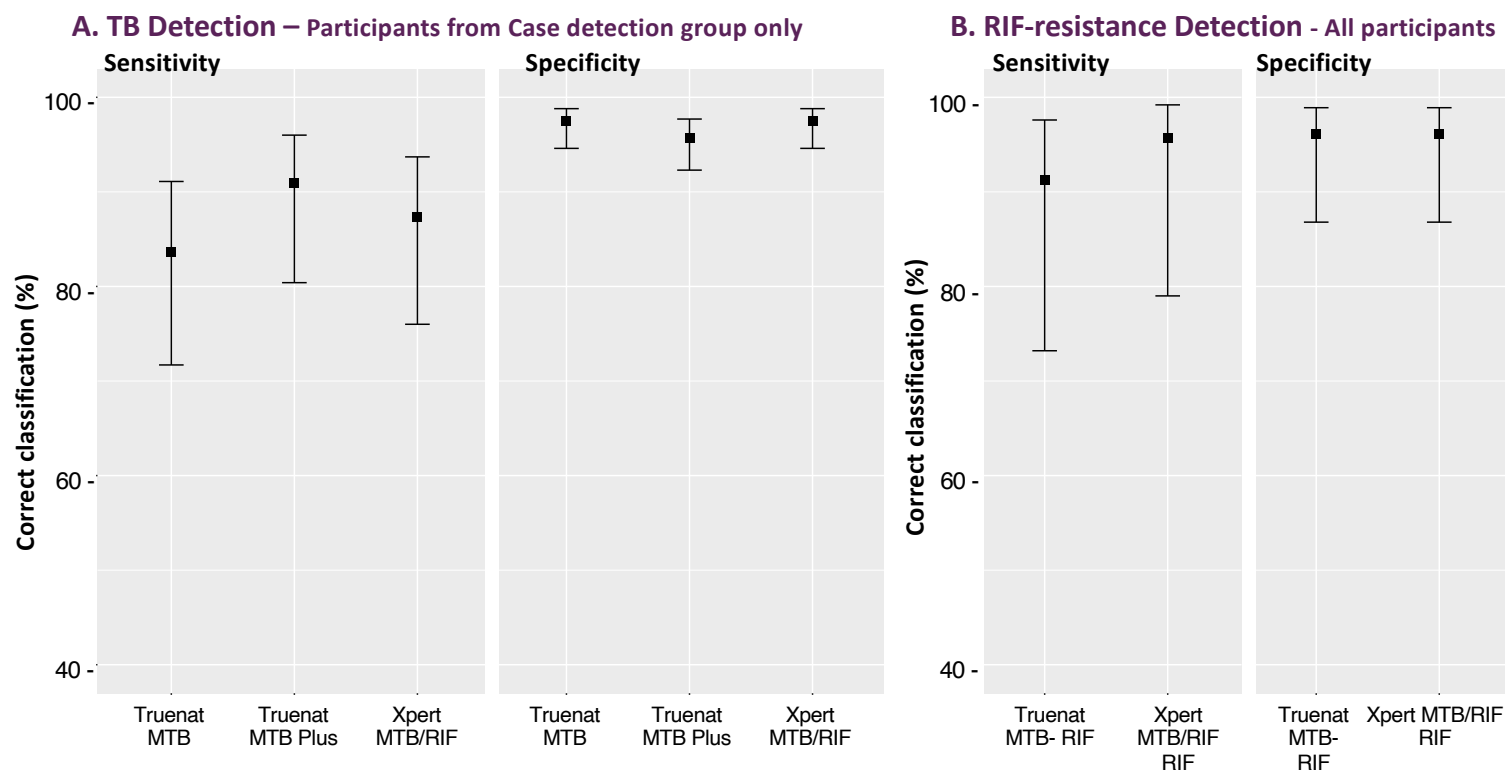
## First results from interim analysis of Molbio solution

### ■ 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





## 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  
Pamela Nabeta  
Adam Penn Nicholson  
Margaretha De Vos  
Audrey Albertini  
Anita Suresh  
Swapna Uplekar  
Tim Rodwell  
Sophia Georghiou  
Andre Trollip

Anna Mantsoki  
Aurelien Mace  
Emmanuel Moreau  
Sandra Kik  
Tobias Broger  
Claudia Denking  
Romain Wyss  
Karishma Saran  
Sarah-Jane Loveday