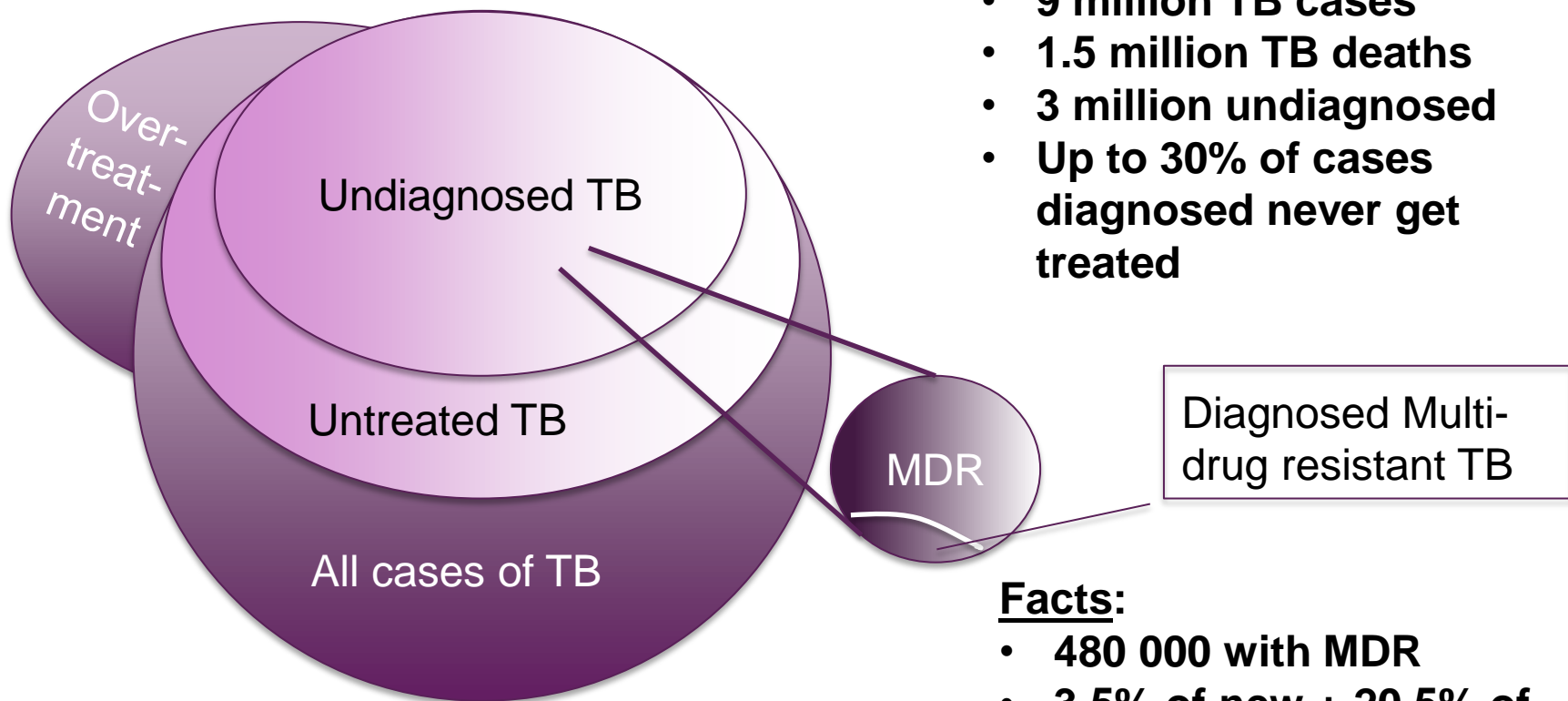# TB Diagnostics Pipeline

Claudia Denkinger
Head of TB, FIND

Koch Metschnikow Forum 2015

The Global TB Epidemic

Over-treat-ment

Undiagnosed TB

Untreated TB

All cases of TB

MDR

Diagnosed Multi-drug resistant TB

Facts:
- **9 million TB cases**
- **1.5 million TB deaths**
- **3 million undiagnosed**
- **Up to 30% of cases diagnosed never get treated**

Facts:
- **480 000 with MDR**
- **3.5% of new + 20.5% of previously treated TB cases**
- **Only 8.5% new + 17% prev. treated are diagnosed**

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WHO Global TB report 2014

Advancements in TB diagnostics

2006	2007	2008	2009	2010	2013	2014
➤ Smear-positive TB case definition	➤ Liquid culture	➤ LPA	➤ LED-FM	➤ Automated NAAT (Xpert MTB/RIF)	➤ Xpert EPTB	
➤ Number of smears	➤ Rapid speciation		➤ Front-loaded microscopy	➤ Negative rec: Serology		
➤ FM			➤ MODS, CRI, NRA cond.			

5-year vision for TB diagnosis

Triage/case finding –
first point of contact

1. Triage test
   - incl. for childhood TB & EDPT
2. Active case finding
   - Highly sensitive, portable
3. Syndromic test (Bact vs viral)

Further work up & treatment –
dedicated unit

1. TB confirmation with rapid DST for critical drugs
   - Incl. for childhood TB & EPTB
2. Treatment monitoring
3. TB infection with high risk of disease progression
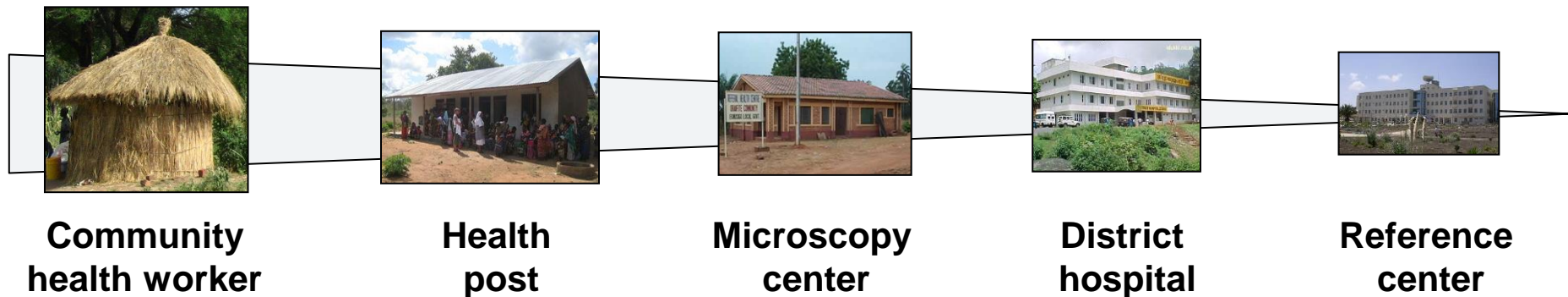
Surveillance, QA –
specialized unit

1. Real-time Surveillance
2. Comprehensive, rapid DST

E-Health supported solutions

Need for new tools spans the healthcare system, but concentrated at lower levels of the system

Community health worker — **Health post** — **Microscopy center** — **District hospital** — **Reference center**

A Passive & active case detection

B Rule out test

D Latent to active progression

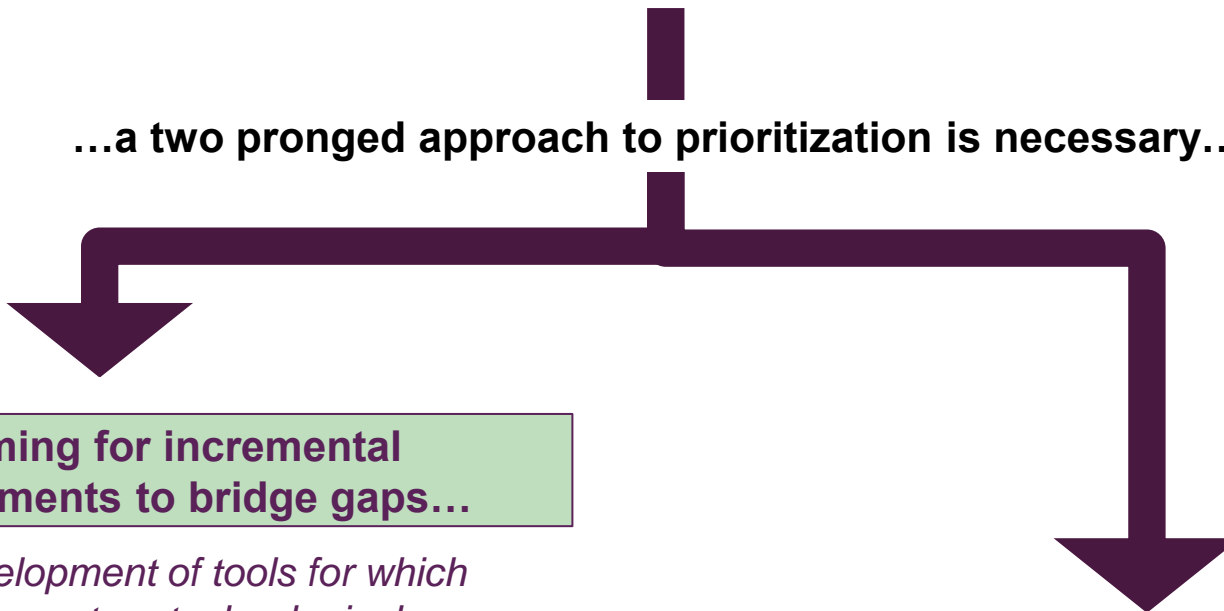**E** Drug susceptibility testing

F Treatment monitoring

eHealth and connectivity solutions

For novel tools, a two pronged approach in development is necessary

Given that tools to address the most critical needs in TB diagnosis are in the early stages of development (i.e. biomarker discover)…

…a two pronged approach to prioritization is necessary….

…aiming for incremental improvements to bridge gaps…

- *Support development of tools for which biomarkers or mature technological approaches (e.g., molecular) already exist*

- *Couple with strategies to maximize impact in the short term*

… and longer term, higher risk work with transformational potential

- *Biomarker discovery*

- *If/when suitable biomarkers are discovered, test development will become a top priority*

Global TB Diagnostic Pipeline

	Early development	Late or completed development	On pathway to WHO evaluation

High complexity assays

Molecular Detection/DST

Early development	Late or completed development	On pathway to WHO evaluation
TruArray MDR-TB (Akkoni) COBAS TaqMan MTB +DST(Roche) Hydra 1K (insilixa) Mycobacterium Real-time MDR (CapitalBio)	TRC Rapid MTB (Tosoh) VereMTB (Veredus Laboratories) LiPA Pyrazinamide (Nipro) LATE-PCR Lights on / Lights off (Hain) TBMDx (Abbott) Meltpro (Zeesan) Mycobacteria RT PCR (CapitalBio) REBA MTB-XDR (YD Diagnostics) EasyNAT TB (Ustar) BD Max (BD)	GenoTYPE MTBDRsl (Hain) LiPA MDR-TB (Nipro) REBA MTB-Rifa (YD Diagnostics)

Culture-based technologies

Early development	Late or completed development	On pathway to WHO evaluation
BNP Middlebrook (NanoLogix) Rapid colorimetric DST	TREK Sensitive MYCOTB (Trek)	

Moderate complexity assays

Molecular Detection/DST

Early development	Late or completed development	On pathway to WHO evaluation
Xpert Ultra and Xtend XDR (Cepheid) Alere Q (Alere) Enigma ML (Enigma Diagnostics) Q-POC (QuantuMDx) EOSCAPE (Wave80) RT-PCR Testing Platform (NWGHF/Guidel) iCubate 2.0 (iCubate) TBDx system (KGI) DiagCORE (STAT Diagnostica) LabChip G2-3 (Nanobiosys)	Genedrive MTB/RIF (Epistem) Truelab/Truenat MTB (Molbio)	TB LAMP (Eiken)

Volatile organic compounds

Early development	Late or completed development	On pathway to WHO evaluation
BreathLink (Menssana) Prototype breathanalyzer (Next Dimensions) TB Breathalyser (Rapid Biosensor Systems) Aeonose (The eNose Company) Breath analysis instrument (Metabolomx)	Giant African Pouch Rats (Apopo)	

Automated Microscopy & Imaging

| Early development	Late or completed development	On pathway to WHO evaluation
TBDx (Applied Visual Sciences) Fluorescent microscopy (ID-FISH Tech.) Automatic TB Screener (Fluorobot)	Microimager (BD) CAD4TB (Delft Imaging Systems)	

Low complexity assays

Antigen & Antibody detection

Early development	Late or completed development	On pathway to WHO evaluation
LAM in sputum (Standard Diagnostics) Multiplex antibody array (mBio)		Alere Determine TB-LAM in urine (Alere)

Enzymatic detection/DST

Early development	Late or completed development	On pathway to WHO evaluation
β-lactamase reporter (Global BioDiagnostics)		

Molecular Tests
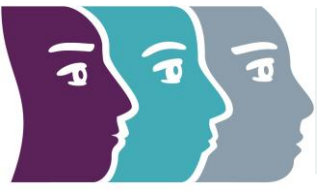
Lessons learned from Xpert

Test

Solution elements

Next generation molecular detection + DST

Strategic approach	**Market diversification**

- Increase portability
- Increase ruggedness
- Improve performance
- Increase DST portfolio

Technical approach	

- PCR
  - Beacon-based approach
  - Melt-curve analysis
  - Line-probe assays
- Isothermal
- Microarrays
- Nano-wires

High complexity assays

Hain GenoType MTBDR*plus* · Veredus Laboratories VereMTB™ · Zeesan MeltPro® · Nipro LiPA PZA & MDR · CapitalBio MTB-MDR · Illumina Next-Generation Sequencing · BD BD Max · Roche Cobas · Abbott *TBMDx* · Hain GenoType MTBDR*sl* · YD REBA MTB-XDR REBA MTB-Rifa · Hain LATE PCR Lights on /Lights off MTB-PZA

Moderate complexity assays

Cepheid Xpert® MTB/RIF · iCubate · NanoBioSys LabChip G2-3 · Cepheid Xpert®Ultra Xtend-XDR · EnigmaML® MDR TB · Ustar MTB · Akkoni MDR-TB · Eiken TBLAMP™ · Veredus Laboratories VereMTB™ · Northwestern GHT/Quidel

MolBio Truelab/Truenat · KGI TBDx System · Wave80 EOSCAPE · Alere™ Q · Epistem Genedrive® · STAT-Diagnostica DiagCORE · InSilixa HYDRA · QuantuMDx Q-POC™

2015 · 2016 · 2017

WHO-endorsed	Limited commercial availability	In development

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What needs do novel platforms address

New NAAT platforms

Needs addressed

Decentralization

Improving time to diagnosis

Improving MTB detection
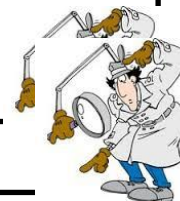
Higher throughput, multiplexing

Extended, timely DST

Insilixa HYDRA

GenePOC

Antibiotic

Resistance

Beyond pulmonary TB

Policy update: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children

Xpert MTB/RIF implementation manual: technical and operational 'how-to'; practical considerations

Recommendations for lymph node aspirates, tissue biopsy, cerebrospinal fluid

→ Invasive procedures still necessary!

Expanding utility of molecular tools

Improving detection of Extrapulmonary & Pediatric TB

Destruction

Cell-free nucleic acid enters bloodstream

Cell-free DNA passes kidneys

Cell-free DNA can be measured in urine

Xpert for MTB detection on stool

Trans-renal DNA detection
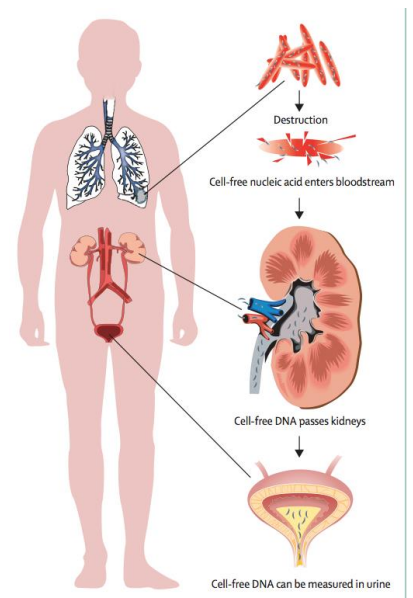
Green Lancet ID 2009

What is coming after NAATs
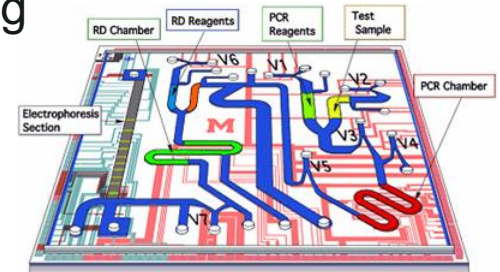
Strategic approach	New NAAT platforms	Sequencing	Lab-on-a-chip
	Simplify solutions & improv performance & increase DST portfolio	Introduce for surveillance & solve specimen processing & data interpretation	
Activities	BD, Alere, molbio, epistem, ABBOTT, QuantuMD, Cepheid	ion torrent, illumina, QIAGEN, PACIFIC BIOSCIENCES	Solving problem of sample volume & specimen processing

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What is coming after NAATs
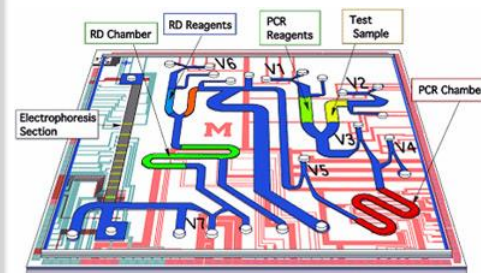
Strategic approach	New NAAT platforms	Sequencing		Lab-on-a-chip
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Activities				Solving problem of sample volume & specimen processing

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Biomarker work –
Detection and triage test

Various biomarker approaches

Level of certainty in Biomarker

Ease of translating onto a point of care platform

VOC (breath)
- Graham
- Menssana
- Next Dimensions
- Rapid Biosensor Systems
- The eNose Company
- Metabolomx
- K-Rith (urease)
- Timmins (INH)

Antibodies (b)
- Anderson
- Lowary
- FIND

Proteins (s, b, u)
- Dobos
- Moritz
- Feldheim
- Campos
- Ochsner
- Kaufmann
- Laal
- Proteinlogic
- FIND

Metabolites (s, b, u)
- Feldheim

Whole Bug (s)
Nucleic Acids (s)
- Fast followers

Enzymes (s, b, u)
- GBD (β-lactamase)

Sugars (s)
- Belisle

Nucleic Acids (u, b)
- LMU
- Levin
- Cirillo

Cellular stimulation (b)
- Geldmacher
- Modlin
- Lewinsohn

Mycolic acids/lipids (u)
- Belisle

microRNA(b, u)
- Cirillo
- Zhou
- Xu

Mycolic acids/lipids (s)
- Belisle
- Bangor U

Requirements:
- **Systematic approaches**
- **Large well-characterized sample repositories**

s – sputum
u – urine
b –whole blood

Biomarker efforts at FIND
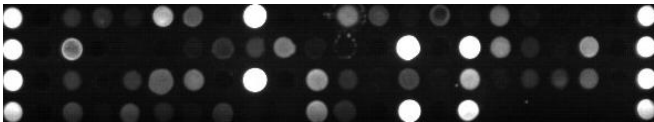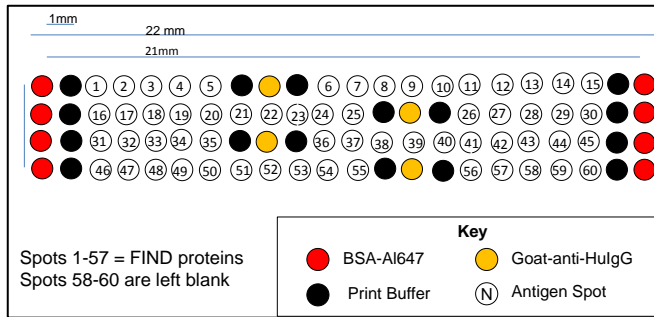
Schematic and representative image of MBio-FIND
TB Serology Array.

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β-lactamase detection

Rapid point-of-care detection of the tuberculosis pathogen using a BlaC-specific fluorogenic probe

Hexin Xie[1†], Joseph Mire[2†], Ying Kong[3†], MiHee Chang[3], Hany A. Hassounah[3], Chris N. Thornton[4], James C. Sacchettini[2], Jeffrey D. Cirillo[3] and Jianghong Rao[1*]

Prior to mapping for lux intensity

After mapping for lux intensity

0   <10   10 10^2 10^3 10^4 10^5
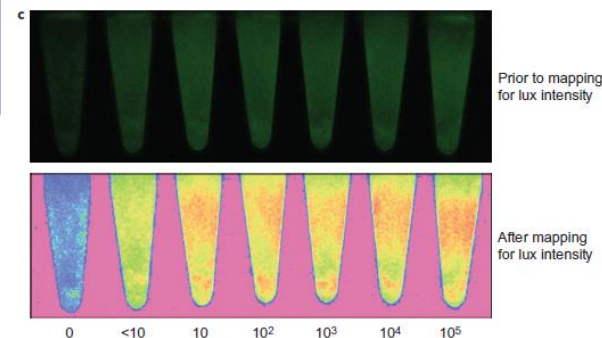
Reporter Enzyme Fluorescence

BlaC Enzyme

M. tb

CDG -3
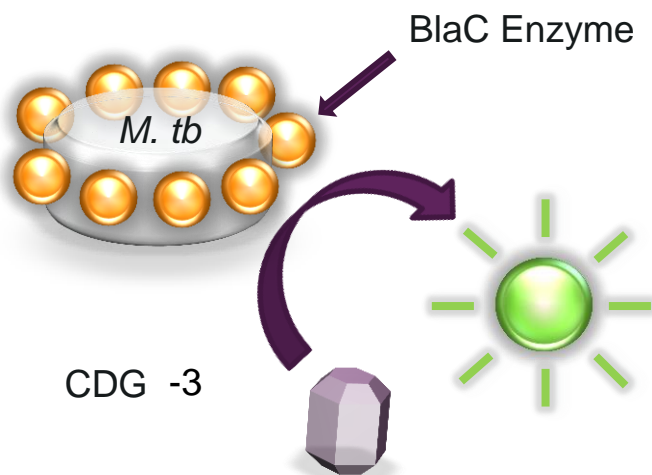
Feasibility study of early prototype reagent system in South Africa

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Incremental improvement on existing technologies

Automating smear microscopy
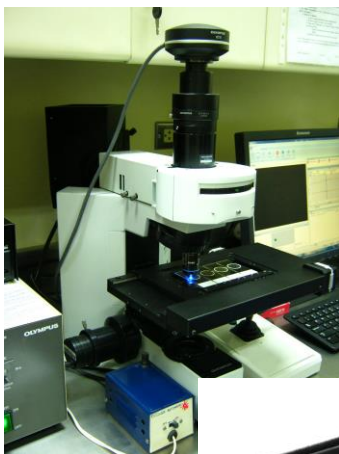
■ Automated reading
- TBDx (Applied Visual Sciences)
- CellScope TB Microscope (UCSF)
- Fluorobot

■ Automated staining
- RALSTAINER (bioMérieux)
- Aerospray TB (ELITechGroup)

■ Combined
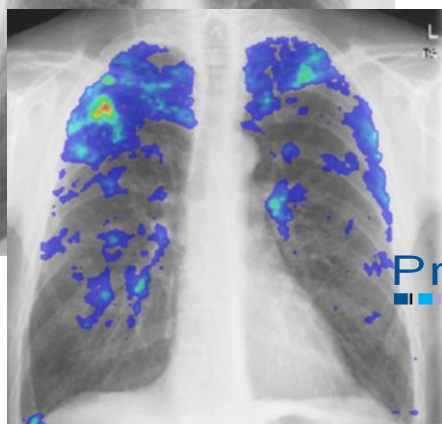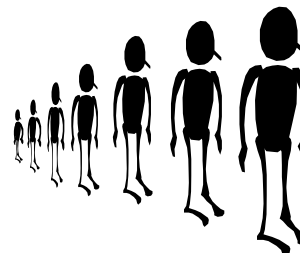- MIAFB2 (BD)

Thinking about novel strategies
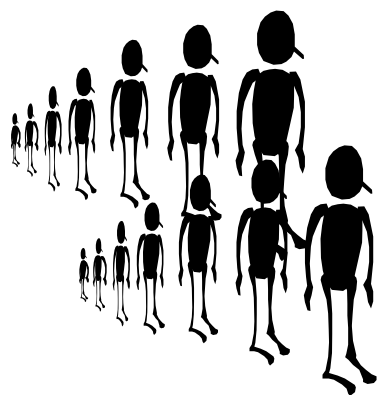
Further testing

High Sensitivity
Lower specificity
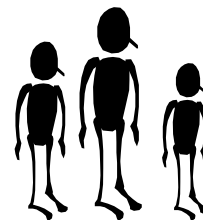
Ruled OUT

Portable digital X-ray + interpretation (e.g. CAD4TB)
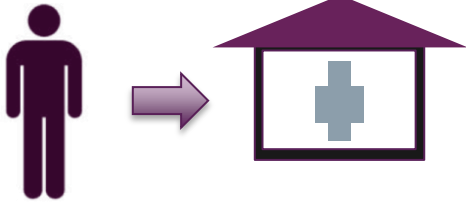
Antibody/antigen-based assay or enzymatic assay

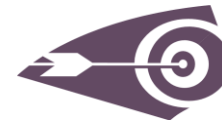Confirmatory test (e.g. Xpert)

ProteinLogic
Pattern-based medicine

Syndromic approach

Fever, cough, weight loss

? Bacterial, viral, TB

? Severity

? Resistance

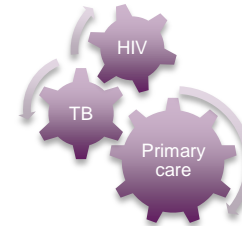**Potential impact**

Targeted therapy

Reduction in antibiotic use

Integrated care

HIV

TB

Primary care

Thank you! Questions?

FIND
Catharina Boehme
Peter Kaspar
David Dolinger
Tobias Broger

Swiss TPH
Klaus Reiter

Rutgers
David Alland
Priya Banada

Path
David Boyle

Hopkins
Maunank Shah