foundation
for innovative new diagnostics

TB Diagnostics: Progress, needs, pipeline

Catharina Boehme

EDCTP Stakeholder Meeting: Tuberculosis and mycobacterial infections

28 – 29 October 2013

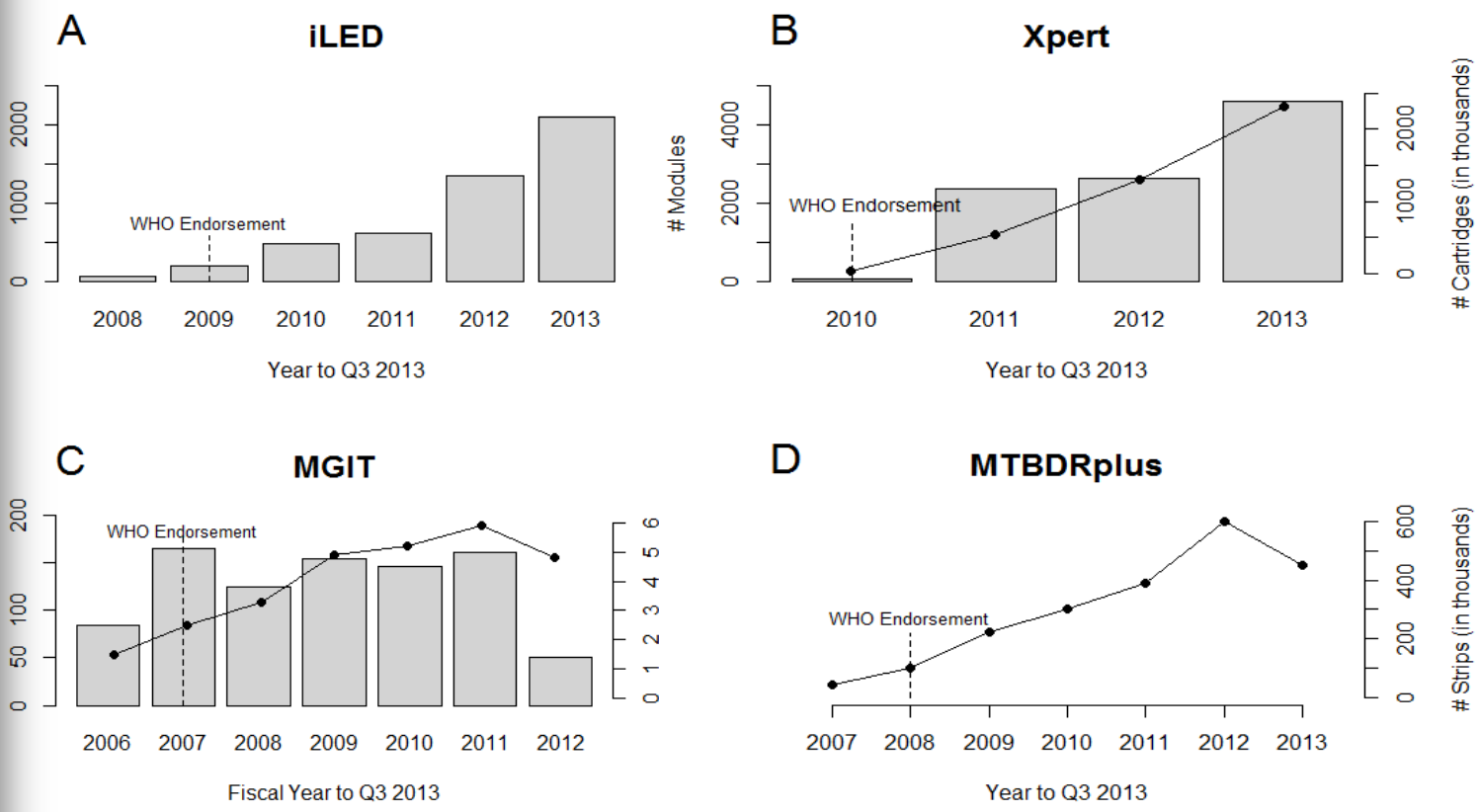
Paris

Partnering for better diagnosis for all

Advancements in TB diagnostics as per WHO recommendations, 2006-2013

2006	2007	2008	2009	2010	2013
➢ Smear-positive TB case definition	➢ Liquid culture	➢ LPA	➢ LED-FM	➢ Automated NAAT (Xpert MTB/RIF)	➢ Xpert in extrapulmonary TB
➢ Number of smears	➢ Rapid speciation		➢ Front-loading microscopy	➢ Against Serology	
➢ FM			➢ MODS, CRI, NRA (conditional)	➢ Against IGRA	

Uptake of new TB diagnostics



Translate opportunities into impact

New WHO endorsed TB tools offer real opportunity to

- Enhance case detection & Rapidly identify drug resistance & Reduce time to treatment & default

Let's learn how to use these and future tools optimally

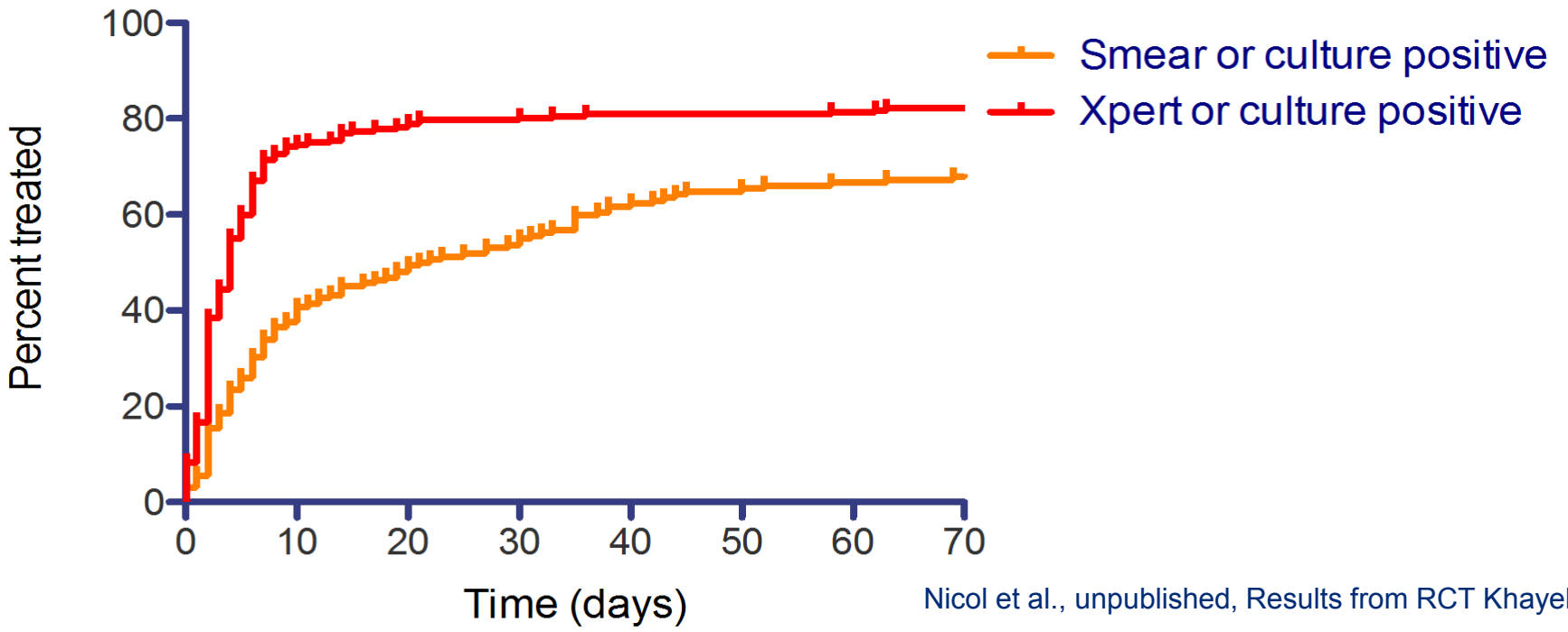
- New insights into broader problems within the health system
- Use this evidence and do more OR to improve infrastructure & linkage to care
- Innovative partnerships help to maximize impact (across diseases; across sectors)
- Preparing the ground for speedy uptake of optimized tools

Supply, customer support, QA, data management, lab integration

Linkage to public and private treatment providers: acceptance, data access, logistics, insentives

Linkage to patients: alerts, insentives, health insurance schemes

Potential impact of new tools greater than actual impact (– where known…)



Nicol et al., unpublished, Results from RCT Khayelitsha/Paarl)

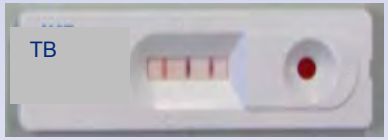
- Patient drop out rates and remaining tx delays
- Patient access limited (tech limitations, coverage, linkage to care)

CAVEAT: Impact measurement challenging: Not only depending on dx intervention; overtreatment at baseline

Major unmet needs remain

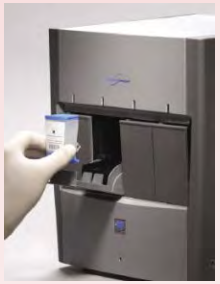
Screening at first point of contact

1. Triaging test
   - Incl. for childhood TB & EPTB
   - Passive / active screening
2. TB infection with high risk of disease progression



Work up & choice of treatment at dedicated unit

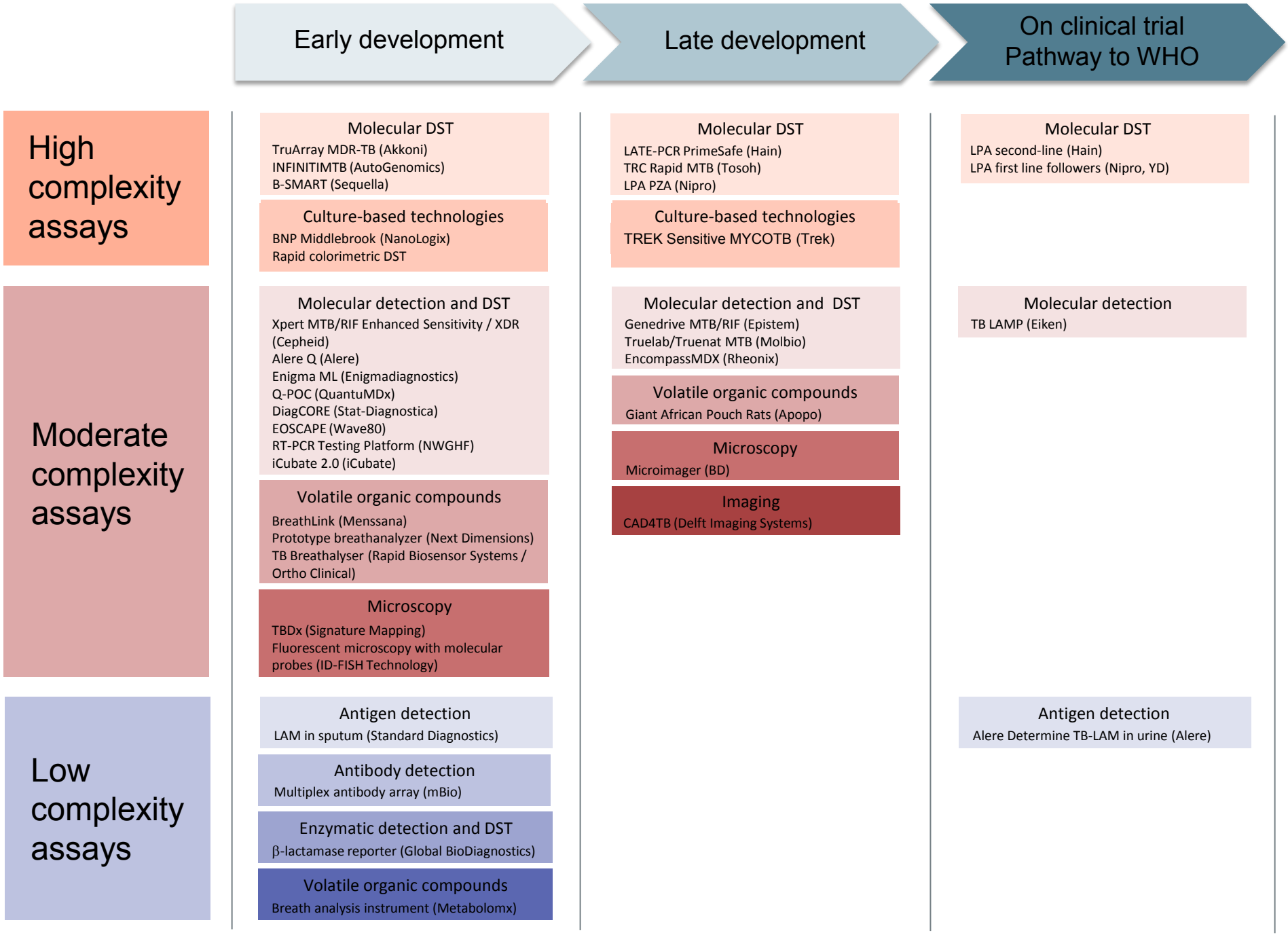
1. TB confirmation with rapid DST to critical drugs
   - Incl. for childhood TB & EPTB
2. Treatment monitoring
3. Multiplex test to manage TB-neg



Support, surveillance, QA at specialized unit

1. Comprehensive, rapid DST

M-Health supported network


Early development
Late development
On clinical trial
Pathway to WHO
High complexity assays
Moderate complexity assays
Low complexity assays
Molecular DST
TruArray MDR-TB (Akkoni)
INFINITIMTB (AutoGenomics)
B-SMART (Sequella)
Culture-based technologies
BNP Middlebrook (NanoLogix)
Rapid colorimetric DST
Molecular detection and DST
Xpert MTB/RIF Enhanced Sensitivity / XDR (Cepheid)
Alere Q (Alere)
Enigma ML (Enigmadiagnostics)
Q-POC (QuantuMDx)
DiagCORE (Stat-Diagnostica)
EOSCAPE (Wave80)
RT-PCR Testing Platform (NWGHF)
iCubate 2.0 (iCubate)
Volatile organic compounds
BreathLink (Menssana)
Prototype breathanalyzer (Next Dimensions)
TB Breathalyser (Rapid Biosensor Systems / Ortho Clinical)
Microscopy
TBDx (Signature Mapping)
Fluorescent microscopy with molecular probes (ID-FISH Technology)
Antigen detection
LAM in sputum (Standard Diagnostics)
Antibody detection
Multiplex antibody array (mBio)
Enzymatic detection and DST
β-lactamase reporter (Global BioDiagnostics)
Volatile organic compounds
Breath analysis instrument (Metabolomx)
Molecular DST
LATE-PCR PrimeSafe (Hain)
TRC Rapid MTB (Tosoh)
LPA PZA (Nipro)
Culture-based technologies
TREK Sensitive MYCOTB (Trek)
Molecular detection and DST
Genedrive MTB/RIF (Epistem)
Truelab/Truenat MTB (Molbio)
EncompassMDX (Rheonix)
Volatile organic compounds
Giant African Pouch Rats (Apopo)
Microscopy
Microimager (BD)
Imaging
CAD4TB (Delft Imaging Systems)
Molecular DST
LPA second-line (Hain)
LPA first line followers (Nipro, YD)
Molecular detection
TB LAMP (Eiken)
Antigen detection
Alere Determine TB-LAM in urine (Alere)

Key approaches to fill TB diagnostics gaps

1. Molecular detection

State of science

>10 NAAT platforms in development

- Development of fast follower platforms slower than expected.
- Promising amplification & detection technologies, but no proof-of-principle for point-of-care.

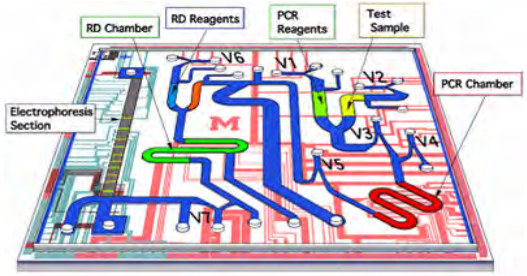
Strategic approach

New generation NAAT platforms

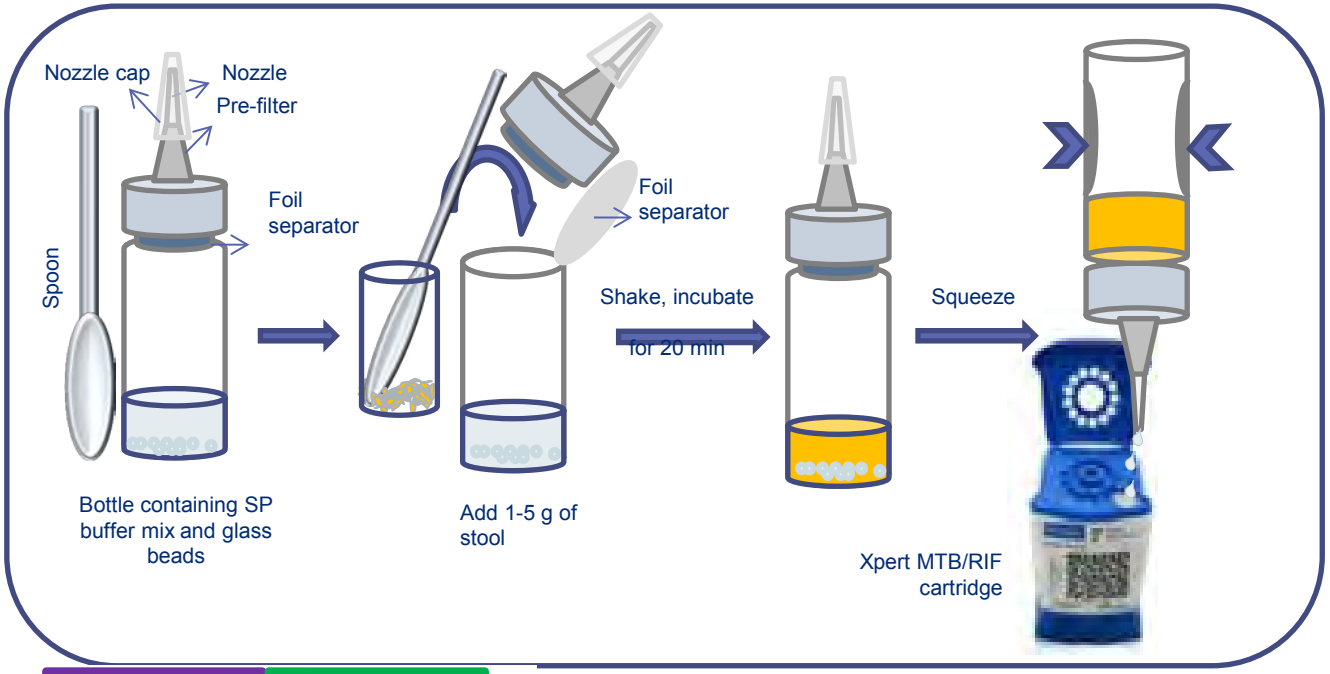
Simplifying & minimizing macrofluidics

Lab-on-a-chip

Isothermal amplification & solving problem of sample volume

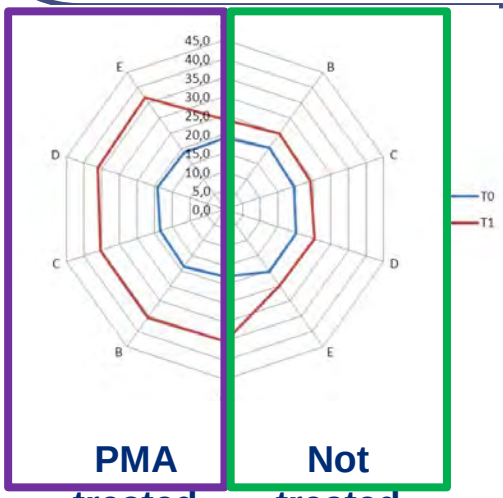


Extending utility of molecular tools



Improving detection of Extrapulmonary & Pediatric TB

David Alland, UMDNJ, US



Treatment monitoring

Target	Targeted strand	Target primers
gyrA QRDR	Sense	gyrA-F
gyrB 500-543	Sense	gyrB-F1, gyrB-F2
katG 315-316	Sense	katG-F
inhA -8 to -16	Antisense	inhA-R
embB 306	Sense	embB-F
Rrs 1400-1484	Antisense	rrs-R
B. globii (control)	Sense	Bg-R

Expanding drug menu

Key approaches to fill TB diagnostics gaps

2. Antigen detection

State of science

Author/Year	Sample
Cho, 1990	Sputum
Sada, 1992	Serum
Lee, 1997	Sputum
Pereira, 2000	Sputum
Hamasur, 2001	Urine
Tessema 2001	Urine
Boehme 2005	Urine

LAM early data - Literature overview

Sensitivity ss+ TB		Sensitivity ss- TB		Specificity Non-TB	Specificity healthy
62% (75/119)		**28%** (22/80)		**93%** (240/258)	**99%** (222/224)
HIV+	HIV -	HIV+	HIV -		
79%	42%	32%	25%		

Chemogen prototype ELISA evaluation in Tanzania, 2006.

- LAM in urine only validated marker

Strategic approach

Novel targets

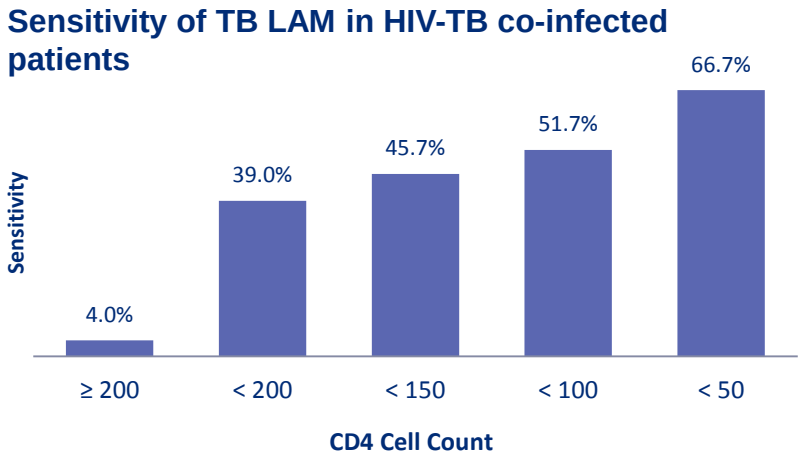
Apply new tools for AG discovery

Better detection technology

Such as fluorescence labeled LFI

Urinary LAM (Alere Determine) as a screening test for TB in HIV positives with low CD4 cell counts?

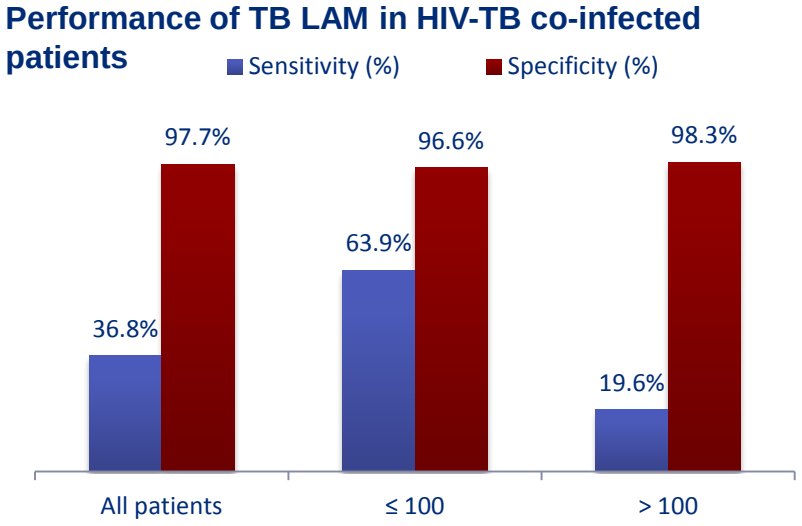
Lawn, SD et al 2012



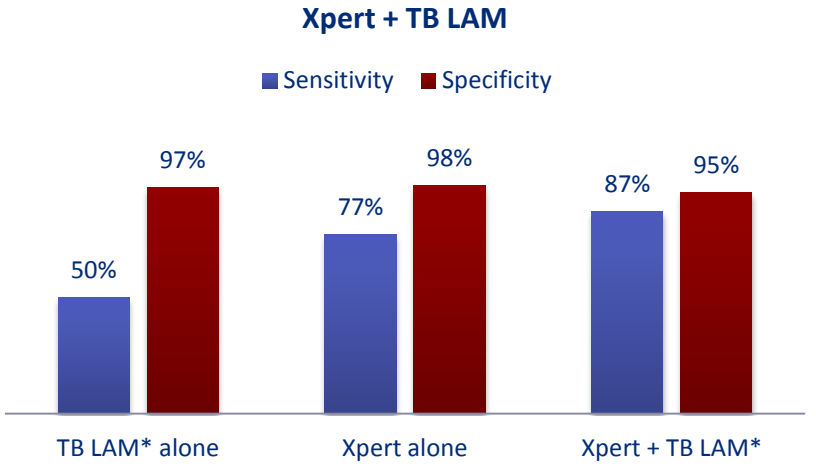
Peter, JG et al 2012

Against composit RS	Sensitivity (%)	Specificity (%)
All patients	45	96
CD4 > 200	29	100
CD4 ≤ 200	52	94

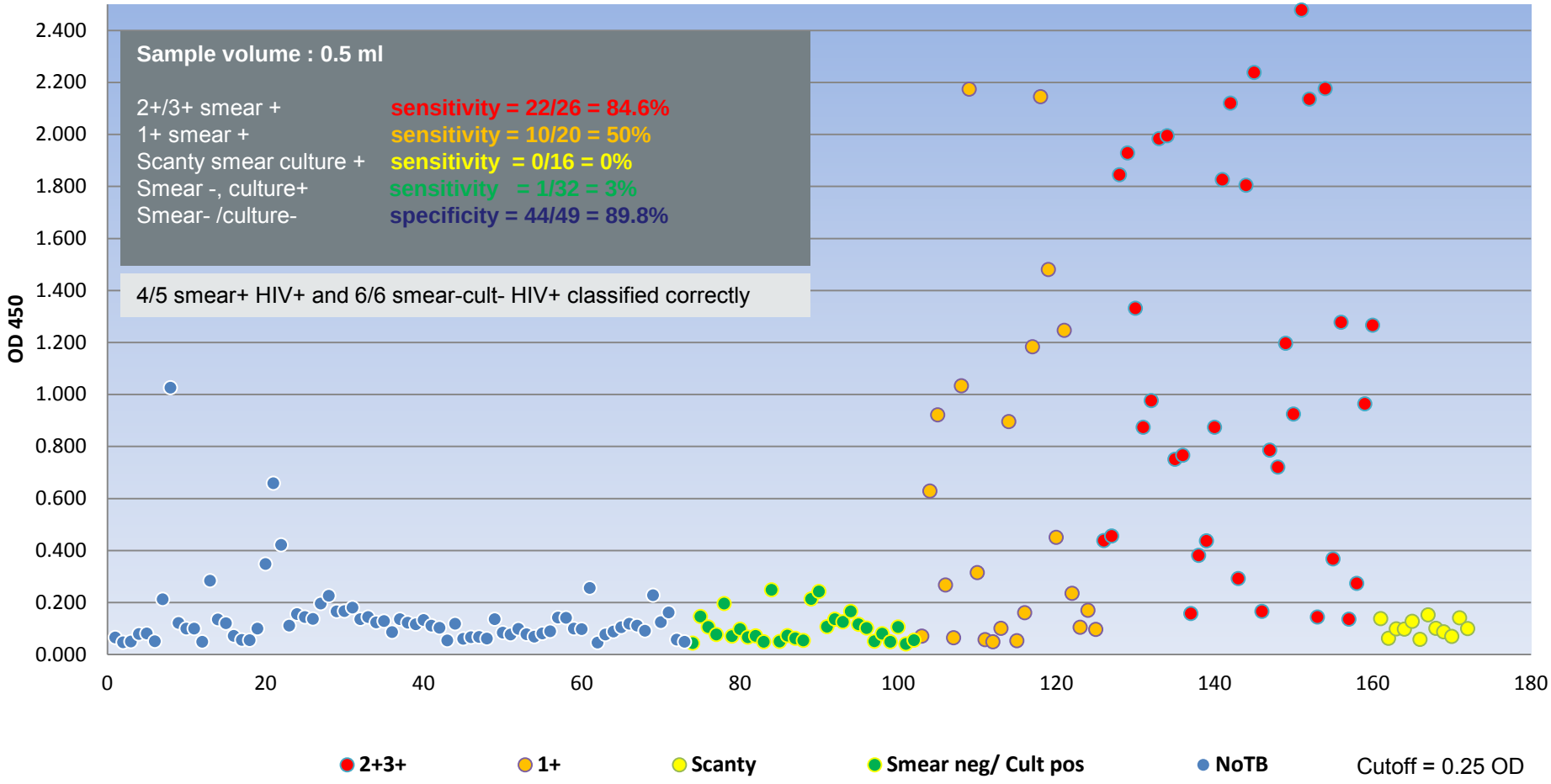
Dorman, S et al 2012



Shah, M et al 2012



LAM in sputum: Prototype accuracy similar to smear microscopy



Automating smear microscopy

β-lactamase detection

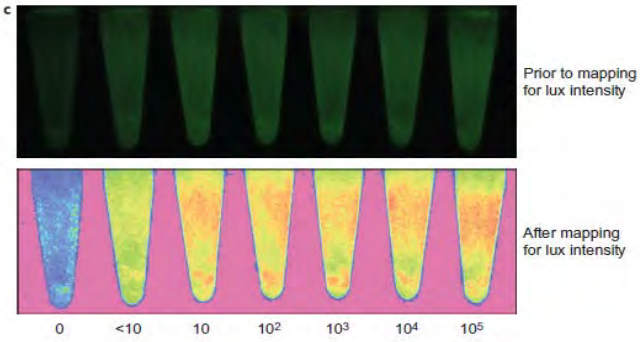
nature chemistry

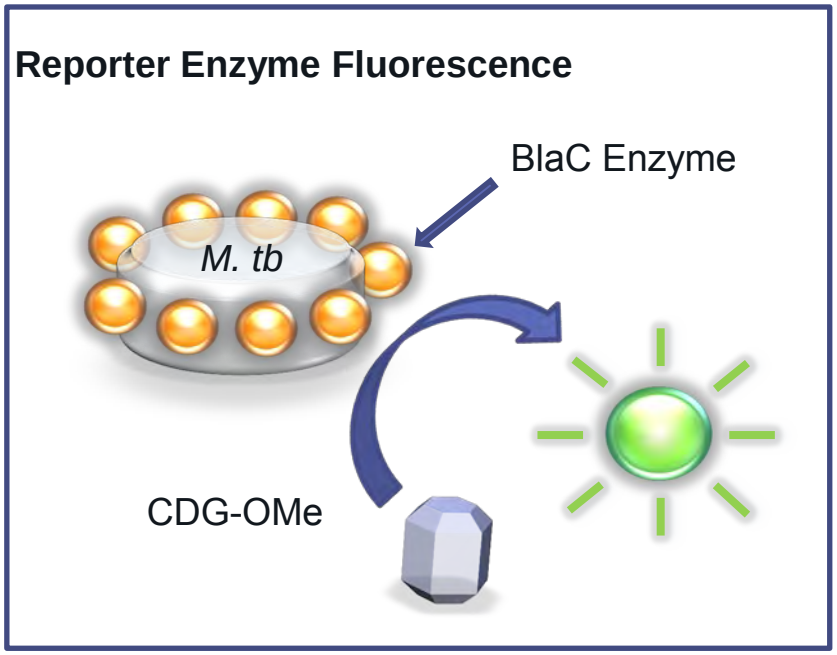
ARTICLES

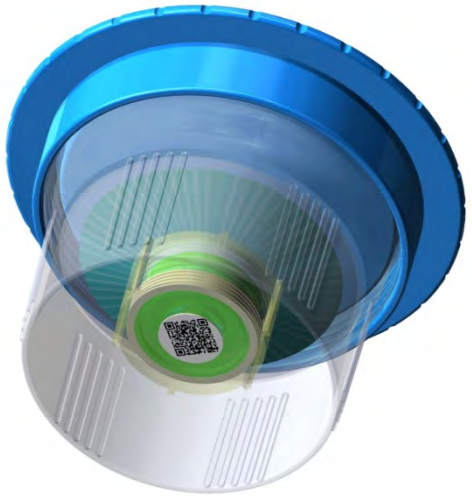
PUBLISHED ONLINE: 2 SEPTEMBER 2012 | DOI: 10.1038/NCHEM.1435

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*]







Key approaches to fill TB diagnostics gaps

3. Volatile Organic Compound detection

State of science

Olfactory sensing

e.g. Apopo

Enoses

VOC interact with polymer to produce change in electrical resistance.

Analytical noses

Miniature mass spec/chromatographic devices.

VOC in	Author/Year
Breath	Phillips, 2007
HS of culture	Trevejo, 2007
HS of culture	Syhre, 2008

- Proof-of-principle data with inadequate performance in feasibility studies

Strategic approach

MTB-specific VOC

Use of high end MS devices

Field-applicable detection technology

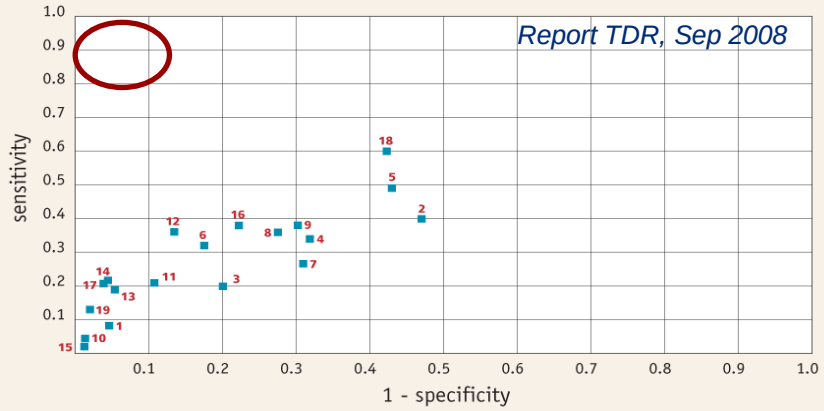
Miniaturization of sensitive MS

Key approaches to fill TB diagnostics gaps

4. Antibody detection

State of science

Figure 4. ROC curve of commercial rapid tests for the diagnosis of pulmonary tuberculosis (all patients, n=355)



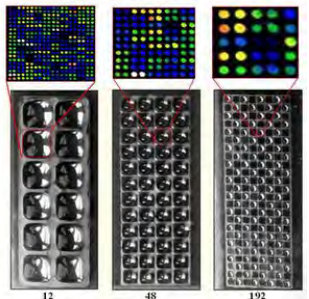
1. ABP Diagnostics **2.** Advanced Diagnostics **3.** American Bionostica **4.** Ameritek USA **5.** Bio-Medical Products **6.** Chembio Diagnostic Systems **7.** CTK Biotech **8.** Hema Diagnostic Systems **9.** Laboratorios Silanes **10.** Millennium Biotechnology **11.** Minerva BiOTECH **12.** Mossman Associates **13.** Pacific Biotech **14.** Premier Medical **15.** Princeton Biomeditech **16.** Span Diagnostics **17.** Standard Diagnostics **18.** Unimed International **19.** VEDA.LAB

Commercial serological antibody detection: Highly inconsistent sensitivity & specificity

- >30 tests based on narrow set of AB with inadequate performance
- WHO recommendation against use

Strategic approach

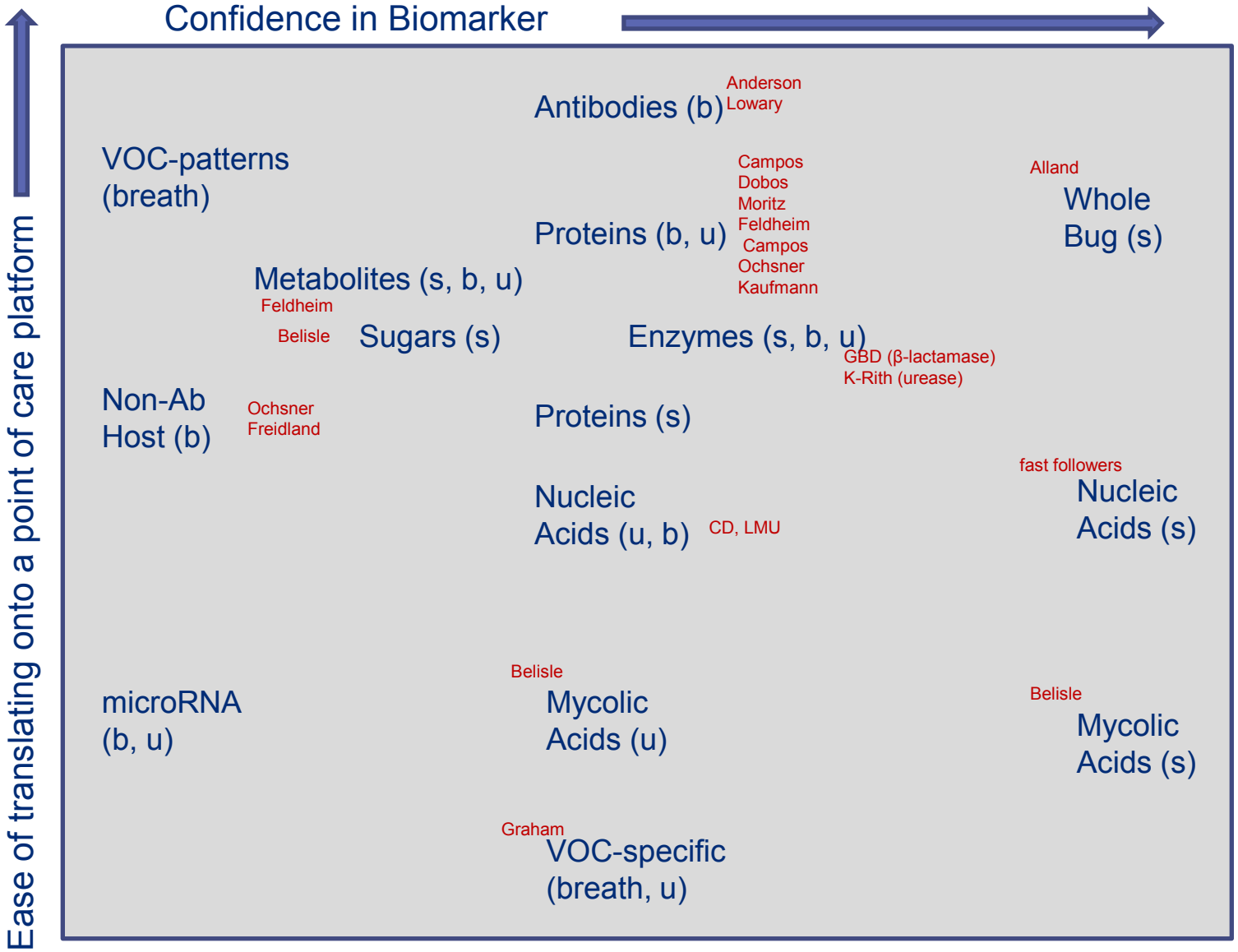
Identify diagnostic AB pattern



Microarray-based screening using high-throughput expression systems

Multiplexing in point-of-care format

Biomarker efforts critical to fill POC gaps



- ***Systematic approaches***
- ***Large sample repositories***
- ***More resources***

INT J TUBERC LUNG DIS 15(10):1279

http://dx.doi.org/10.5588/ijtld.11.0425

Reexamining the role of radiography in tuberculosis case finding

Image Science Institute of the Medical Centre of Utrecht University

Reader	1	2	3	4	5	6	CAD
sensitivity	0,31	0,8	0,79	0,64	0,77	0,79	0,87
specificity	0,87	0,27	0,13	0,78	0,63	0,25	0,49

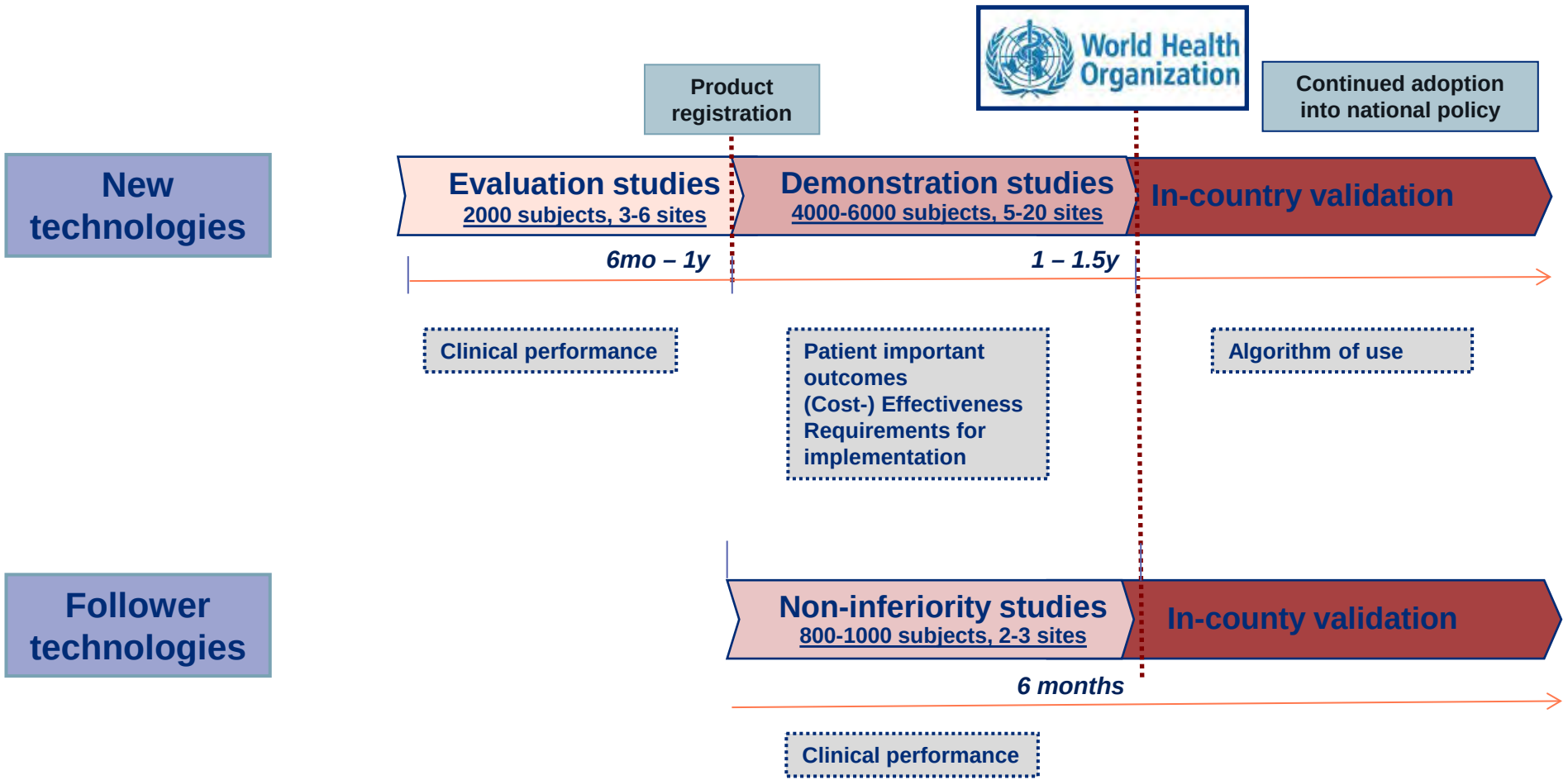
Diagnostics trial needs are substantial

>90,000 study participants recruited in TB diagnostic trials in 2012

Evaluation	Demonstration	Post-WHO validation
~9,500	~1,500	~80,000

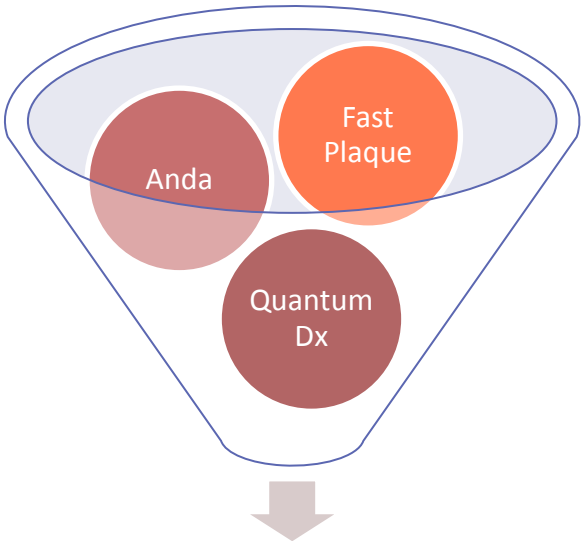
Clinical pathway to WHO for TB

- *WHO endorsement is key to public sector uptake*
- *Solid evidence base required for WHO expert review*



Access to a flexible clinical feasibility platform key for technology selection and development

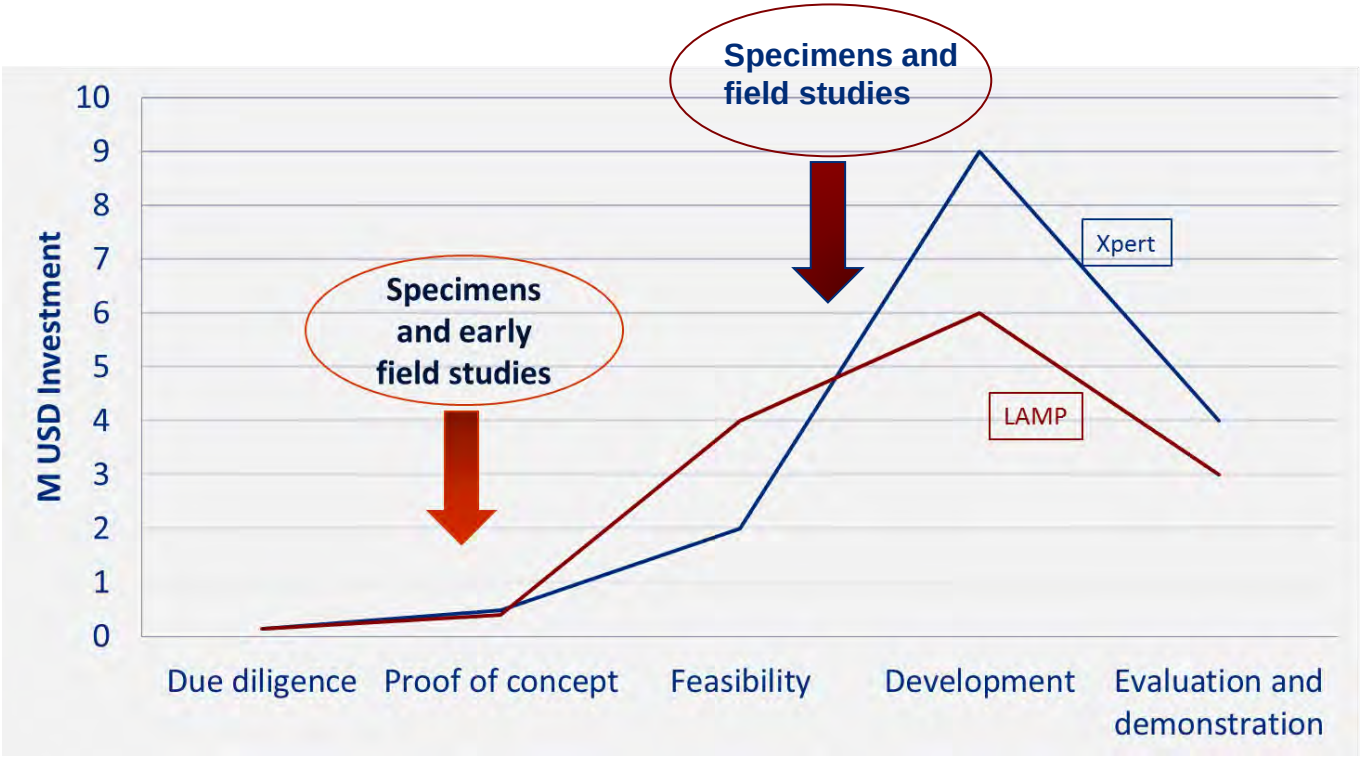
Down-select fast and terminate early



1 out of 5 into clinical feasibility

1 out of 5 through feasibility

Effective development



Strengthening the enabling infrastructure…

… to accelerate access to the diagnostics tools we need

Effective development and informed policy decisions:

- Access to specimen
- Trial platform (certified trial sites; reference lab networks)
- Expert guidance / training around WHO-defined needs and standards

Maximize impact of new tools

- Track impact of diagnostic-guided interventions
- Pragmatic operational research & in country capacity building
- Post-market quality assurance (sentinel sites; product and lot testing initiatives)

Global trial site and laboratory network