

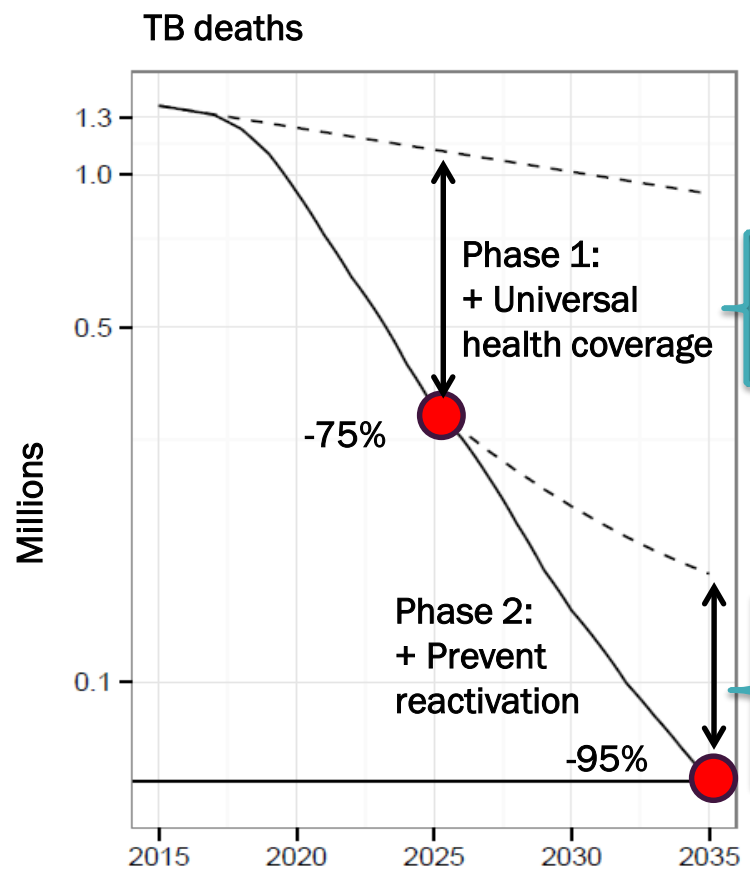


**New TB diagnostics:  
landscape and pipeline**

Catharina Boehme  
8<sup>th</sup> December 2014

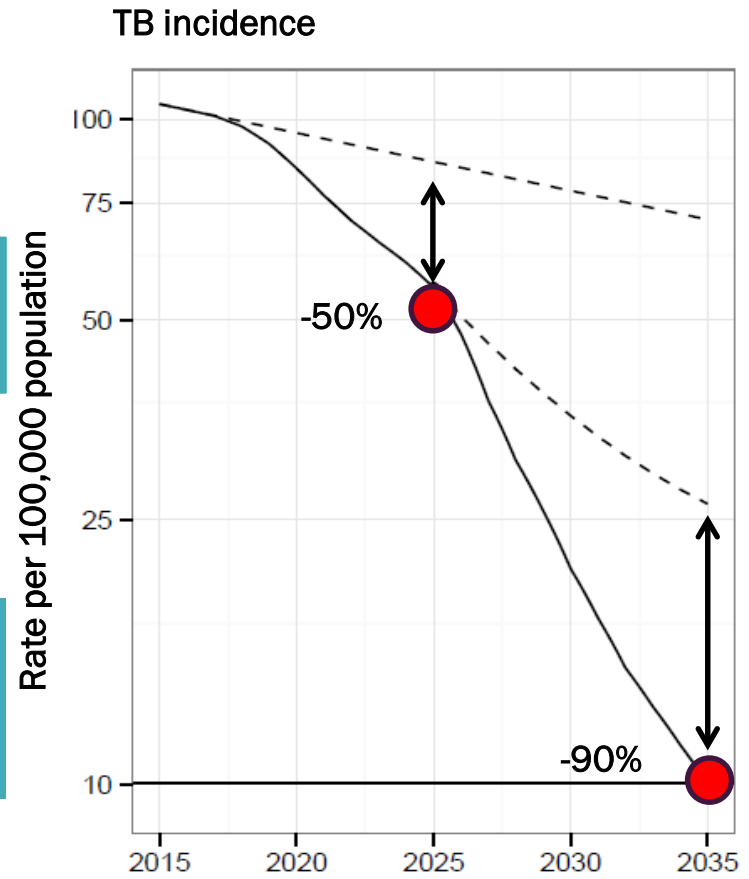


# To reach global TB targets, we rely on novel diagnostics and testing strategies in both phases



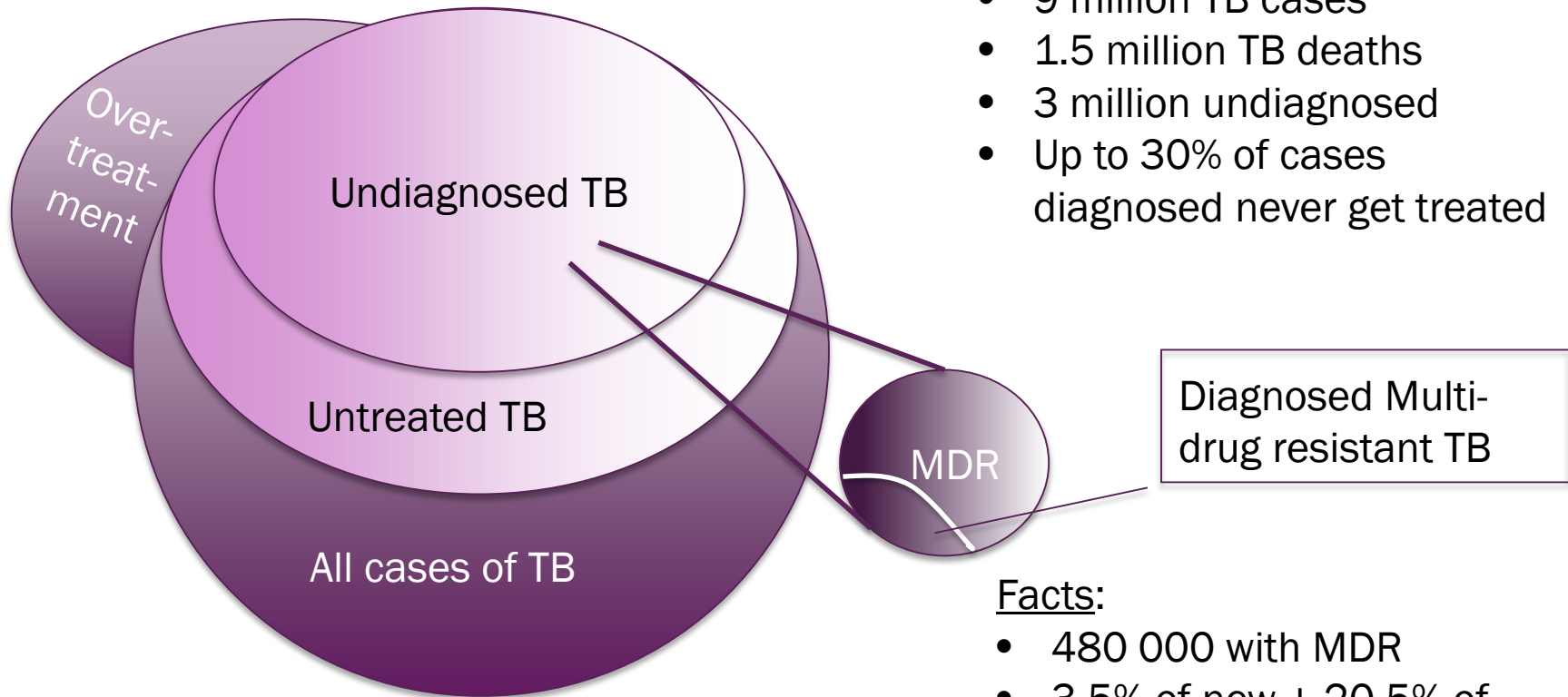
EARLY diagnosis + DST for ALL cases

Identifying those AT RISK among pool of infected





# Universal, early diagnosis and DST – where do we stand?



## 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
- 45% of those 300k detected are diagnosed



# Advancements in TB diagnostics



✓ Smear-positive TB case definition	✓ Liquid culture	✓ LPA	✓ LED-FM	✓ Automated NAAT (Xpert MTB/RIF)	✓ Xpert EPTB / children	
✓ Number of smears	✓ Rapid speciation		✓ Front-loaded microscopy	✓ Negative rec: Serology		
✓ FM			✓ MODS, CRI, NRA cond.			

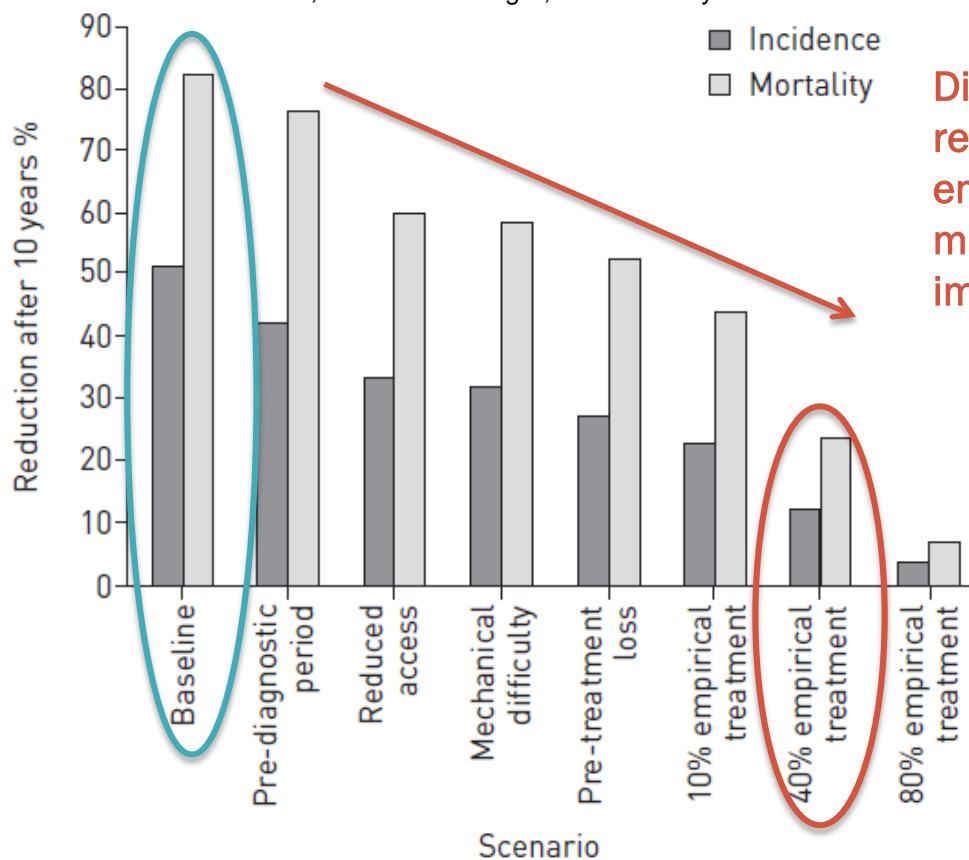




# Can our new TB tests impact incidence and mortality? Yes, but -

## The impact of novel tests for TB depends on the diagnostic cascade

Amanda Sun, Claudia Denking, David Dowdy



Diagnostic delays, reduced access and empirical treatment minimize potential impact



# Limited impact of Xpert MTB/RIF as smear replacement test

Published and unpublished data from India, South Africa and Brazil show:

✓ Substantially increased number of bacteriologically confirmed cases

■ Does not necessarily result in increased case notifications (or patients on treatment)

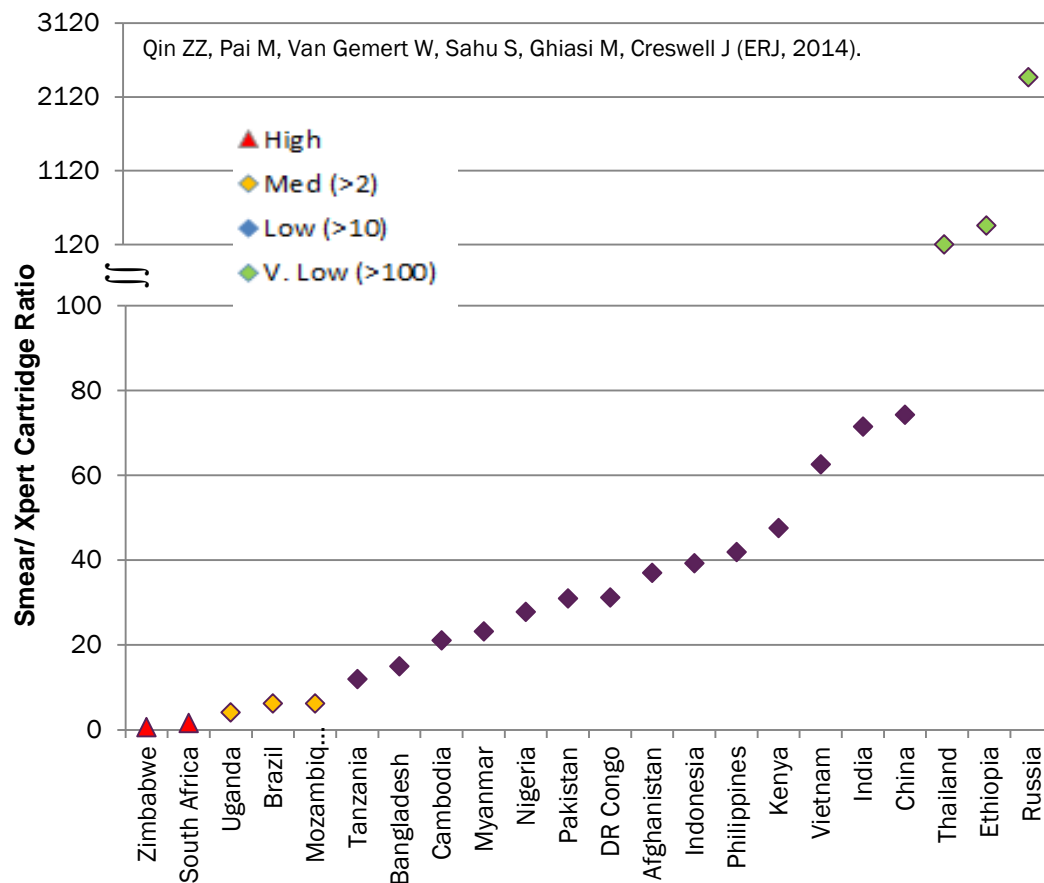
Do high rates of empirical treatment undermine the potential effect of new diagnostic tests for tuberculosis in high-burden settings?

*Grant Theron, Jonny Peter, David Dowdy, Ivar Langley, S Bertel Squire, Keertan Dheda*

■ At least 1 in 10 confirmed TB patients not started on treatment

■ Low coverage

Insufficient Xpert coverage in 22 high burden countries



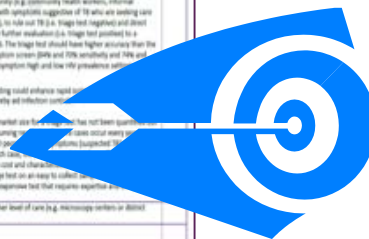


# Limited fit of Xpert as smear replacement test – as defined in target product profiles

- Performance characteristics
  - Sensitivity/specificity for TB detection, treatment monitoring, DST
- Operational characteristics
  - Specimen type
  - Manual steps
  - **Infrastructure requirements** (e.g. power, temperature control)
  - Time to result
  - Requirements for reporting and **connectivity**
  - Importance of subgroups such as HIV-infected and children
- **Price targets**

TPP for a community-based triage/referral test for identification of TB suspects

Characteristics	Optimal (ideal)	Minimal	Explanations	Rat
<b>Intended use</b>				
Goal of test and Potential Market	Test used at the first encounter to the health care system to identify, among patients suspected of having active TB (any site), those who do not have TB and those in need of referral for further confirmatory testing.	Test used at the first encounter to the health care system to identify, among patients suspected of having active TB (any site), those who do not have TB and those in need of referral for further confirmatory testing.	Since most individuals with suspected TB do not have TB, a triage test can help screen down the population that needs confirmatory testing. A triage test needs to be a simple to use, low cost test for use by first contact providers in the community (e.g. community health workers, informal providers) or persons with symptoms suggestive of TB who are seeking care (not active case finding), to rule out TB (i.e. triage test negative) and direct individuals who require further evaluation (i.e. triage test positive) to a confirmatory test for TB. The triage test should have higher accuracy than the currently available sputum smear (sensitivity and PPV) and also have high specificity for any symptom type and low risk populations with respect to TB. Furthermore, triage testing could enhance rapid identification and thereby reduce infectious control. Potential market: The market size for this product has not been quantified. It is likely to be large. Assuming that the test is used at every health facility, ensuring that nearly all patients with symptoms suggestive of TB are screened to identify each case. The number of patients screened will also depend on the cost and characteristics of the test. The test should be simple to use (single test as opposed to culture) and should be a more expensive test that requires expertise in culture techniques. TPP will be done at higher level of care (e.g. microscopy centers or district level).	0-45
Drug resistance screening	None	None		
Target population	Adults and children suspected to have active TB (any site)	Adults and children suspected to have active TB (any site)		
Target user of the test	Minimally trained community health workers and informal providers	Training at the level of an auxiliary nursing staff		
Setting (health system level)	Community/village level	Health post and primary care clinics	The level of deployment of a triage test is lower than the level of microscopy centers where TB testing and drugs are currently available. Implementation at the peripheral level will considerably increase the number of patients screened for TB with the triage test and potentially shorten the diagnostic pathway.	01



# Our 5-year vision for TB diagnosis

## Triage/case finding – first point of contact



1. Triage test
  - incl. for childhood TB & EDPT
2. Syndromic test (bac vs viral)



## Further work up & treatment – dedicated unit



1. Highly sensitive TB confirmation with rapid DST for critical drugs
2. Treatment monitoring
3. TB infection with high risk of disease progression



## Surveillance, QA, training – specialized unit



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





# Global TB dx R&D pipeline (case detection/DST)

Early development

Late or completed development

On pathway to WHO evaluation

## Molecular Detection/DST

MDR-TB (Akkoni)  
COBAS TaqMan MTB +DST(Roche)

VereMTB (Veredus Laboratories)  
LiPA Pyrazinamide (Nipro)  
LATE-PCR Lights on / Lights off (Hain)  
TBMDx (Abbott)  
Meltpro (Zeesan)  
MTB-MDR (CapitalBio)  
REBA MTB-XDR (YD Diagnostics)  
BD Max (BD)

GenoTYPE MTBDRsl (Hain)  
LiPA MDR-TB (Nipro)  
REBA MTB-Rifa (YD Diagnostics)

BNP Middlebrook (NanoLogix)  
Rapid colorimetric DST

## Culture-based technologies

TREK Sensitive MYCOTB (Trek)



High complexity assays

## Molecular Detection/DST

Xpert Ultra and XDR (Cepheid)  
Alere Q (Alere)  
Enigma ML (Enigma Diagnostics)  
Q-POC (QuantuMDx)  
EOSCAPE (Wave80)  
RT-PCR Testing Platform (NWGHF/Quidel)  
iCubate 2.0 (iCubate)  
TBDx system (KGI)  
DiagCORE (STAT-Diagnostica)  
LabChip G2-3 (Nanobiosys)  
Hydra 1K (InSilixa)  
EasyNAT TB (Ustar)

Genedrive MTB (Epistem)  
Truelab/Truenat MTB (Molbio)

TB LAMP (Eiken)



Moderate complexity assays

## Volatile organic compounds

BreathLink (Menssana)  
Prototype breathalyzer (Next Dimensions)  
TB Breathalyser (Rapid Biosensor Systems)  
Aeonose (The eNose Company)  
Breath analysis instrument (Metabolomx)

Giant African Pouch Rats (Apopo)

## Automated Microscopy & Imaging

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

LAM in sputum (Standard Diagnostics)  
Multiplex antibody array (mBio)

Alere Determine TB-LAM in urine (Alere)



## Enzymatic detection/DST

$\beta$ -lactamase reporter (Global BioDiagnostics)





# DNA - the only solid biomarker for TB Dx

High complexity assays

Moderate complexity assays

<p>Hain GenoType MTBDR<i>plus</i></p>	<p>Roche Cobas</p> <p>Abbott TBMD<i>x</i></p>	<p>Zeesan MeltPro<sup>®</sup></p> <p>Hain GenoType MTBDR<i>s/</i></p>	<p>Nipro LiPA PZA &amp;</p> <p>YD REBA MTB-XDR REBA MTB-Rifa</p>	<p>CapitalBio MTB-MDR</p> <p>Hain LATE PCR Lights on /Lights off MTB-PZA</p>	<p>Illumina Next- Generation Sequencing</p>	<p>BD BD Max</p> <p>Akkoni MDR-TB</p>
<p>Cepheid Xpert<sup>®</sup> MTB/RIF</p>	<p>iCubate</p> <p>Eiken TBLAMP<sup>™</sup></p>	<p>NanoBioSys LabChip G2-3</p> <p>Veredus Laboratories VereMTB<sup>™</sup></p>	<p>Cepheid Xpert<sup>®</sup> Ultra Xtend-XDR</p>	<p>Enigma ML<sup>®</sup> MDR TB</p> <p>Northwestern GHT/Quidel</p>	<p>Ustar MTB</p>	
			<p>Alere<sup>™</sup> Q</p>	<p>MolBio Truelab/Truenat</p> <p>Epistem Genedrive<sup>®</sup></p>	<p>KGI TBD<i>x</i> System</p> <p>STAT- Diagnostica DiagCORE</p>	<p>Wave80 EOSCAPE</p> <p>InSilixa HYDRA</p> <p>QuantuMD<i>x</i> Q-POC<sup>™</sup></p>

2015 2016 2017+

WHO- endorsed	Limited commercial availability	Expected completion of development
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## R&D highlight 1: Taking molecular a step further



**Xpert® MTB/Rif Ultra** in late development, with the goal of closing the sensitivity gap with culture

- Sensitivity as low as 5 cfu/ml, depending on strain.
- Runs on existing systems
- Cost is the same at \$9.98
- Anticipated release Q1 2016 (trials as of Q2 2015)



**Rapid diagnosis of additional 30% Sm-Cul+ patients (or > in HIV+ and children); addressing overtreatment.**



**Xpert® XDR** in development, which will detect resistance to INH, fluoroquinolones, and aminoglycosides

- Alpha study ongoing in 2 countries
- Runs on existing modules (10 color)
- Cepheid development and release plan is underway



**MDR/XDR triaging in high DR settings; addressing INH concerns; preparedness for new FQ-based regimens<sup>11</sup>**





## R&D highlight 2: Bringing molecular closer to patients



- **Alere™ q TB** in late development, targeting microscopy centers
  - Fully integrated.
  - Time to result 20 min
  - Runs on HIV VL systems
  - Anticipated release & start of validation/impact trials Q4 2015

- **Alere™ q DST** in development, which will detect resistance to RIF, INH, FQ, and potentially PZA
  - Time to result 40 min (from DNA of TB assay)
  - Resistance SNPs on microarray





## R&D highlight 3: Making molecular local



### ■ Molbio - Truenat; India. In late development.

- Realtime-PCR
- A more automated TB assay developed, RIF integration planned.
- In first multi-center study now.



### ■ Ustar – Easynat; China. In development.

- Cross-priming amplification
- Started work on more automated version.



If successful, could save costs and ease access (shipment, import)



# Beyond pulmonary TB



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

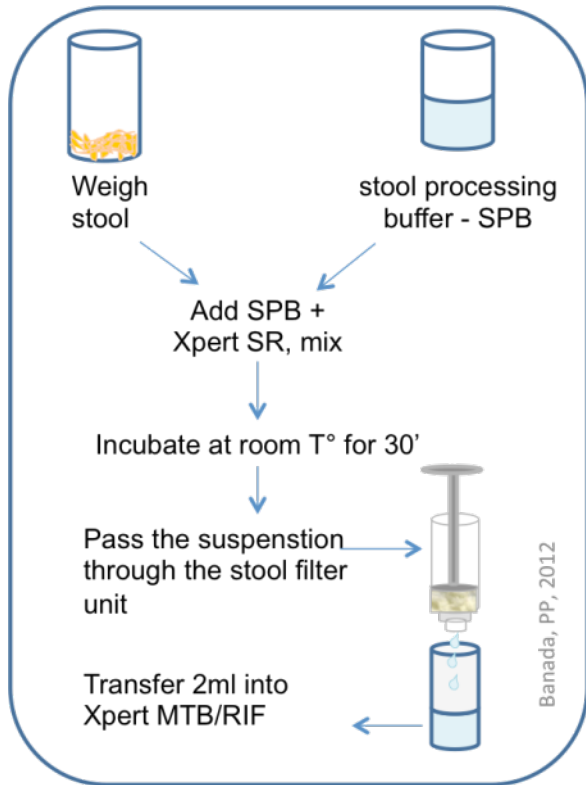


Xpert MTB/RIF implementation manual: technical and operational 'how-to'; practical considerations

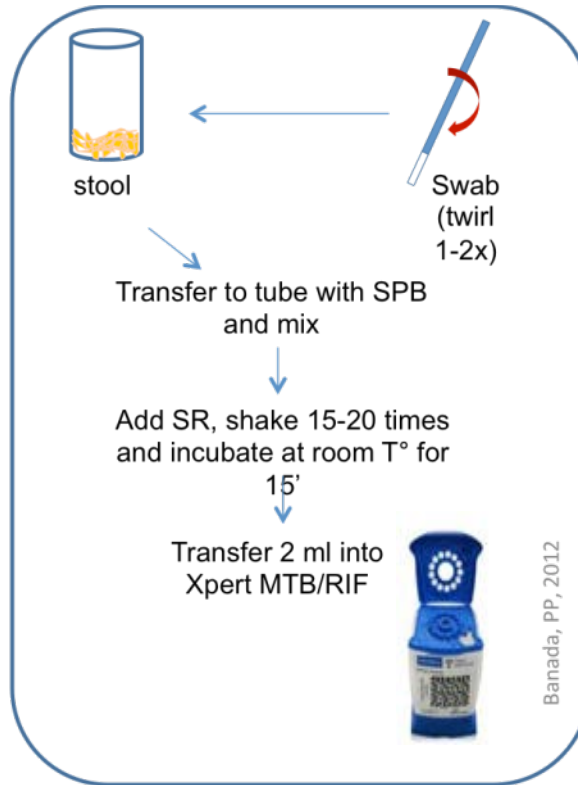
Recommendations for lymph node aspirates, tissue biopsy, cerebrospinal fluid

→ Invasive procedures still necessary!

# Expanding utility of molecular tools

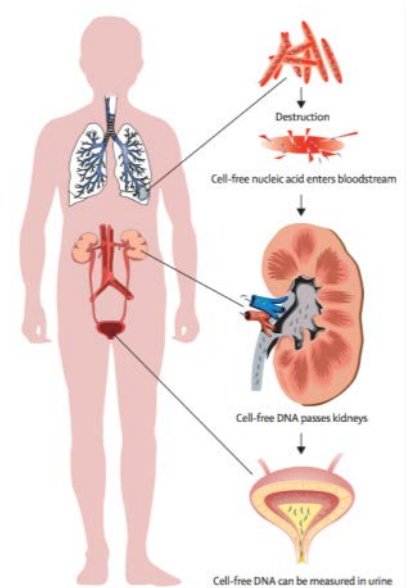


TB detection using stool



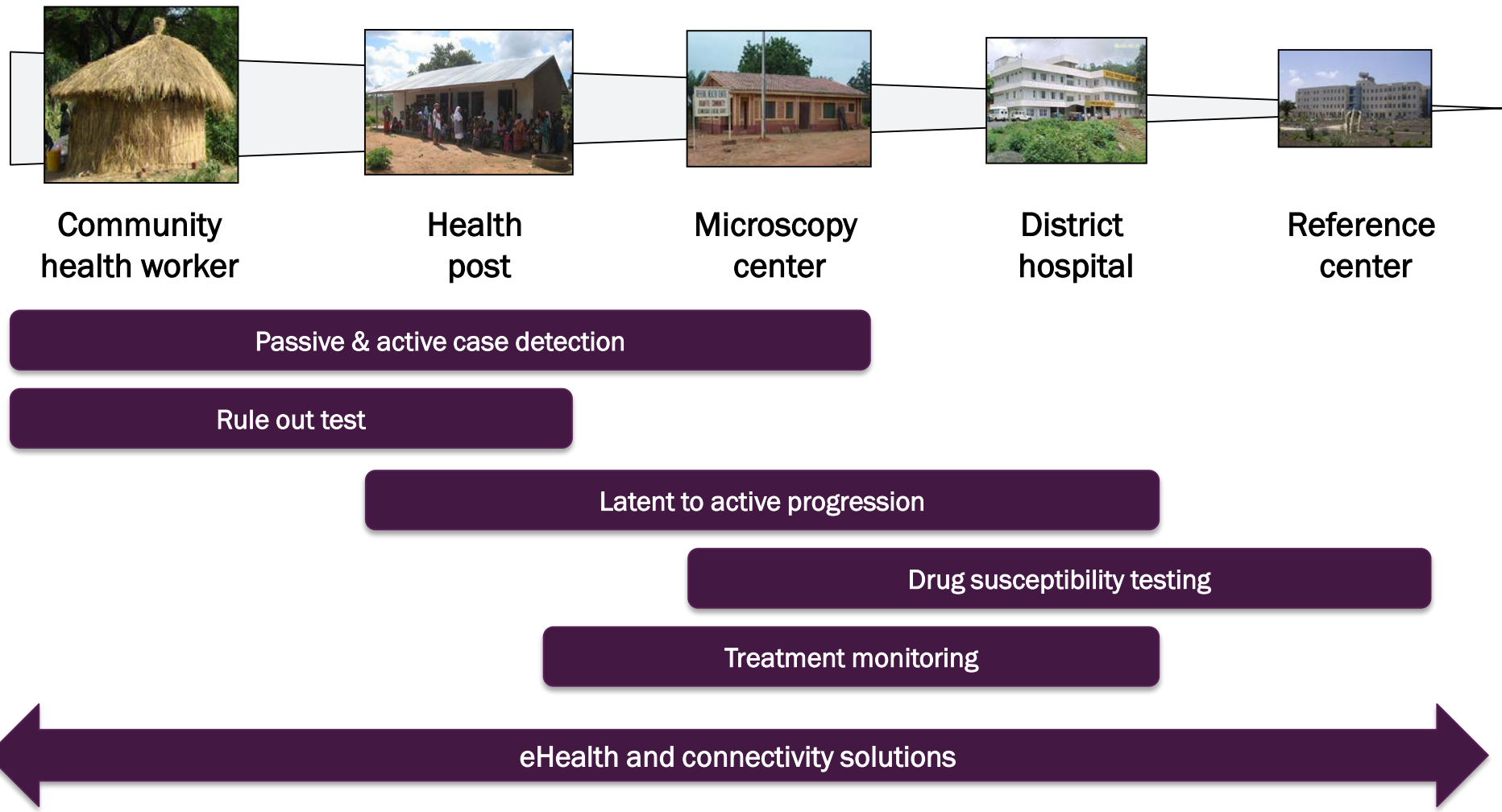
TB detection using urine

Improving detection of Extrapulmonary & Pediatric TB



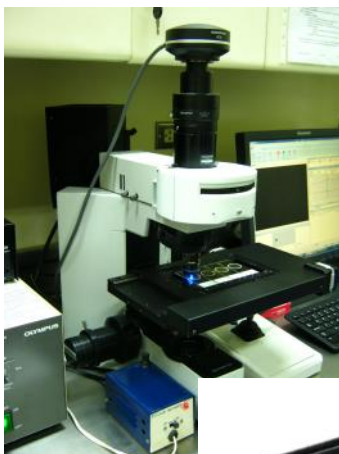


# Need for new tools spans the healthcare system, but concentrated at lower levels of the system





## Incremental improvements: Automating smear microscopy



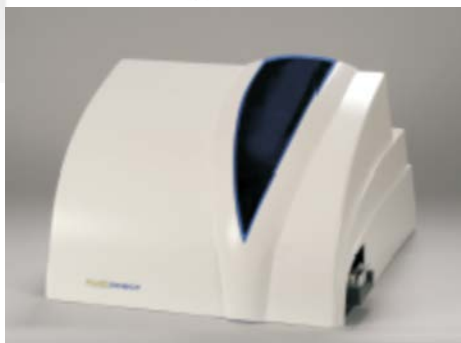
### ■ Automated reading

- TBDx (Applied Visual Sciences)
- CellScope TB Microscope (UCSF)
- Fluorobot



### ■ Automated staining

- RALSTAINER (bioMérieux)
- Aerospray TB (ELITechGroup)



### ■ Combined

- MIAFB2 (BD)

# LAM for TB Screening or Diagnosis



Setting	Patients (%TB, #studies)	Pooled estimates: Grade 2 % (95% CI)	
		Sensitivity	Specificity
Inpatient	1805 (42%, 5)	48% (43-54)	92% (81-97)
Outpatient	1961 (24%, 5)	21% (15-29)	99% (95-100)

## LAM among inpatients at Grade 2

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Unpublished 4	11	8	7	47	0.61 [0.36, 0.83]	0.85 [0.73, 0.94]		
Unpublished 6	53	3	83	274	0.39 [0.31, 0.48]	0.99 [0.97, 1.00]		
Nakiyingi 2014	114	19	132	287	0.46 [0.40, 0.53]	0.94 [0.90, 0.96]		
Peter 2012	58	31	58	94	0.50 [0.41, 0.59]	0.75 [0.67, 0.82]		
Unpublished 3	130	26	119	251	0.52 [0.46, 0.59]	0.91 [0.87, 0.94]		

## LAM among outpatients at Grade 2

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Unpublished 4	18	38	19	393	0.49 [0.32, 0.66]	0.91 [0.88, 0.94]		
Unpublished 2	22	2	99	322	0.18 [0.12, 0.26]	0.99 [0.98, 1.00]		
Unpublished 7	41	27	140	361	0.23 [0.17, 0.29]	0.93 [0.90, 0.95]		
Unpublished 7	5	1	38	237	0.12 [0.04, 0.25]	1.00 [0.98, 1.00]		
Unpublished 3	19	0	76	103	0.20 [0.12, 0.29]	1.00 [0.96, 1.00]		

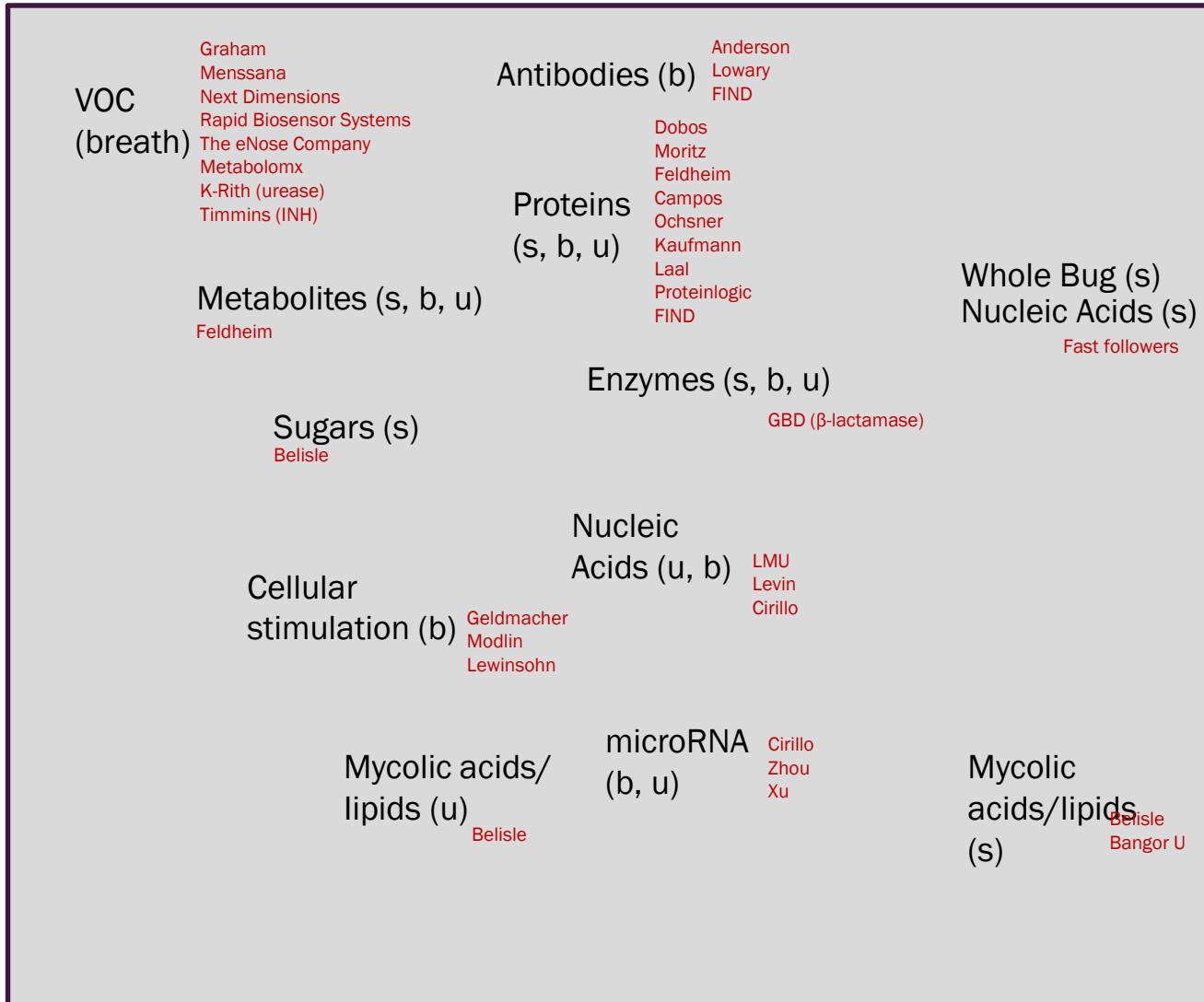
# Various biomarker efforts towards a rapid diagnostic test



Level of certainty in Biomarker



Ease of translating onto a point of care platform



## Requirements:

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

s – sputum  
u – urine  
b – whole blood



# $\beta$ -lactamase detection

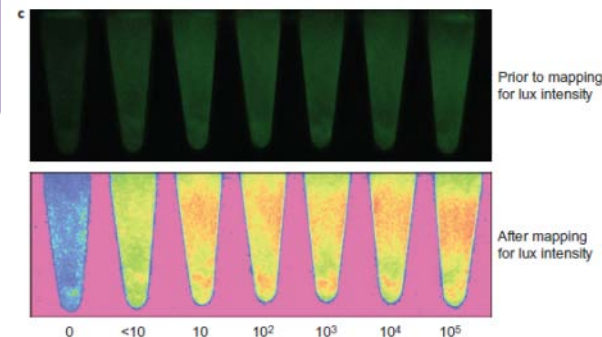
nature  
chemistry

ARTICLES

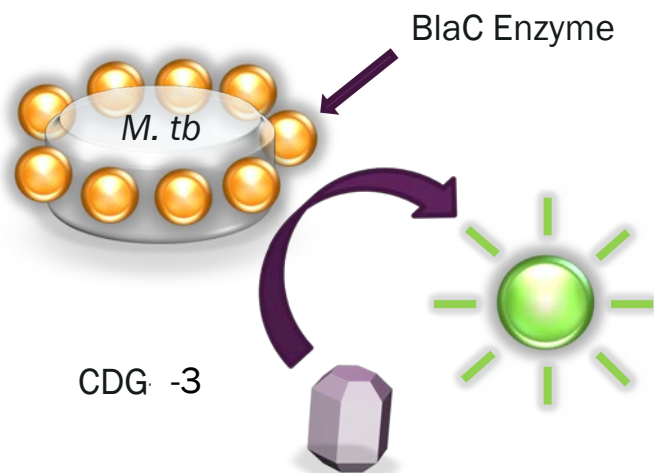
PUBLISHED ONLINE: 2 SEPTEMBER 2012 | DOI: 10.1038/NCHEM.1435

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

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

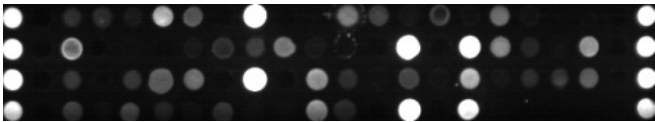
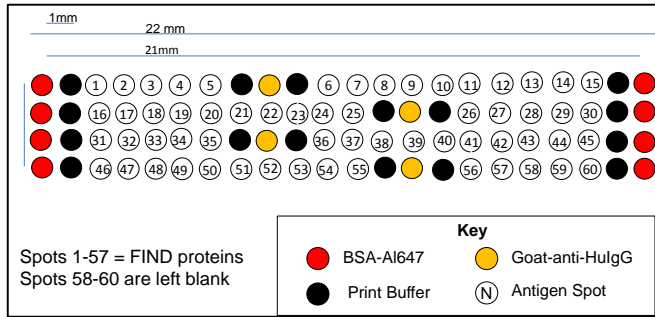


### Reporter Enzyme Fluorescence



Feasibility study of early prototype reagent system in South Africa

# Biomarker efforts towards a blood-based triaging test

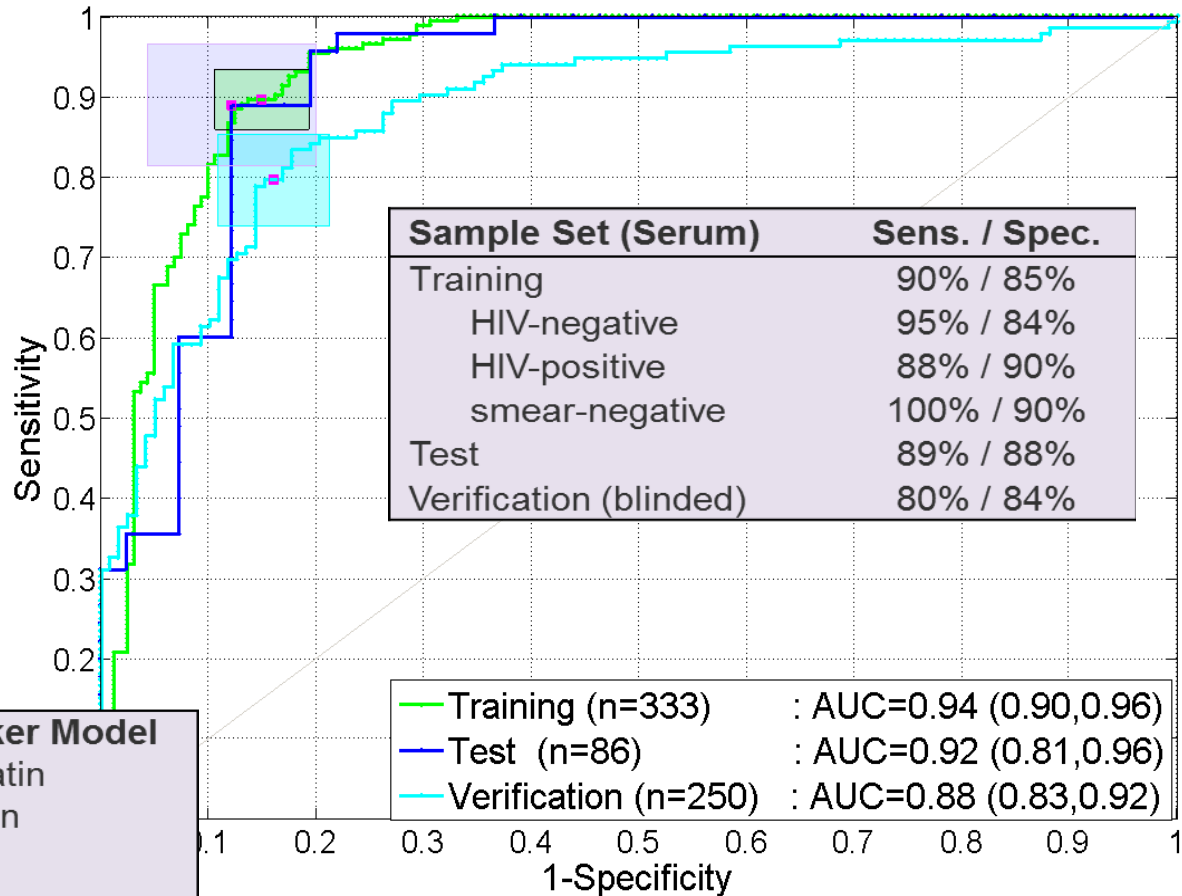


Schematic and representative image of MBio-FIND TB Serology Array.



- 9-Marker Model**
- Kallistatin
  - Gelsolin
  - TSP4
  - Afamin
  - BGH3
  - C9
  - Testican-2
  - FCG3B
  - DERM

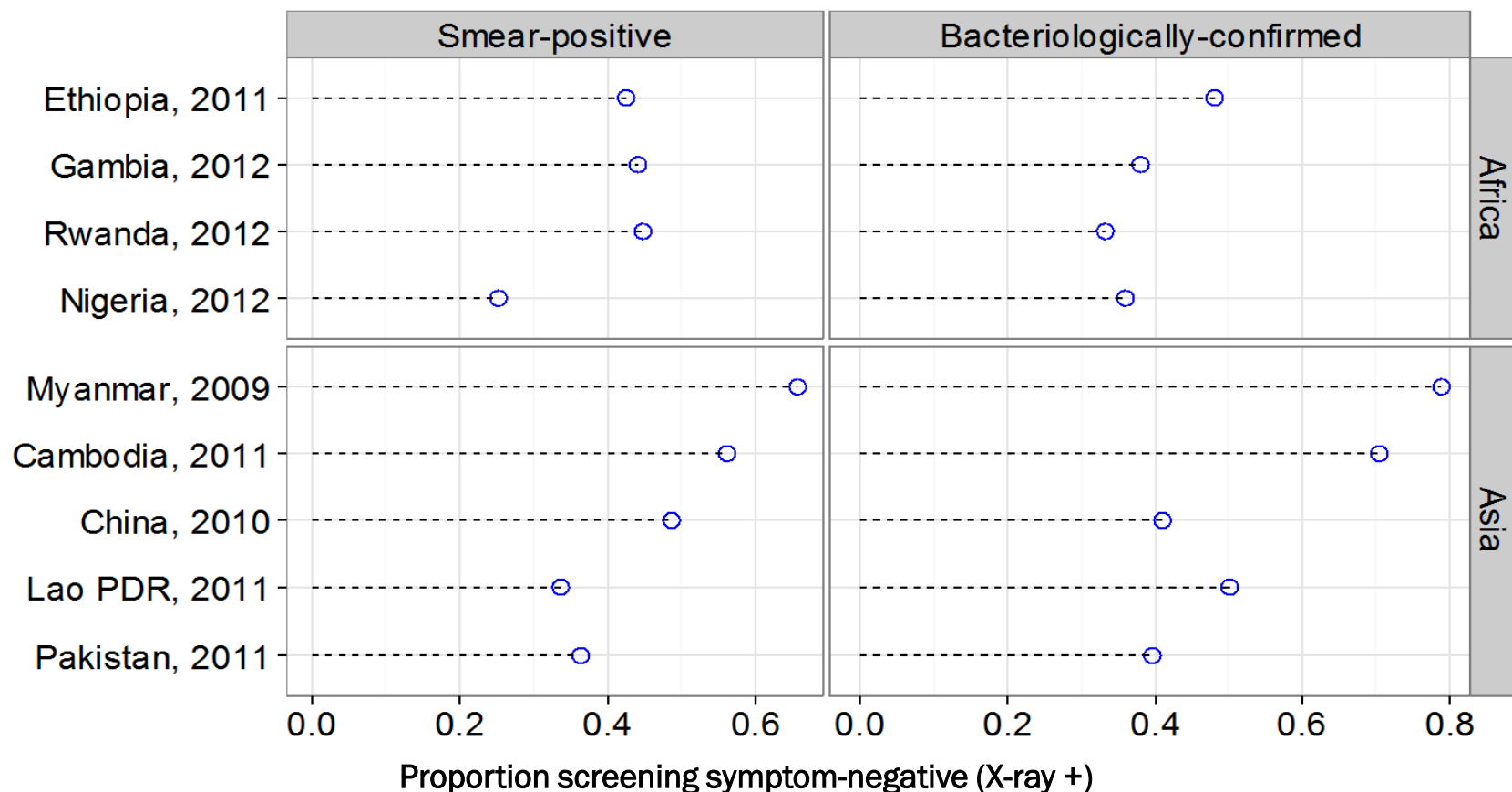
ROC Curve: TB Host Response Signature in Serum



SOMAmer-based Detection of TB in Serum



## Novel strategies to reach patients as important as novel tools

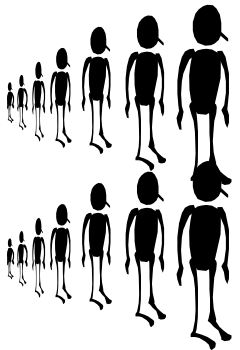


- 40–60% of TB patients without reported symptoms – challenge for early detection
- Need for inclusive symptom screening / active screening + highly sensitive and widely available test.



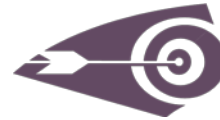
# Triaging at first point of contact

Fever, cough, weight loss



- ? Bacterial, viral, TB
- ? Severity

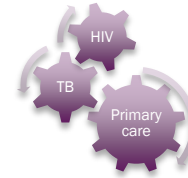
Potential impact



Targeted therapy



Reduction in antibiotic use and preservation of drugs



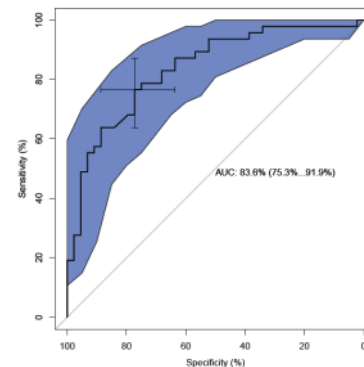
Integrated care

## Example 1: First fever point-of-care tests



RPS Diagnostics obtains CE mark for test to **differentiate viral and bacterial acute febrile respiratory infection** based on Myxovirus Resistance Protein A (MxA) and C-reactive Protein (CRP)

## Example 2: TB triaging

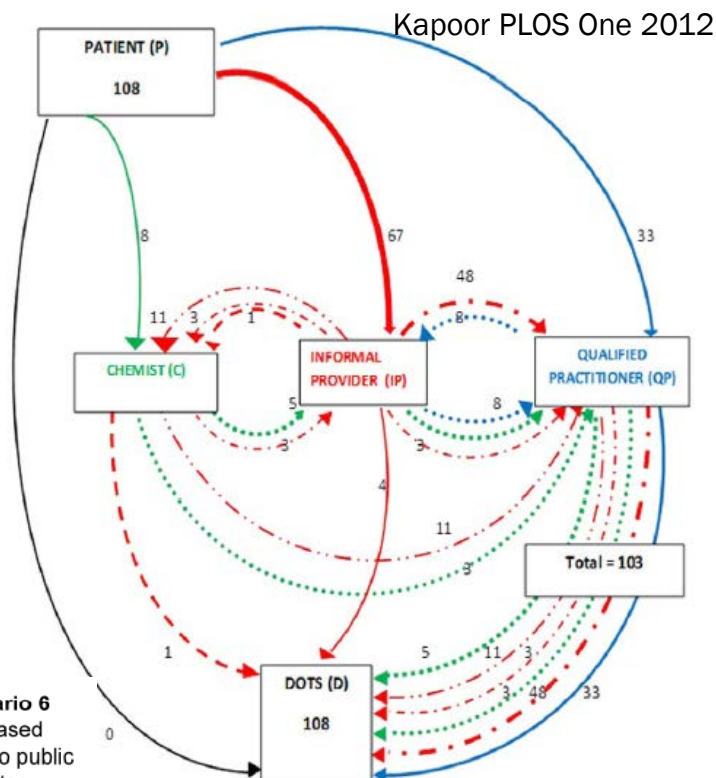
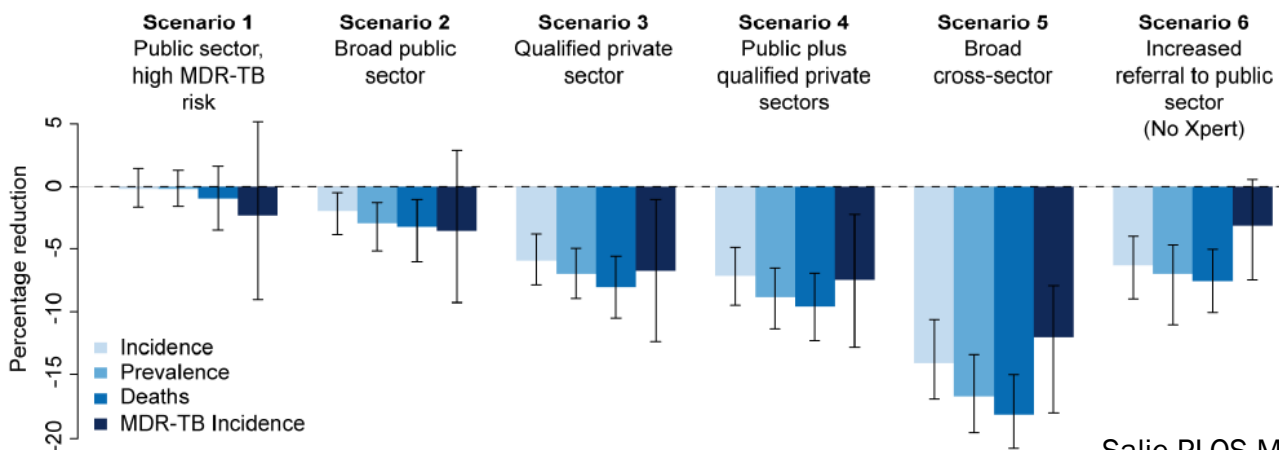




# Combining new tools with a patient-centered approach

- The importance of integrated care for early diagnosis and diagnostic impact
- A holistic approach needs to include the private health sector

## The right implementation strategy in scaling up Xpert in the Indian health care system



Pathways to TB treatment in India (> 2 providers prior to RNTCP)

# Lessons learned from Xpert and Pima: The need for solutions, not tools.

Test

2010 2011 2012 2013 2014

Xpert

Launch Being used in 108 high burden countries

Solution elements

Policy & regulatory guidance

Policy endorsement at unprecedented speed (2 years after design lock / trial start) Expanded guidance for pediatric & extrapulmonary TB

Quality assurance

Strong built-in controls Calibration tool Validation panels Remote monitoring

Support & supply chain

Clear procurement system but long time to repair / replacement Clear warranty conditions & coverage

Impact measurement

Strong trial data informed rapid policy (w/some impact data) Early rollout not accompanied by data collection & feedback on implementation Scarce impact data available; only from trials (not routine collection)

Connectivity & IT

Connectivity to lab management information systems First independent IT tools to enable data transfer, mobile use Chance to reach potential: linkage to care & connectivity by 2015

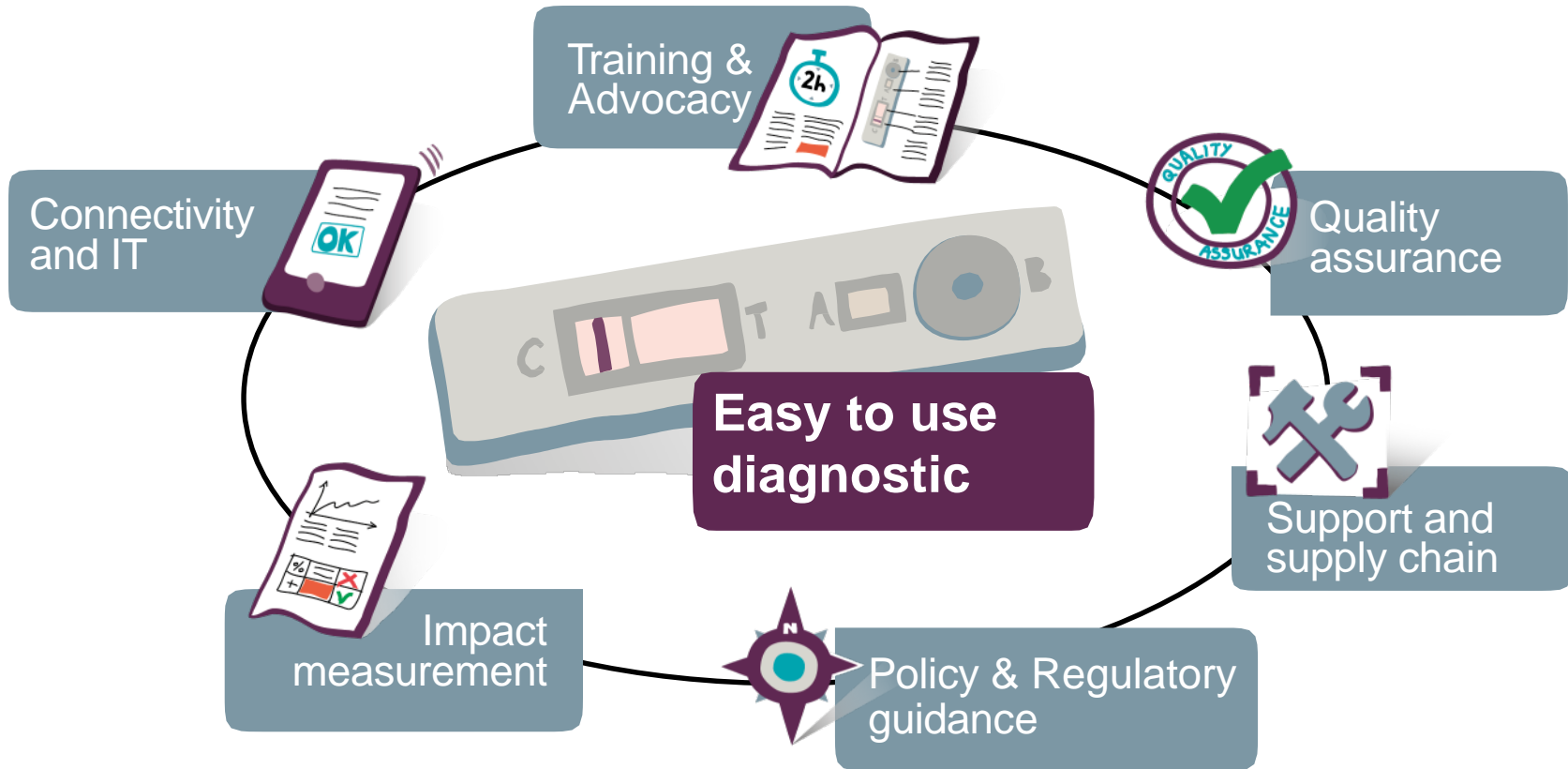
Training & user manuals

1<sup>st</sup> implementation & basic training guide More complete job aids & training package Comprehensive online training

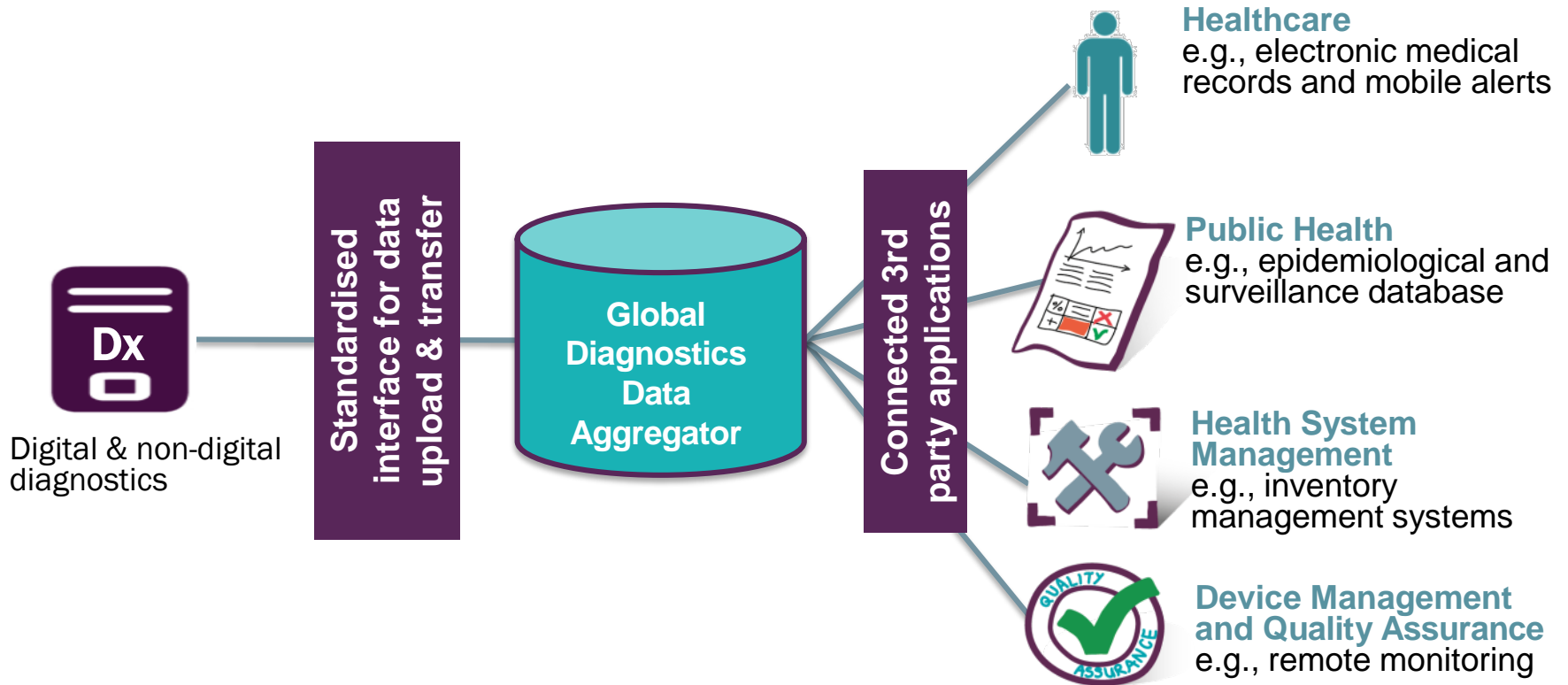
Key Not available Partially available but doesn't fully meet need Meets the need



# From tests to comprehensive diagnostic solutions



# Capitalizing on Connectivity





# Getting to universal rapid diagnosis & DST: What will it take?

## ■ Novel tools implemented as comprehensive solutions

- Highly sensitive smear replacement test (by 2016);
- Rapid, expanded DST (by 2017); Sequencing gold standard (by 2018).
- TB, Fever and Cough triaging RDT (by 2018?);
- Latent to active disease progression (by 2020?)

## ■ Novel testing strategies

- Implementation strategies targeted to include first points of contacts
- Inclusive symptom screening and active screening

## ■ Strong, integrated lab and health systems

- With engagement of communities, and public/private care providers

## ■ Transformed diagnostic ecosystem

- Measure and communicate impact of dx
- Foster and sustain willingness to invest / pay
- Innovative partnerships across the diagnostic value chain



**Towards a 90-90-90 TB target: 90% of vulnerable groups screened, 90% diagnosed, /treated, & 90% cured**

BRICS Health Ministers Make Historic Commitment and Agree to Cooperation Plan on TB at BRICS Ministers of Health Meeting in Brazil



**Requires: Selection and use of best-fit dx tools and testing strategies; and thus an active role in dx studies**