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Because diagnosis matters

Next-generation TB tests: what do we need

Samuel G. Schumacher, PhD MSc

Scientific Officer, FIND

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Outline

1. Introduction to Target Product Profiles (TPPs)
   - Why TPPs
   - TPP development process
   - WHO high priority TPPs

2. Changes in the landscape and other important diagnostic needs
   - Centralized solutions for TB and DST
   - Sequencing
   - Latent to active progression

3. Beyond tests and TPPs: what else do we need?

Introduction to Target Product Profiles (TPPs)

The role of a TPP

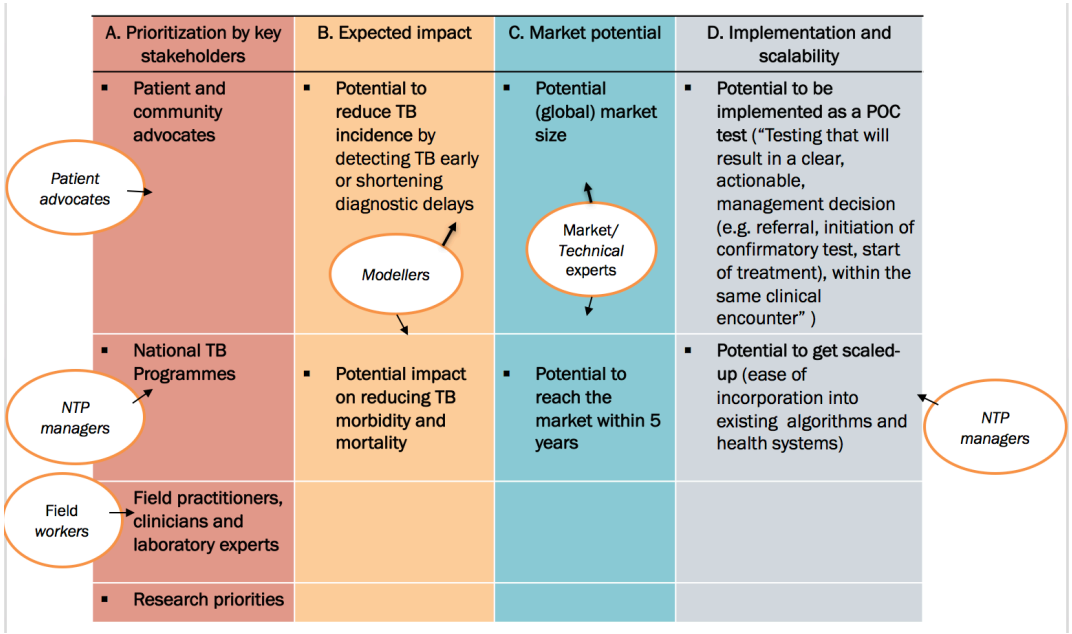
- Strategic planning tool
- Communication tool with investors, partners and stakeholders
- Tool for communicating, supporting, and tracking results

→ Traditionally (as originally defined by the FDA) the TPP is a dynamic document that is revisited in the development process

TPP Prioritization Exercise

Broad group of stakeholders prioritized based on 10 criteria

TRIAGE, RULE OUT AND SYSTEMATIC SCREENING	
1.	Triage test for those seeking care
2.	An HIV/ART clinic-based test to rule out active TB
3.	Systematic screening test for active case finding
RAPID TB DIAGNOSIS (WITH OPTIONAL DRUG SUSCEPTIBILITY TESTING)	
4.	Rapid, sputum-based, cartridge-based, molecular test for microscopy centers (with the option of add-on DST cartridge)
5.	Rapid biomarker-based instrument-free test for non-sputum samples (which can also detect childhood and extrapulmonary TB)
6.	Multiplexed test for TB and other infectious diseases
NEXT-GENERATION DRUG SUSCEPTIBILITY TEST	
7.	Centralized, high-throughput, drug susceptibility test (incorporating new drugs to support the roll out of new TB Rx regimens post 2014)
TREATMENT MONITORING TEST	
8.	Treatment monitoring test (test for cure)
PREDICTIVE TEST FOR LATENT TB INFECTION	
9.	Predictive test for latent TB infection at high risk of active TB



	Target product profiles for potential new TB diagnostic tests	Prioritization by key stakeholders				Impact		Market		Implementation and scalability		Score	Priority rank
		Patients and community advocates	National tuberculosis programmes	Field practitioners	Researchers	Potential to reduce TB incidence	Potential to reduce TB morbidity and mortality	Potential (global) market size	Potential to reach the market in the next 5 years	Potential use as a point-of-care test	Potential to get scaled-up		
	TRIAGE, RULE OUT AND SYSTEMATIC SCREENING TEST												
A	Triage test for those seeking care	high	high	high	medium	high	medium	high	low	high	high	26	3
B	An HIV/ART clinic-based test to rule out active TB	high	high	high	high	low	high	medium	medium	high	high	26	3
C	Systematic screening test for active case finding	high	high	medium-high	medium	high	medium	medium	low	high	high	24.5	5
	RAPID TB DIAGNOSIS TEST (WITH OPTIONAL DRUG SUSCEPTIBILITY TESTING)												
D	Rapid, sputum-based, cartridge-based, molecular test for microscopy centers (with the option of add-on drug susceptibility testing cartridge)	medium-high	high	high	high	high	high	high	high	high	high	29.5	1
E	Rapid biomarker-based instrument-free test for non-sputum samples (which can also detect childhood and extrapulmonary TB)	high	high	high	high	high	high	high	low	high	high	28	2
F	Multiplexed test for TB and other infectious diseases	high	medium-high	low	medium	medium	medium-high	medium-high	low	high	medium	19	8
	NEXT-GENERATION DRUG SUSCEPTIBILITY TEST												
G	Centralized, high-throughput, drug susceptibility test (incorporating new drugs to support the roll out of new TB treatment regimens post 2014)	medium	high	medium	medium	low	medium	low	high	low	medium	18	9
	TREATMENT MONITORING TEST												
H	Treatment monitoring test (test for cure)	high	high	medium	medium	low	medium	low-medium	low	low	high	19.5	7
	PREDICTIVE TEST FOR LATENT TB INFECTION												
I	Predictive test for latent TB infection at high risk of active TB	high	high	medium	high	high	high	high	low	low	low	23	6

Triage/rule-out test

Sputum-based, smear replacement

Biomarker-based, non-sputum

Kik S et al. ERJ 2014

Target Product Profiles

Stop TB Partnership
New Diagnostics Working Group

Centre international de TB McGill
McGill International TB Centre

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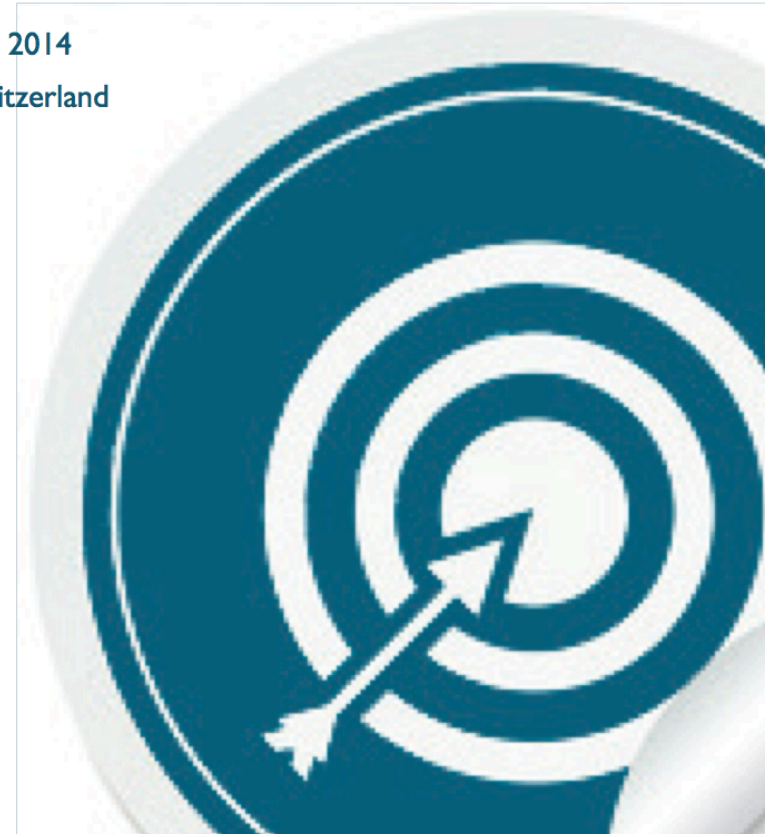
- Prioritized TPPs:
  - Point-of-care, non-sputum based test
  - Point-of-care triage test
  - Point-of-care sputum based test for microscopy replacement
  - Point-of-care DST -microscopy center
- Iterative process with input from many stakeholders
- WHO Consensus Meeting
  - Delphi process leading up to the meeting
  - > 75% agreement amongst stakeholders

Meeting Report

High-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting

28–29 April 2014
Geneva, Switzerland



Unmet Needs

Community health worker | Health post | Microscopy centre | District hospital | Reference centre

- A: Passive & active case detection
- B: Rule-out test
- C: Drug susceptibility testing
- D: Latent to active progression
- E: Treatment monitoring

eHealth and connectivity solutions

Unmet Needs

WHO high priority TPPs

Community health worker | Health post | Microscopy centre | District hospital | Reference centre

A Passive & active case detection

B Rule-out test

C Drug susceptibility testing

D Latent to active progression

E Treatment monitoring

eHealth and connectivity solutions

Unmet Needs

Biomarker-based & smear-replacement

Community health worker | Health post | Microscopy centre | District hospital | Reference centre

A Passive & active case detection

Currently used tools	Limitations of existing tools	Desirable new tools	Translational challenges for new tool development
1. Sputum smear microscopy **2.** Nucleic acid amplification tests (NAATs)	**1.** Smear microscopy lacks sensitivity and cannot detect drug resistance. **2.** NAATs are expensive and not easily deployable at the peripheral level.	A sputum-based replacement test for smear microscopy A non-sputum-based biomarker test for all forms of TB, ideally suitable for use at levels below microscopy centers	While several NAATs are being developed for microscopy centers, they will need to be evaluated in field conditions for policy. For the nonsputum TB test, the biggest challenge is lack of validated biomarkers.

- Omni
- TrueNat
- QuantuMDx

- LAM
- ?

Pai et al, 2016

Unmet Needs

Point-of-care triage test

Community health worker | Health post | Microscopy centre | District hospital | Reference centre

B Rule-out test

Currently used tools	Limitations of existing tools	Desirable new tools	Translational challenges for new tool development
1. TB symptoms (e.g., 2 weeks of cough) **2.** Chest X rays	**1.** Symptoms lack sensitivity and specificity, especially in HIV-infected populations and children. **2.** Chest X rays are sensitive, but not specific for TB.	A simple, low-cost triage test for use by first-contact health care providers as a rule-out test, ideally suitable for use by community health workers	Lack of validated biomarkers

- CXR (CAD)
- CRP
- VOC

Pai et al, 2016

Unmet Needs

Point-of-care DST

Community health worker | Health post | Microscopy centre | District hospital | Reference centre

C Drug susceptibility testing

Currently used tools	Limitations of existing tools	Desirable new tools	Translational challenges for new tool development
1. Nucleic acid amplification tests **2.** Cultures	**1.** Current NAATs cannot reliably detect all mutations and sensitivity for drugs other than rifampin is poor. **2.** Cultures are expensive and require BSL3 laboratories, and results take time. Reliability of phenotypic is poor for second-line drugs.	A new molecular DST for use at a microscopy center level, which can evaluate for resistance to rifampin, fluoroquinolones, isoniazid, and pyrazinamide, and enable the selection of the best drug regimen	Lack of good data on the correlation of mutations with phenotypic results and clinical outcomes and the association with cross-resistance. There is also a need to align emerging TB drug regimens with companion diagnostics.

- Omni + XDR cartridge
- QuantuMDx

Pai et al, 2016

Changes in the landscape and other important diagnostic needs

Additional TPPs

Advanced drafts (recent WHO meetings)

- Latent to active progression
- Sample transport solutions

Other TPPs in development

- Centralized platforms for TB/DST
- Sequencing
- Treatment monitoring

Additional TPPs

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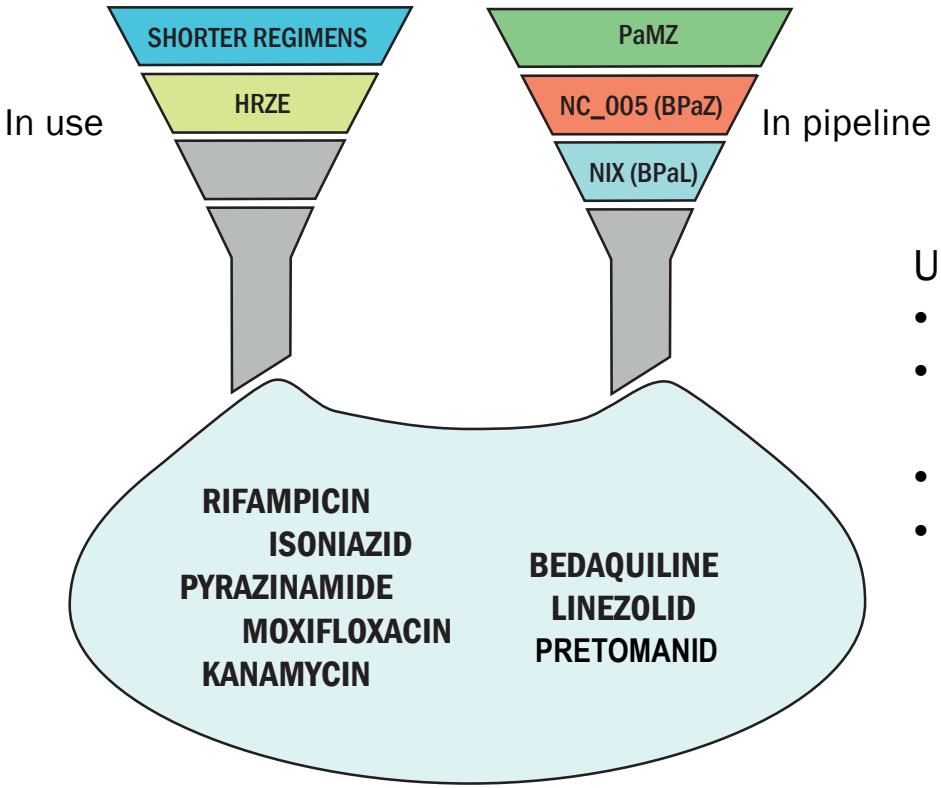
What is the TB drug pipeline telling us about future diagnostic needs?

TPP: Drug prioritization: RIF > FQ (incl. Mox)> INH = PZA



Uncertainties:

- Success of regimens
- For DS, MDR, XDR? > defines level of implementation
- Barrier to resistance; cross-resistance
- Basis of resistance

Revised prioritization?: RIF > FQ > INH >PZA>BDQ >LZD= PA

WHO report 2014; TB Alliance pipeline

Unmet Needs

Point-of-care DST

Community health worker | Health post | Microscopy centre | District hospital | Reference centre

C Drug susceptibility testing

Currently used tools	Limitations of existing tools	Desirable new tools	Translat… for new…	challenges …levelopment
1. Nucleic acid amplification tests 2. Cultures	1. Current NAATs cannot reliably detect all mutations and sensitivity for drugs other than rifampin is poor. 2. Cultures are expensive and require BSL3 laboratories, and results take time. Reliability of phenotypic is poor for second-line drugs.	A new molecular DST for use at a microscopy center level, which can evaluate for resistance to rifampin, fluoroquinolones, isoniazid, and pyrazinamide, and enable the selection of the best drug regimen	Lack of g… correlati… phenoty… outcom… with cro… also a n… TB drug… compan…	…ta on the …utations with …ts and clinical …e association …nce. There is …n emerging …with …stics.

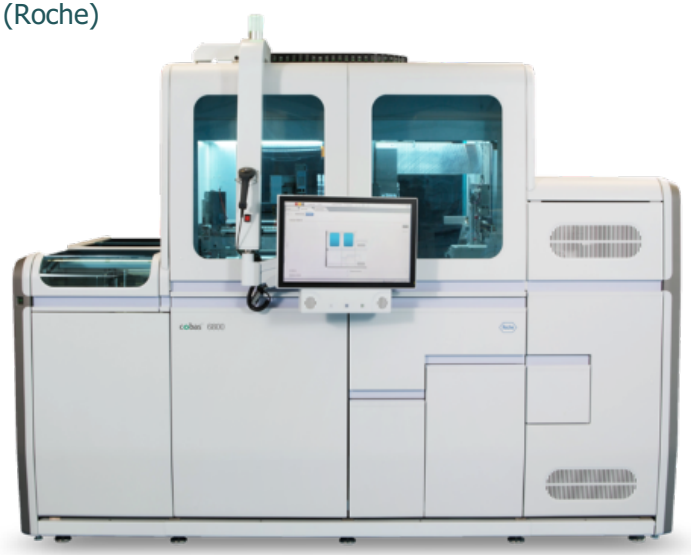
- Centralized platforms
- Sequencing

Pai et al, 2016

Existing (and upcoming) centralized solutions for TB and DST

m200sp, m200rt Realtime MTB RIF/INH (Abbott)

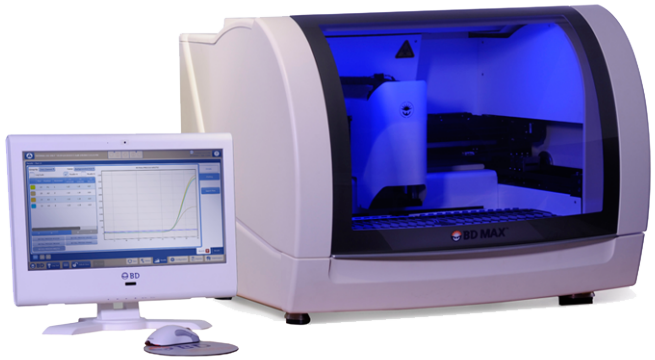
Cobas Taqman MDR TB (Roche)



GenoType MTBDR and MTBDRsl (Hain Lifescience)

FluoroType MTBDR (Hain Lifescience)

BD MAX MDRTB (BD)



Centralized testing – necessary links

Optimized sample transport

- Improves upon the current routine methods in terms of recovery of mycobacteria on liquid and solid culture
- Reduction of contamination
- Simplification of laboratory workflows (cold chain requirements), biohazard

Target Product Profile: Transport solution for samples to undergo Mycobacterial culture

CHARACTERISTIC	OPTIMAL	MINIMAL	EXPLANATIONS/ LIMITATIONS
Intended Use			
Goal / Intended use	Transport solution which improves upon the current routine methods in terms of recovery of mycobacteria on liquid and solid culture and which simplifies laboratory workflows and standardization.		A novel solution must show improved performance over these standard methods to justify change.
Target user of the test	Health care workers with no or minimal laboratory training		A transport solution would be expected to be implemented at the point of sample collection. This may be a health post or similar basic level of the health care system where staff will often have no or only minimal laboratory training.
Setting (lowest level of implementation in health care system)	Health post		
Target sample type	Any specimen with no change to protocol	Sputum specimens	The key target sample type are sputa, since these samples are at high risk of contamination and are often collected in peripheral settings and thus

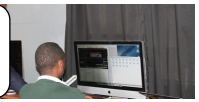
Optimized communication solutions

A patient gets notified via SMS that a test result is ready

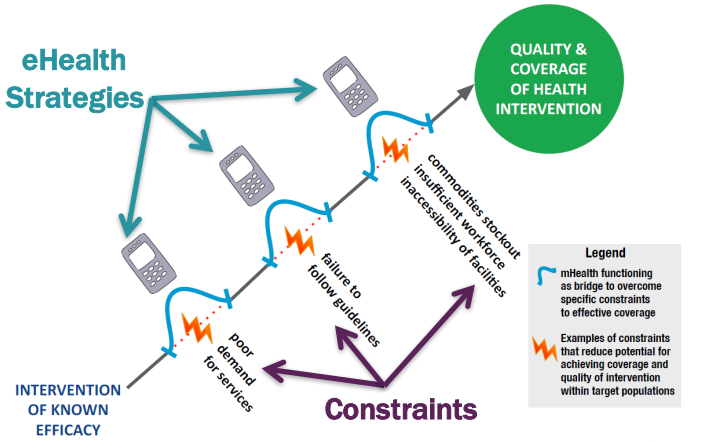
DOTs programme gets notified and ensures patients is started on therapy

A clinician gets notified that an HIV patient tested + for TB in TB clinic

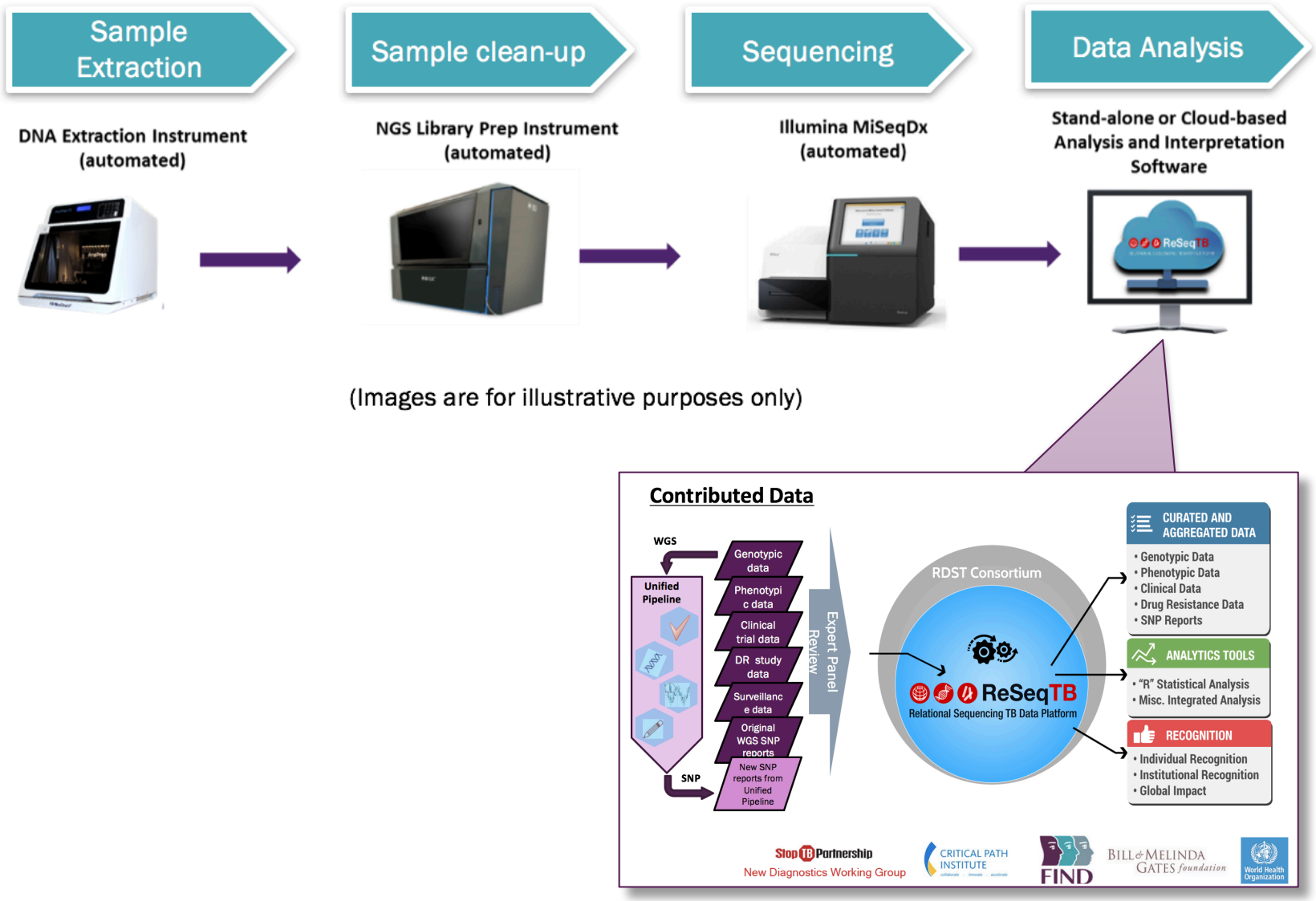
A national programme manager identifies stock-outs early and organizes the shipment from another site



A high error rate of diagnostic system is detected. A new system is sent.



Sequencing: integrated solution from sample to result



Unmet Needs

Latent to active progression test

Community health worker | Health post | Microscopy centre | District hospital | Reference centre

D Latent to active progression

Currently used tools	Limitations of existing tools	Desirable new tools	Translational challenges for new tool development
1. Tuberculin skin test (TST) **2.** Interferon-gamma release assays (IGRA)	Neither TST nor IGRA can separate latent infection from active disease. Neither test can accurately identify those at highest risk of progression to active disease.	A test that can resolve the spectrum of TB, and identify the subset of latently infected individuals who are at highest risk of progressing to active disease and will benefit from preventive therapy	Lack of validated biomarkers

- QFT+
- COR (mRNA)

Test conceptualization

Predict progression

TB infection

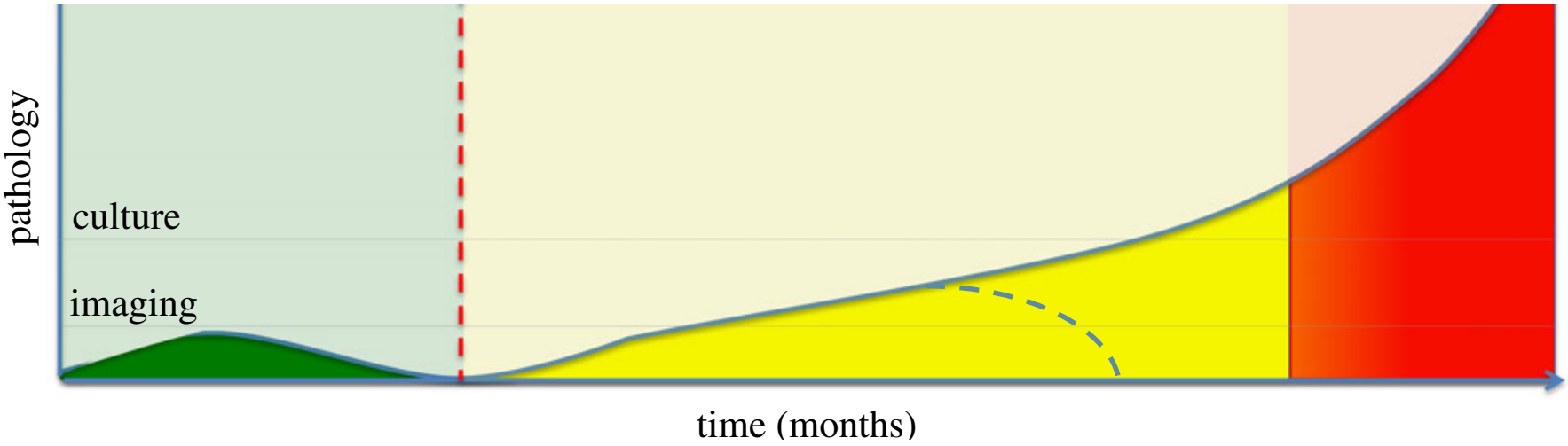
- Asymptomatic
- Positive TST / IGRA
- Without microbiological, radiological, or clinical evidence of active TB

~~Incipient TB disease~~

- Disease progressing but still asymptomatic
- May or may not
  - have evidence of TB on radiographic and/or microbiological examination
  - develop active disease after initial evaluation

TB disease

- Symptomatic
- With
  - positive microbiological test (confirmed TB)
  - or compatible clinical and/or radiology and/or histology for TB and started TB treatment (clinical TB)



Adapted from Esmail 2014

Beyond tests and TPPs: what else do we need?

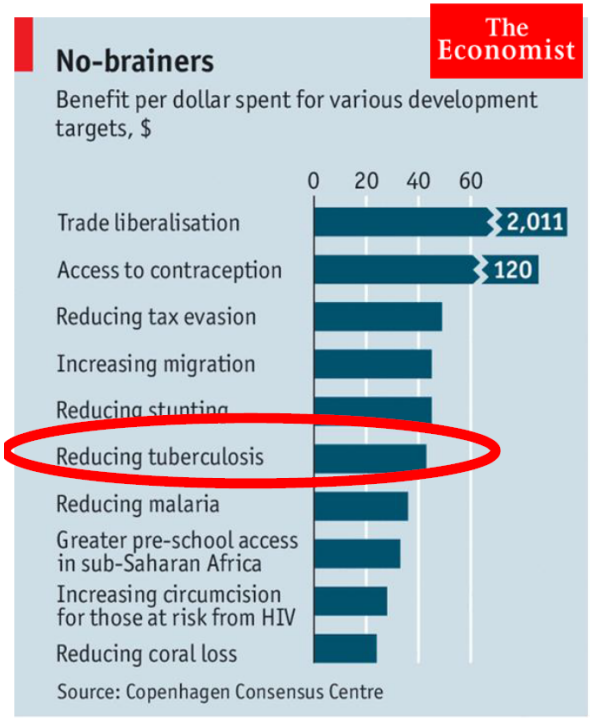
Overcoming challenges on the way to essential diagnostics

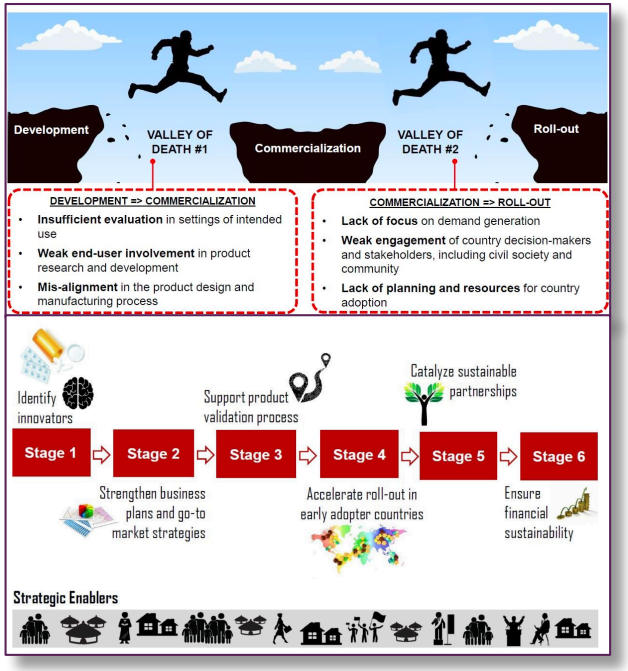
1 Few tests in development or don't make it to market	2 Slow market penetration in low-/middle-income countries	3 Impact stifled
• Gaps in science & knowledge sharing • Limited understanding of needs / priorities • Low market incentives given high development risks • Lack of supporting infrastructure for innovators	• Fragmented regulatory and policy pathways • Unclear financing/ procurement pathways • Complex delivery channels	• Weak health and lab systems • Poor links from testing to care & treatment • Limited logistics capacity, support or quality use

4 Prioritization of diagnostics low

- Limited understanding of diagnostics' value and thus minimal investment
- Since 2007, R&D funding for diagnostics has stagnated at 3-4% of global health commodity R&D

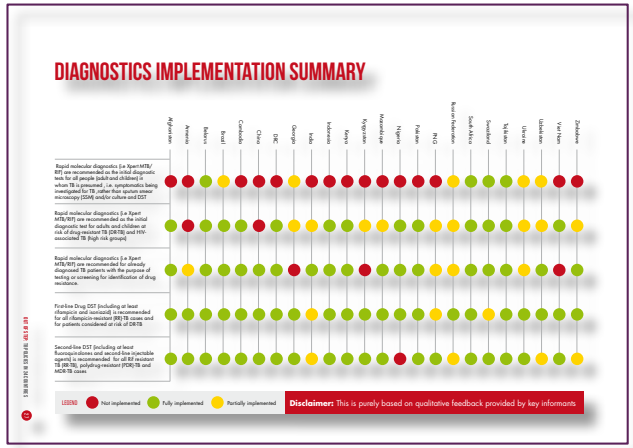
We need more awareness, more country engagement and better financing





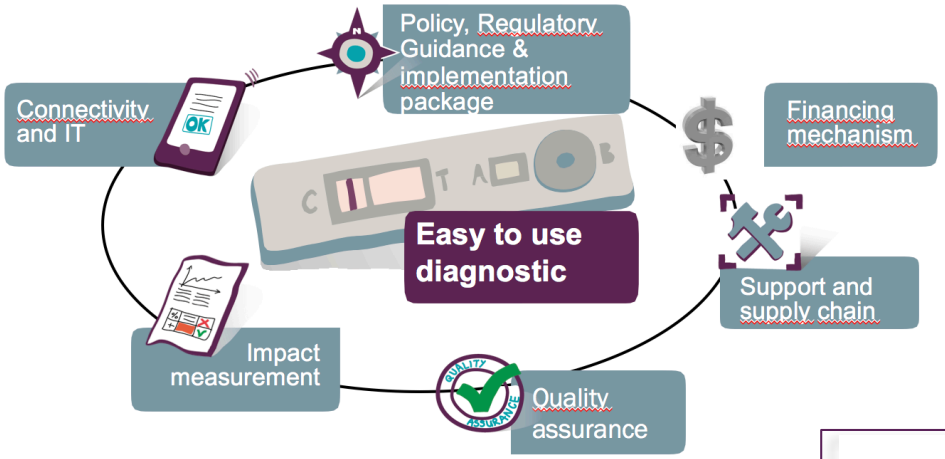
Ditiu/Boehme, 2017

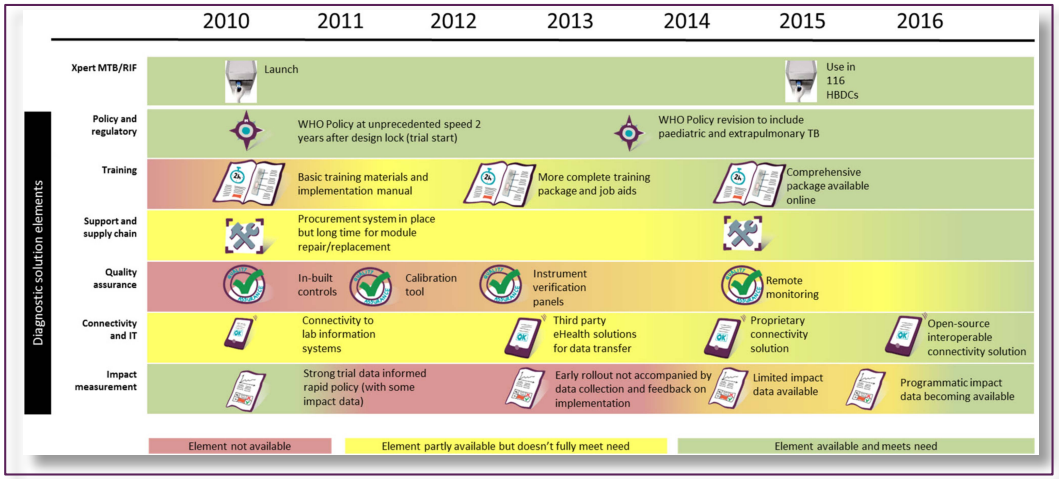
MSF, 2015



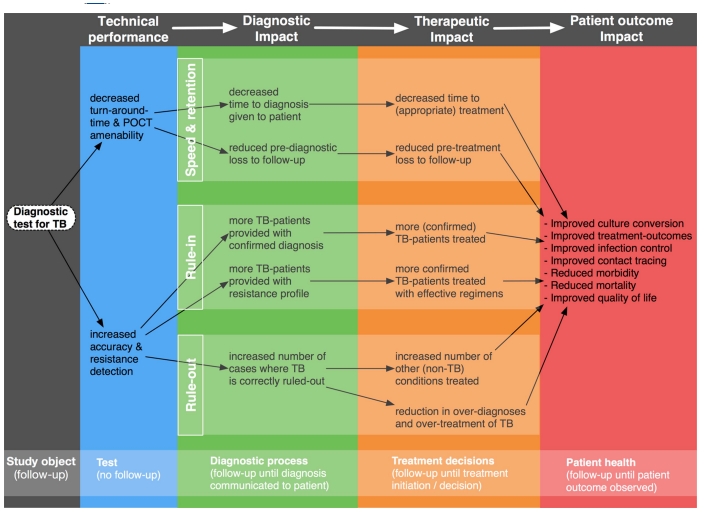
Mugambi, 2017

We need complete diagnostic solutions to support efficient uptake and use

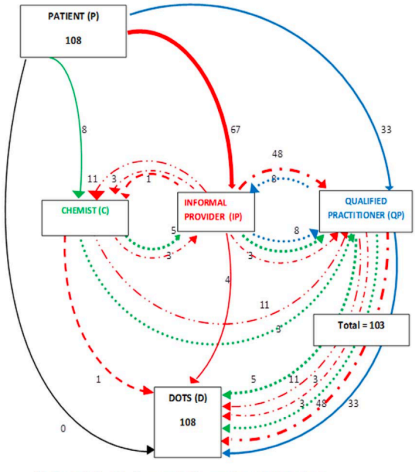




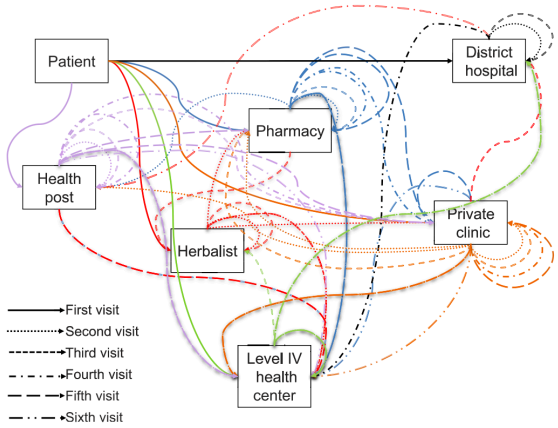
We need to understand and address systems issues to maximize impact



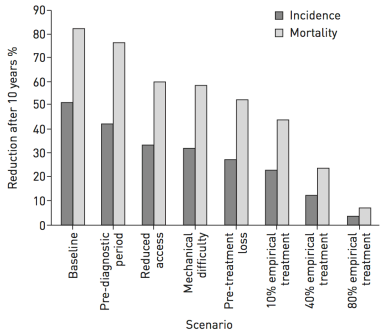
Schumacher, 2016



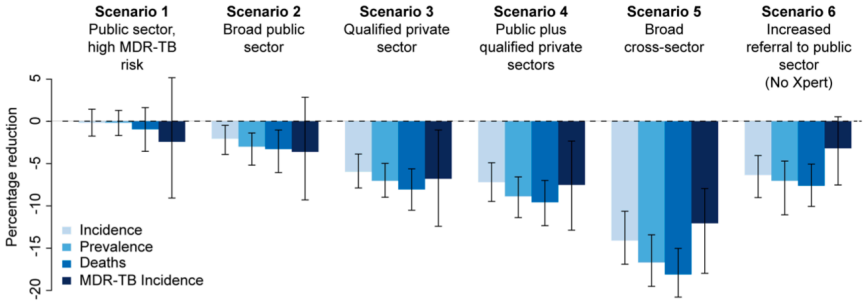
Kapoor, 2012



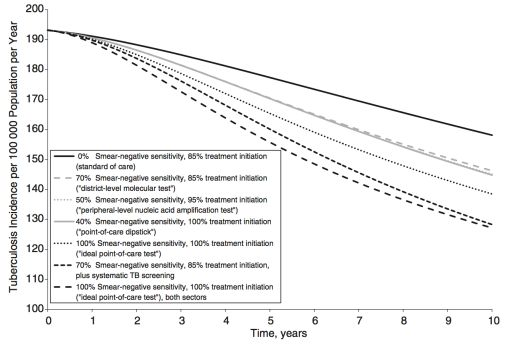
Shete, 2015



Sun, 2014



Salje, 2014

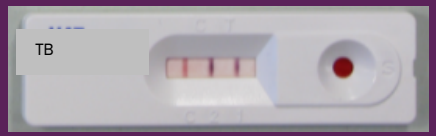


Sun, 2013

Vision for TB diagnostics in 2020

Case finding –
first point of contact

1.Triage tests



Further work up & treatment –
dedicated unit

2. Confirmation & rapid drug susceptibility testing (critical drugs)

Surveillance, QA, training –
specialized unit

3. Comprehensive, rapid drug susceptibility testing

E-Health supported solutions

Thank you/ Questions?

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Claudia Denkinger
Timothy Rodwell
David Dolinger
Tobias Broger
Catharina Boehme