Target product profiles for next generation TB diagnostics
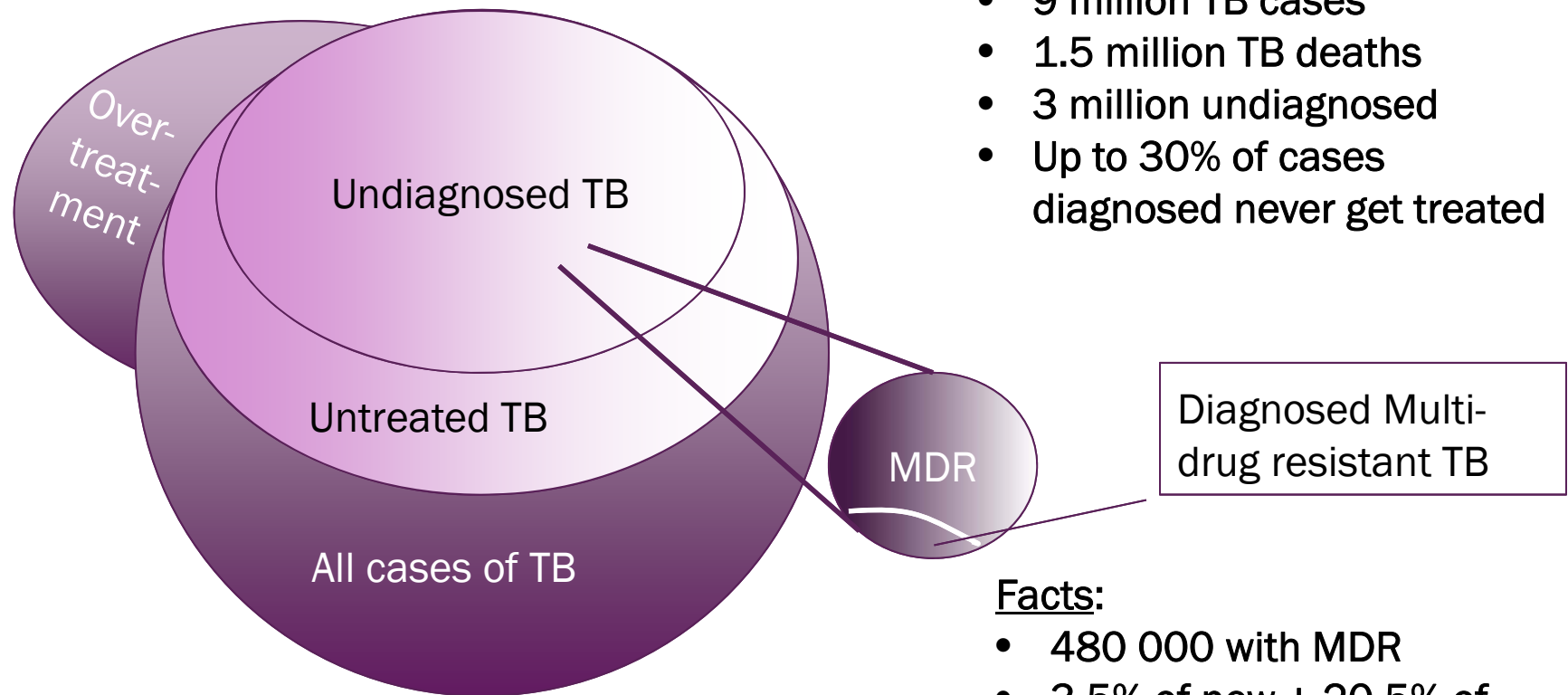
Claudia Denkinger, MD PhD MSc
Head of TB, FIND

29th October 2014

The Global TB Epidemic

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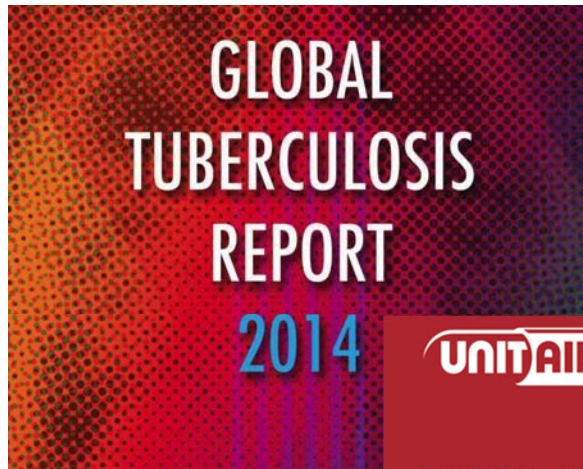- Up to 30% of cases diagnosed never get treated

Diagnosed Multi-drug resistant TB

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

20 November 2014

WHO Global TB report 2014

Need for new diagnostics

What are product developers looking for?

GLOBAL TUBERCULOSIS REPORT 2014

UNITAID 2014
TUBERCULOSIS
Diagnostics Technology and Market Landscape
3RD EDITION

Market Assessment of Tuberculosis Diagnostics in Brazil in 2012

TB Diagnostics Market Analysis Consortium**

Abstract

Background: Improved diagnostics for the diagnosis of tuberculosis (TB) are urgently needed. However, test developers and investors require market size data to support new product development. This study assessed the served available market for TB diagnostics in Brazil in 2012 and the market segmentation in the public and private sectors.

Methods: Data were collected on test volumes done in the public and private sectors for the diagnosis of latent and active TB, drug susceptibility testing and treatment follow-up. Tests included were tuberculin skin tests, interferon-gamma releases assays, smear microscopy, solid and liquid cultures, nucleic acid amplification tests and phenotypic drug susceptibility tests. The data were collected by means of an electronic survey via the Brazilian State laboratories and from sales information provided by manufacturers. Test costs for the public sector were calculated using a components approach, while costs for the private sector were based on prices paid by patients. The overall market value (expenditure) for the entire country was calculated using the public sector test costs.

Results: During 2012, an estimated total of 2.4 million TB diagnostic tests were done in Brazil, resulting in an estimated overall market value of USD 17.2 million. The public sector accounted for 91% of the test volumes and 88% of the market value. Smear microscopy was the most commonly test (n = 1.3 million; 55% of total) at an estimated value of USD 3.7 million. Culture overall (n = 302,761) represented 13% of test volumes and 40% (USD 6.9 million) of the market value. On average, USD 208 was spent on TB diagnostics for every notified TB patient in Brazil, in 2012.

Conclusion: The TB diagnostics market value in Brazil in 2012 was over USD 17 million. These study results will help test developers to understand the current and potential market for replacement or add-on diagnostic technologies.

TB Diagnostics: Top 10 FAQs By Test Developers

1   TB BURDEN AND TREATMENT LANDSCAPE

What is the global burden of TB (including latent TB, TB/HIV and MDR/XDR-TB) and what is the current and future TB treatment landscape? (Read more)

2   CURRENT DIAGNOSTICS LANDSCAPE AND PIPELINE

What is the current testing landscape for TB (including latent TB and DST), and what diagnostics are in the pipeline? What is the level of access to current TB diagnostics? (Read more)

3   MARKET SIZE, POTENTIAL AND DYNAMICS

What is the market size and potential for new TB diagnostics, and what are the market dynamics around TB diagnostics? (Read more)
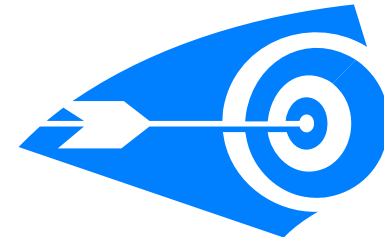
4   TARGET PRODUCT PROFILES

What are the unmet diagnostic needs and target product profiles (TPPs) of greatest relevance? (Read more)

What are target product profiles?

- Define the medical/public health need (goal of test; target population; setting of intended use; user)

- Make the need transparent to test developers by defining features and characteristics of the desired test
  - Performance characteristics
  - Operational characteristics
  - Desired price

- Outline features that would provide a competitive advantage

- Communication tool with investors and stakeholders

- Tool for tracking results

Tuberculosis diagnostics: which target product profiles should be prioritised?

Sandra V. Kik[1,2], Claudia M. Denkinger[1,2,3], Martina Casenghi[4], Caroline Vadnais[1,2] and Madhukar Pai[1,2]

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Test needs considered

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

Prioritization

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

⬅ POC Triage/rule-out test

⬅ POC Sputum-based, smear replacement

⬅ POC Biomarker-based, non-sputum

Kik S et al. ERJ 2014

POC testing

Goal-oriented definition:

"Testing that will result in a clear, actionable, management decision (e.g. referral, initiation of confirmatory test, start of treatment), within the same clinical encounter (e.g. day)."

TB MAC meeting Amsterdam April 2013
http://tb-mac.org/

TPP development

- **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 drug susceptibility tests (microscopy center)
- **Iterative process with input from many stakeholders**
- **Consensus Meeting on high-priority TPPs convened in April 2014 by WHO**
  - Delphi-like process leading up to the meeting
  - > 75% agreement amongst stakeholders across defined characteristics

The TPPs

gli
global laboratory initiative
advancing TB diagnosis

FIND
Because diagnosis matters

Centre international de TB McGill

McGill International TB Centre

Stop TB Partnership
New Diagnostics Working Group

Meeting Report

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

28–29 April 2014
Geneva, Switzerland
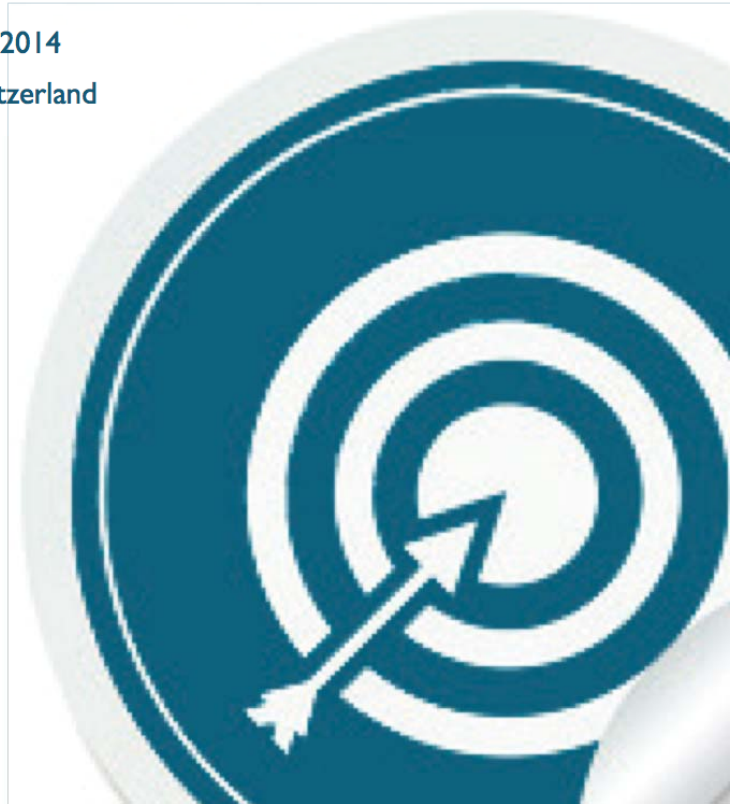
Biomarker TPP

	Optimal	Minimal
Clinical purpose	A highly sensitive and specific, rapid, biomarker-based test that can diagnose pulmonary TB (PTB) and ideally also extrapulmonary TB (EPTB) using non-sputum samples (e.g., urine, blood, oral mucosal transudates, saliva, exhaled air) with the purpose of initiating TB treatment within the same clinical encounter (or same day).	
Target population	Countries with medium to high TB prevalence. Target groups are adults +children (incl HIV) with suspected active TB; either PTB or EPTB	
Setting	Health posts without attached laboratories (a level lower than MCs)	Primary health clinics (with attached laboratories); Peripheral MCs
User	Health care workers with minimal training	Trained microscopy technicians

The concept of triage testing

Further testing

High Sensitivity
Lower specificity

Ruled OUT
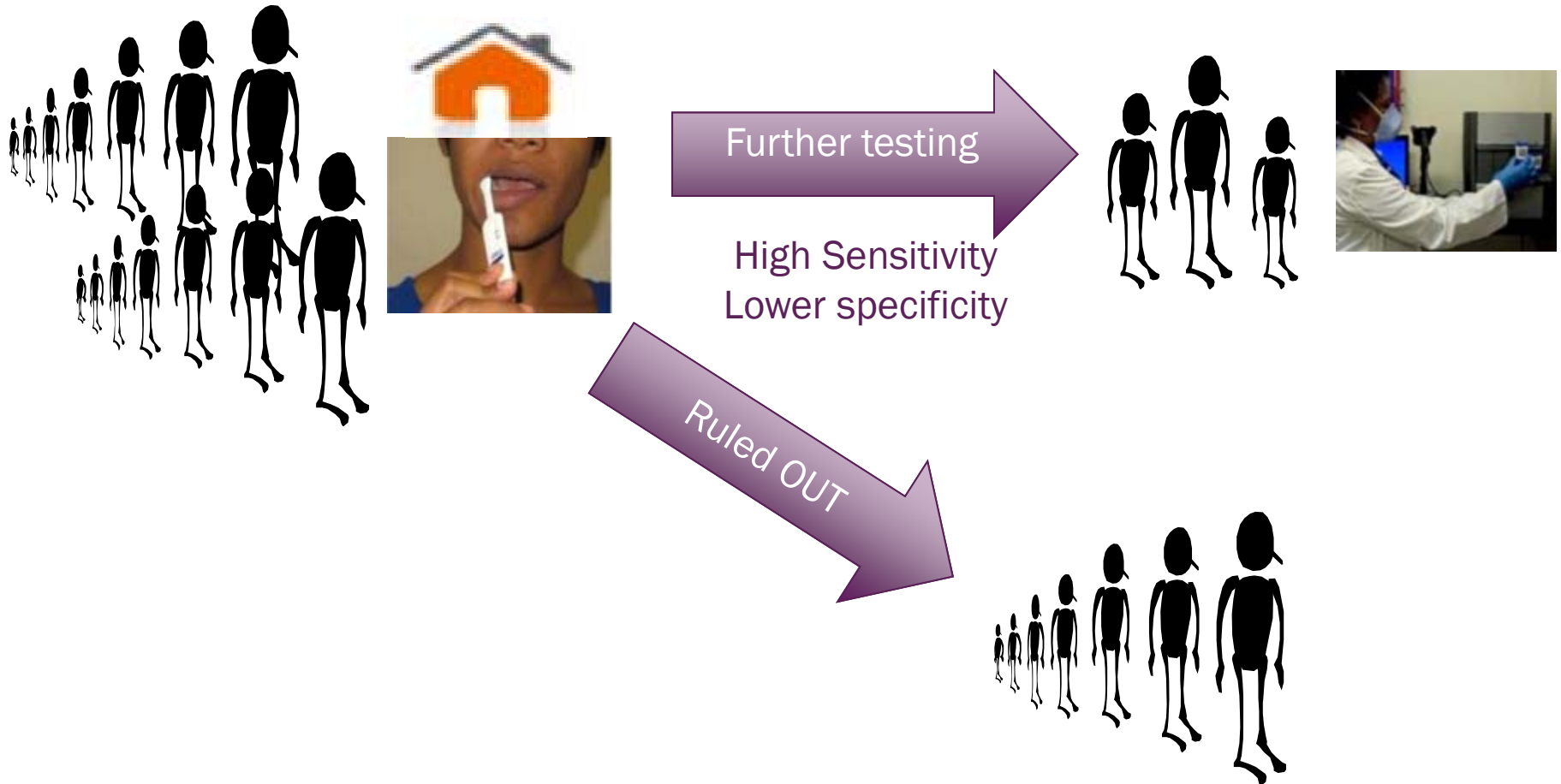
Triage test

	Optimal	Minimal
Clinical purpose	A highly sensitive test used at the first encounter to the health care system to identify, among patients with <u>symptoms or risk factors</u> of <u>active TB,</u> including HIV coinfected patients, those who do not have TB and those in need of referral for further confirmatory testing.	A highly sensitive test used at the first encounter to the health care system to identify, among patients with <u>symptoms or risk factors</u> of active <u>pulmonary TB</u>, including HIV coinfected patients, those who do not have TB and those in need of referral for further confirmatory testing.
Target population	Countries with medium to high TB prevalence (WHO Categories). Adults and children.	Countries with medium to high TB prevalence (WHO Categories). Adults and children.
Setting	Community/village level	Health post and primary care clinics
User	Minimally trained community health workers and informal providers	Training at the level of an auxiliary nursing staff

Smear-replacement tests

→ Increased portability, ruggedness, performance, and DST portfolio

Sputum-based smear replacement test

	Optimal	Minimal
Clinical purpose	A highly sensitive and specific test for sputum-based <u>pulmonary TB</u> detection (NAAT or other) at the level of a microscopy center with the purpose of supporting initiation of TB therapy within the same clinical encounter (or same day) with a higher sensitivity of smear microscopy.	
Target population	Countries with medium to high TB prevalence (WHO Categories). Target groups are all patients suspected of having pulmonary TB and able to produce sputum.	
Setting	Microscopy center level (primary health centers with attached peripheral laboratories)	
User	Microscopy center technicians	

Drug-susceptibility tests

	Optimal	Minimal
Clinical purpose	A highly sensitive and specific test for the rapid detection of drug resistance to inform decision-making concerning optimal first line therapy (HRZE, REMox, vs. PaMZ), possibly presence of additional second line drug resistance and need for further testing.	
Target population	Countries with medium to high TB prevalence (WHO Categories). Target groups are all patients suspected of having TB with a special focus on those at high risk of morbidity and mortality from drug-resistant TB such as people living with HIV, and those at high risk of having MDR-TB	
Drugs	**RIF > FQ (incl. Mox)> INH = PZA > AG/CAP**	
Setting	Microscopy center level	
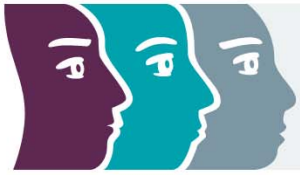
Interplay of novel diagnostic tests

Status quo:
- Smear microscopy
- Xpert
- Very little Culture
- Even less DST

PULMONARY
PEDIATRIC
EXTRA-PULMONARY

NUMBER OF PATIENTS WITH PRESUMPTIVE TB THAT SHOULD BE TESTED

NUMBER OF PATIENTS WITH EACH TYPE OF TEST

SMEAR

SPUTUM-BASED WITH OR WITHOUT DST

TRIAGE

NON-SPUTUM

TIME (YEARS)

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
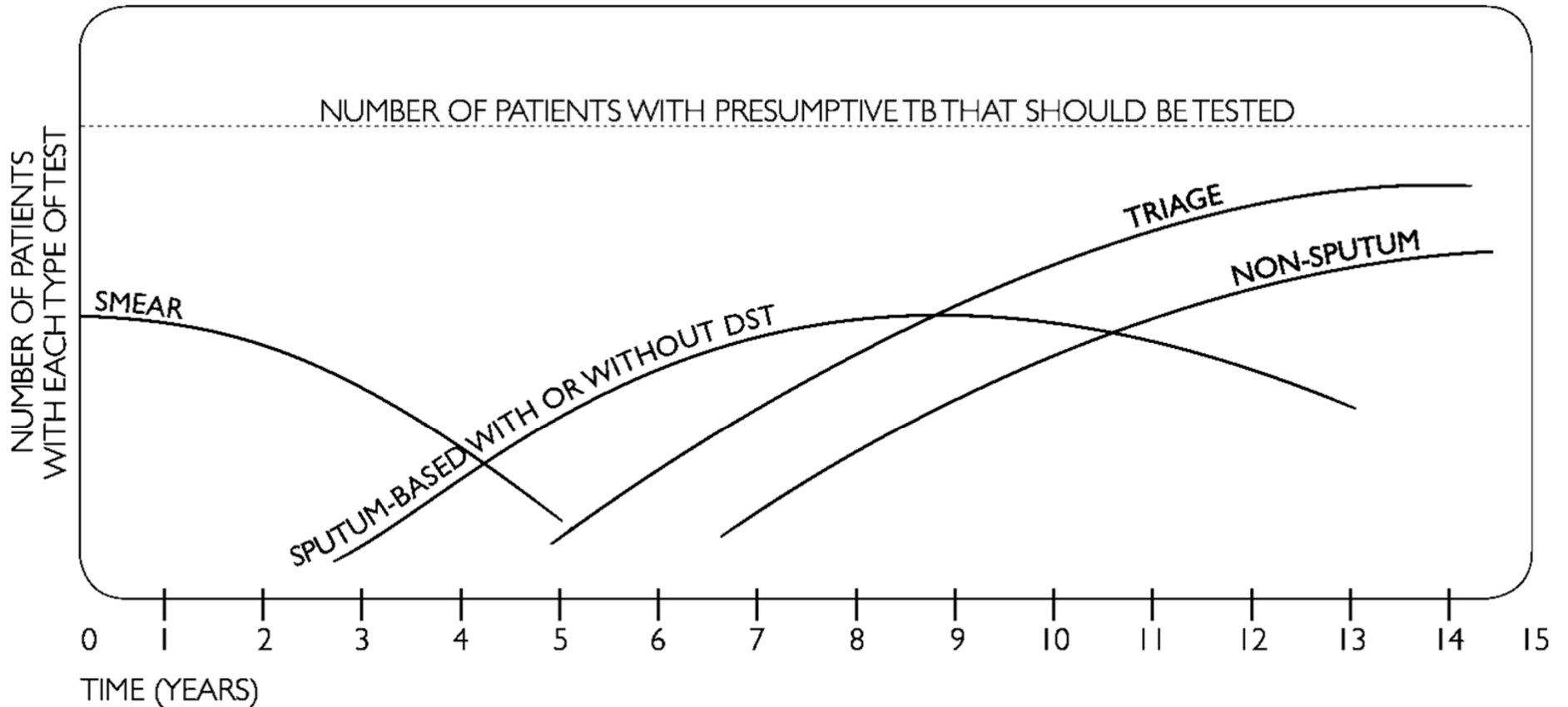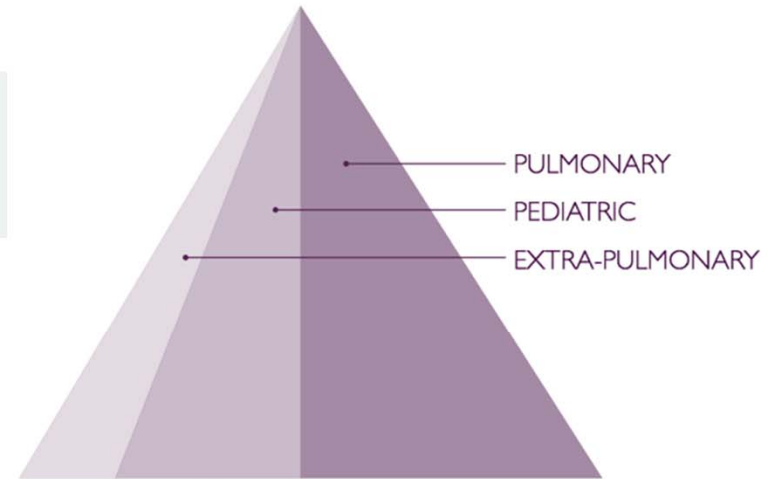
POTENTIAL MARKET FOR PRIORITY TPPS

PARTNERS: MCGILL, FIND, UNITAID, NDWG & NTP IN COUNTRIES

POTENTIAL IMPACT OF PRIORITY TPPS

PARTNERS: HOPKINS, AIGHD, LSHTM, HARVARD, TB-MAC, MCGILL, FIND

OPEN ACCESS Freely available online

Do We Need to Detect Isoniazid Resistance in Addition to Rifampicin Resistance in Diagnostic Tests for Tuberculosis?

Claudia M. Denkinger[1,2], Madhukar Pai[2,3], Davi

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5 Center for Tuberculosis Research, Johns Hopkins University, School of Med

OPEN ACCESS Freely available online

**Optimal Triage Test Characteristics
Effectiveness of the Xpert MTB/RIF
Diagnosis: A Decision Analysis**

Anna H. van't Hoog[1,2]*, Frank Cobelens[1,2], Anna Vassall[3], Sanne van Kampen[4], Susan E. Dorman[5], David Alland[6], Jerrold Ellner[7]

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PLOS ONE

Modeling the Impact of Alternative Strategies for Rapid Molecular Diagnosis of Tuberculosis in Southeast Asia

Amanda Y. Sun, Madhukar Pai, Henrik Salje, Srinath Satyanarayana, Sarang Deo, and David W. Dowdy*

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Thank you - Questions

McGill
- Sandra Kik
- Madhu Pai

FIND
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- Catharina Boehme
- David Dolinger

Others
- CPTR working group
- WHO team
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- Carol Jefferson
- Janet Ginnard - UNITAID

BMGF team
- Jim Gallarda
- Michael Kimerling
- Jennifer Gardiner

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BILL & MELINDA GATES *foundation*

Additional slides

Target product profile attributes

- Scope
  - The clinical purpose of the test (e.g. triage)
  - Target population (children, adults, community or HIV-clinic)
  - Intended level of implementation in the health care system and user
- Performance characteristics
  - Sensitivity/specificity for TB detection
  - Treatment monitoring
  - DST
- Operational characteristics
  - Sputum type
  - Manual steps
  - Infrastructure requirements (e.g. power, temperature control)
  - Time to result (how important is same-day results?)
  - Requirements for reporting and connectivity
  - Importance of subgroups such as HIV-infected and children
- Price targets