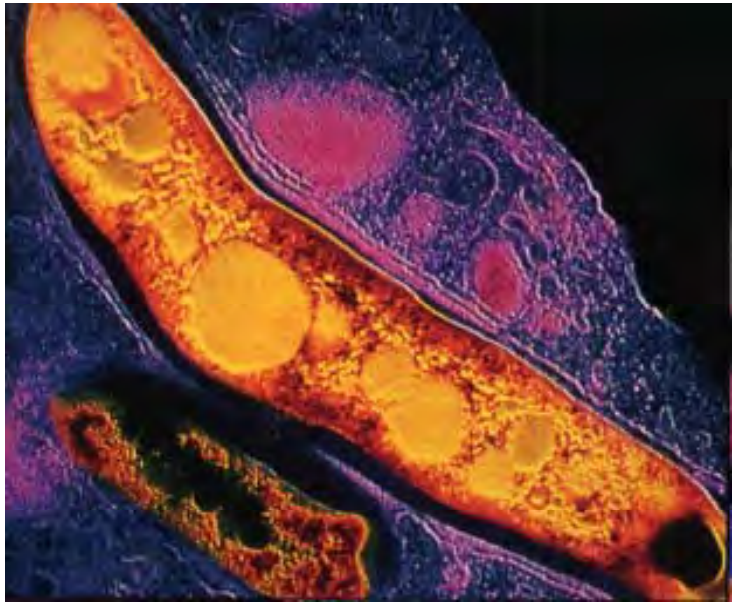
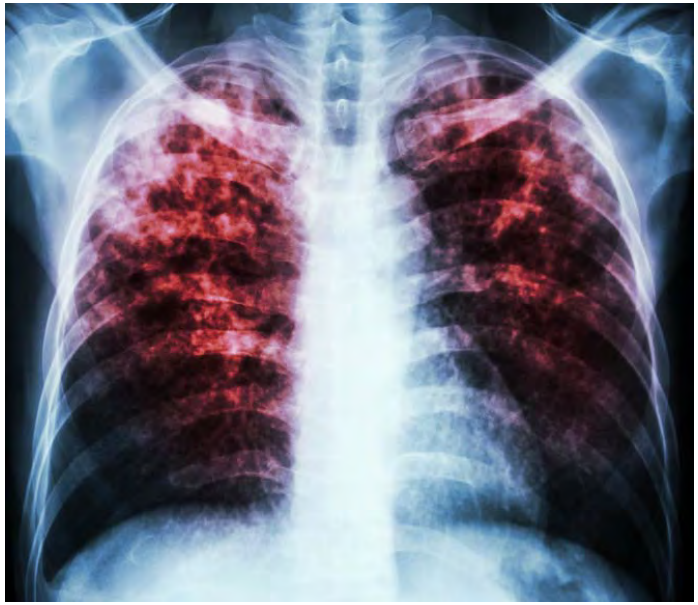
Triage Testing for TB
McGill Advanced TB Dx Course 2018





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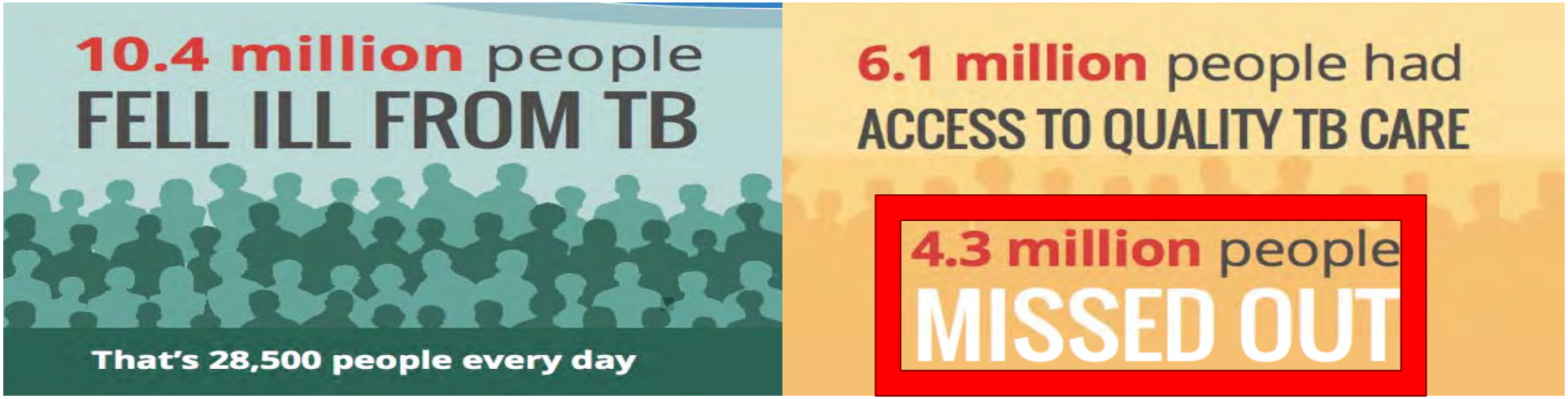

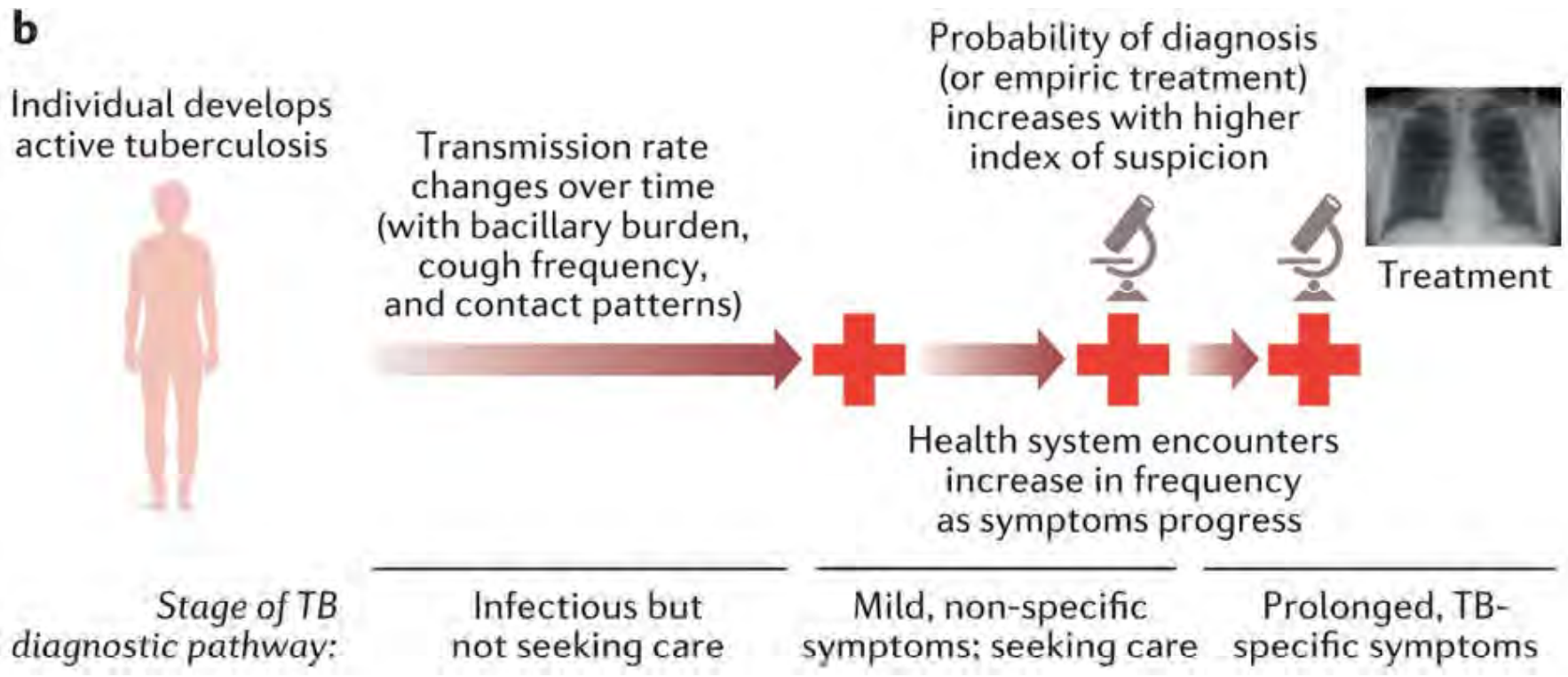

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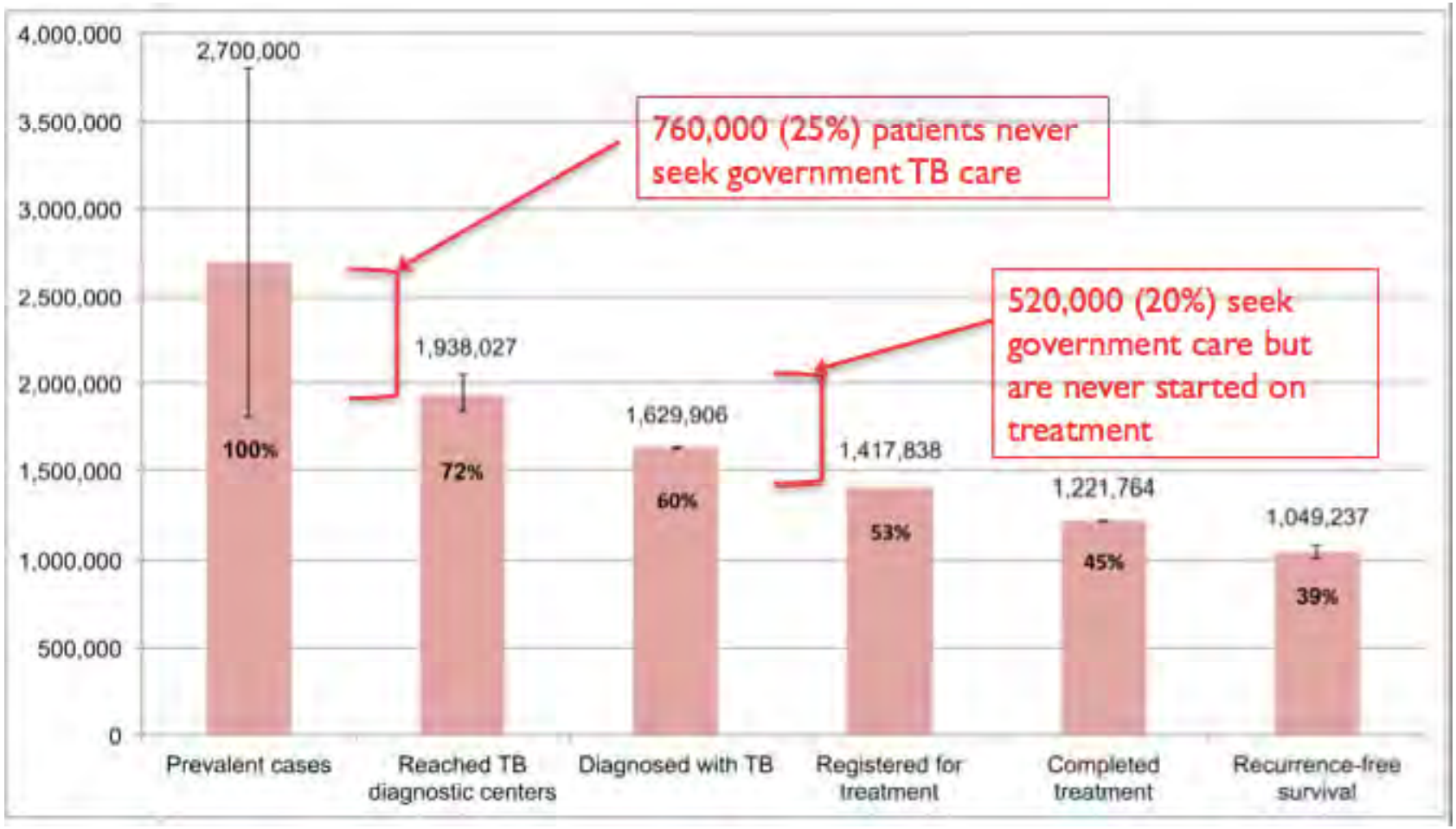
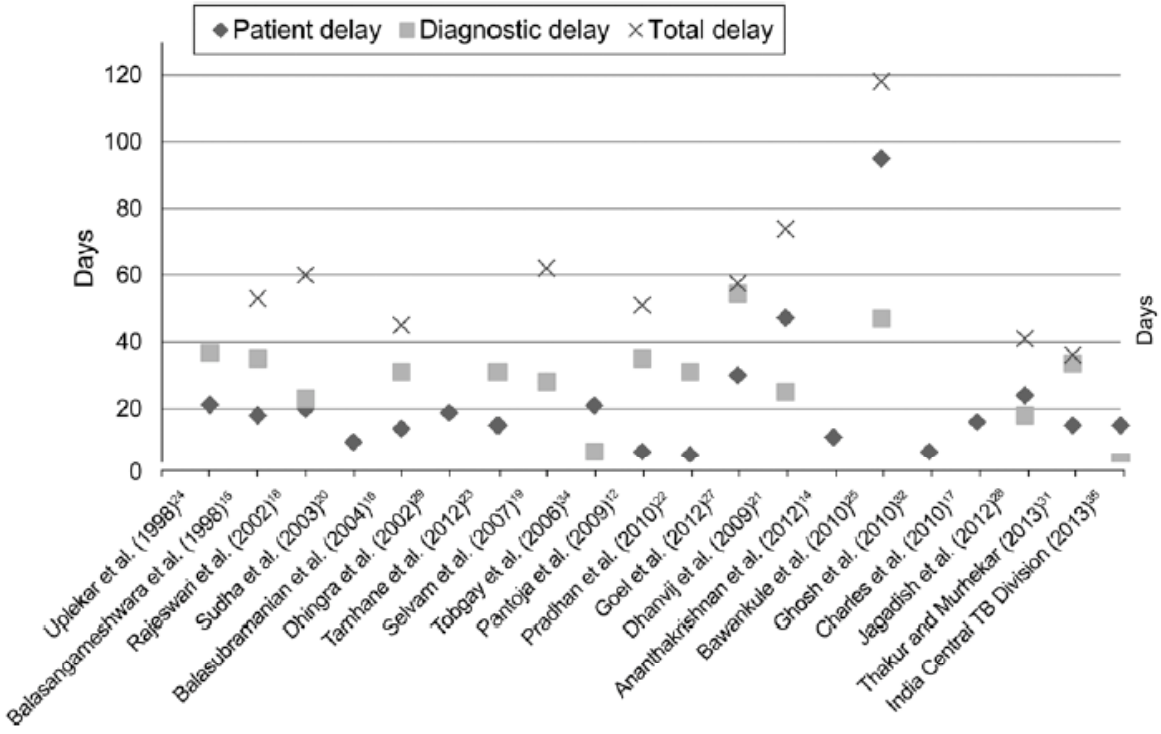
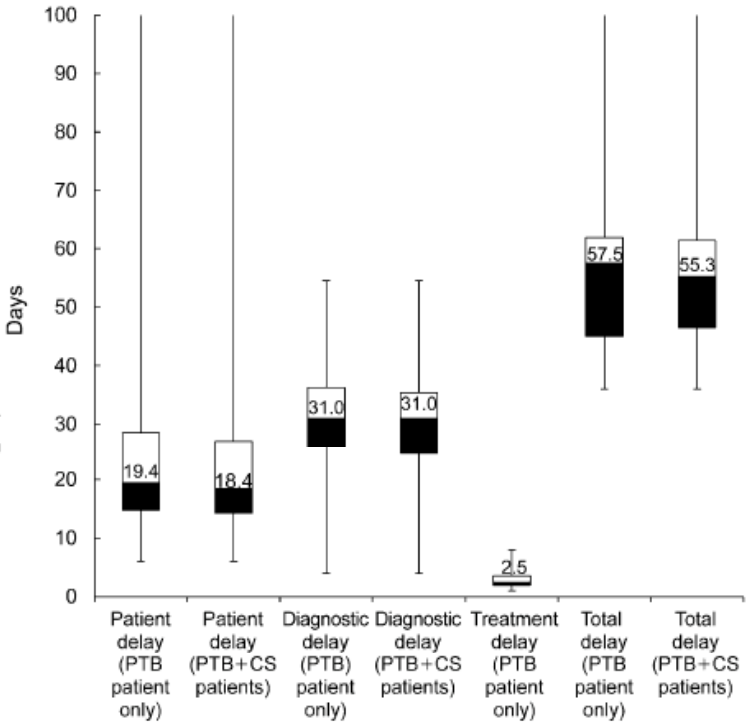
WHO Global TB Report 2017
Pathy Nature 2015

Mind the Gap:
TB Cascade of Care in India



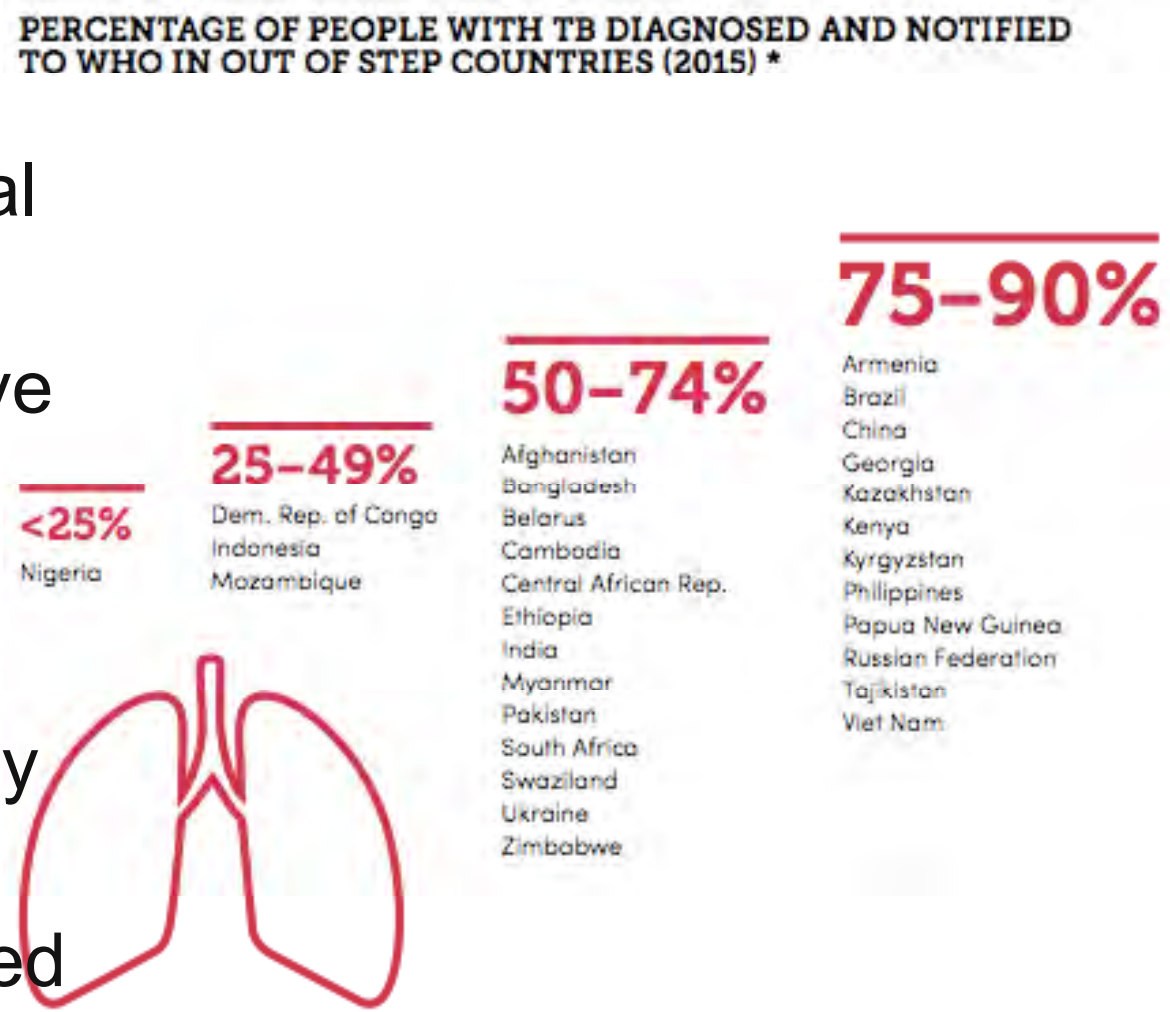
Diagnostic delays experienced by PTB patients in India





Diagnostic Gap – what about Xpert?

- WHO stated Xpert may be used as initial test (2016 update)
- 52% of 29 HBCs have adopted Xpert for all
- Only 50% of HBCs providing Xpert to 'high risk' have widely implemented it
- Xpert often centralised
- Limited impact



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MSF Out of Step Report 2017
WHO Xpert policy statement 2016

Target Product Profiles (TPPs)

	Target product profiles for potential new TB diagnostic tests	Prioritisation by key stakeholders				Impact		Market		Implementation and scalability		Score	Priority rank
		Patients and community advocates	National TB programmes	Field practitioners	Research	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	A HIV/ART clinic-based test to tule 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
	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

Potential value of a Triage or Rule Out TB Test

- Transmission is not from TB patients on effective treatment but rather from those with unsuspected TB
- A triage test for TB could have a large global market and a high impact potential to reduce TB
- Decision analysis modeling demonstrated that a TB triage test with equal sensitivity to Xpert and 75% specificity at a cost of $5 could reduce diagnostic costs by ~40% if Xpert was only performed in patients with a positive triage test
- Goal – enhance case finding and ↑ Xpert affordability

Kantor Am J Med 1988
Brennan ICHE 1988
Moran Ann Em Med 1995
Barrera IJTLD 2015
Kik ERJ 2014
Van't Hoog PLoS One 2013

Symptom screening

- WHO recommends three options: cough >2 weeks vs. any symptom vs. CXR followed by diagnostic test algorithm depending on availability of smear/Xpert/CXR
- Sensitivity variable: 25-50% for prolonged cough vs. 77-84% for any symptom
- Specificity may drop from ~92-96% for prolonged cough to 67-74% for any TB symptom
- Clinic-based exit screening: 20-50% with identified TB symptoms undergo sputum-based TB testing

Van't Hoog BMC ID 2014
Chihota PLoS One 2015
Claasens IJTLD 2013
Roy JAIDS 2016
Kweza IJTLD 2018

Is cough the optimal screening strategy? How does this vary by setting?

- 10 901 patients screened at a tertiary hospital in Lima
  - Cough > 2 weeks: 36 (0.3%) [any cough: 250 (2.2%)]
  - Smear+ PTB: 16 (44.4%), 5 of whom had new Dx
- 8028 patients screened at PHCs
  - Cough or resp symptoms: 259 (3.2%)
  - Smear + PTB: 11 (4.2%)

- 19 000 patients screened: 16 previously cases of previously undiagnosed TB detected

➢need to understand local epi to adapt screening

FAST, unpublished data

Frequency of cough varies across studies

- Rapid literature review: 297 abstracts, 52 full-texts, extracted from 17 papers
- Total patients screened: 31 267 (median, wide range)

- Any cough 13% (mean, range 2-90%)
- Prolonged cough 3% (median 1-35%)
- Patients with cough dx with TB: 9% (range 2-24%)

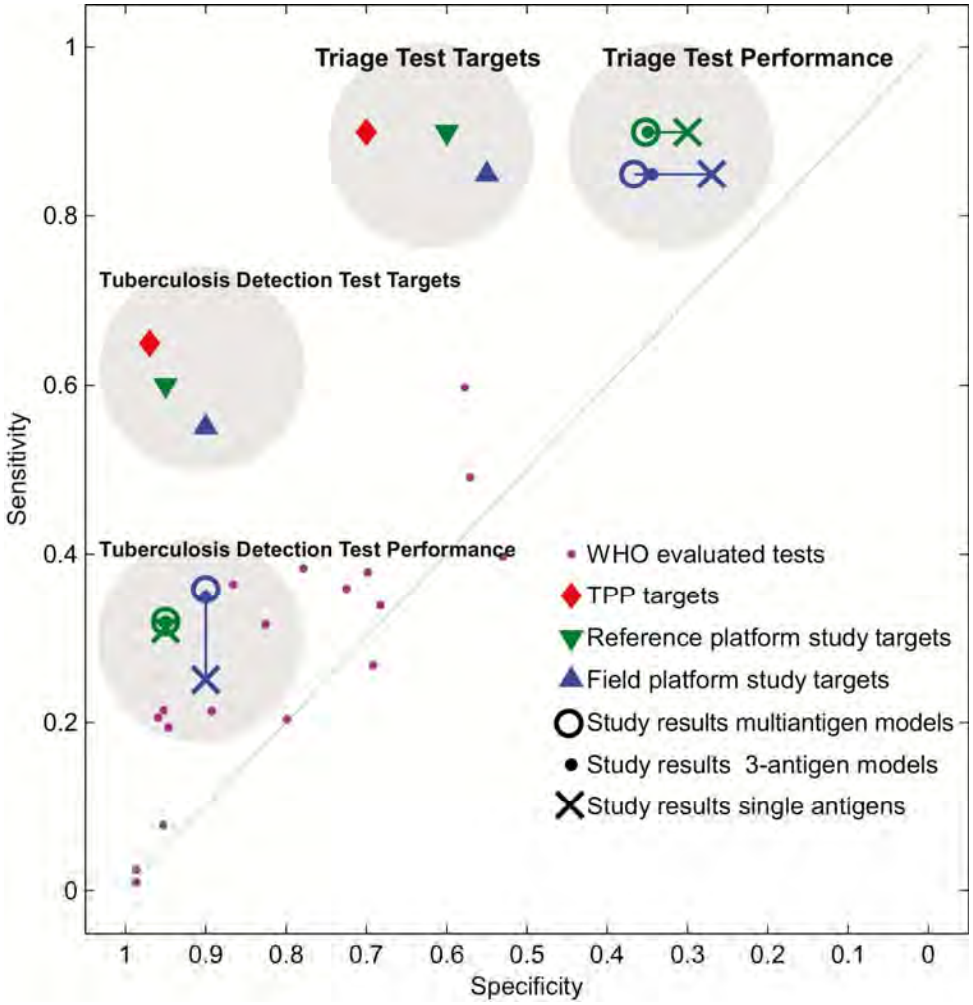
➢Cough prevalence/epidemiology is highly variable

FAST, unpublished data

Triage Test: Definition, Characteristics

- To test people with TB symptoms to determine who requires confirmatory or follow on TB diagnostic testing (for triage test-positive patients) versus investigation of non-TB aetiologies (for triage test-negative patients)
- Can be used as part of PCF versus ACF
- Needs high NPV (rule out)
- Optimal use in adults and children with symptoms and signs of any form of active TB (minimal for active PTB)
- Ideally non-sputum based, scalable, affordable
- Different use case to screening test

Triage Test Performance Criteria



- Optimal sensitivity >95%
- Minimal sensitivity >90%

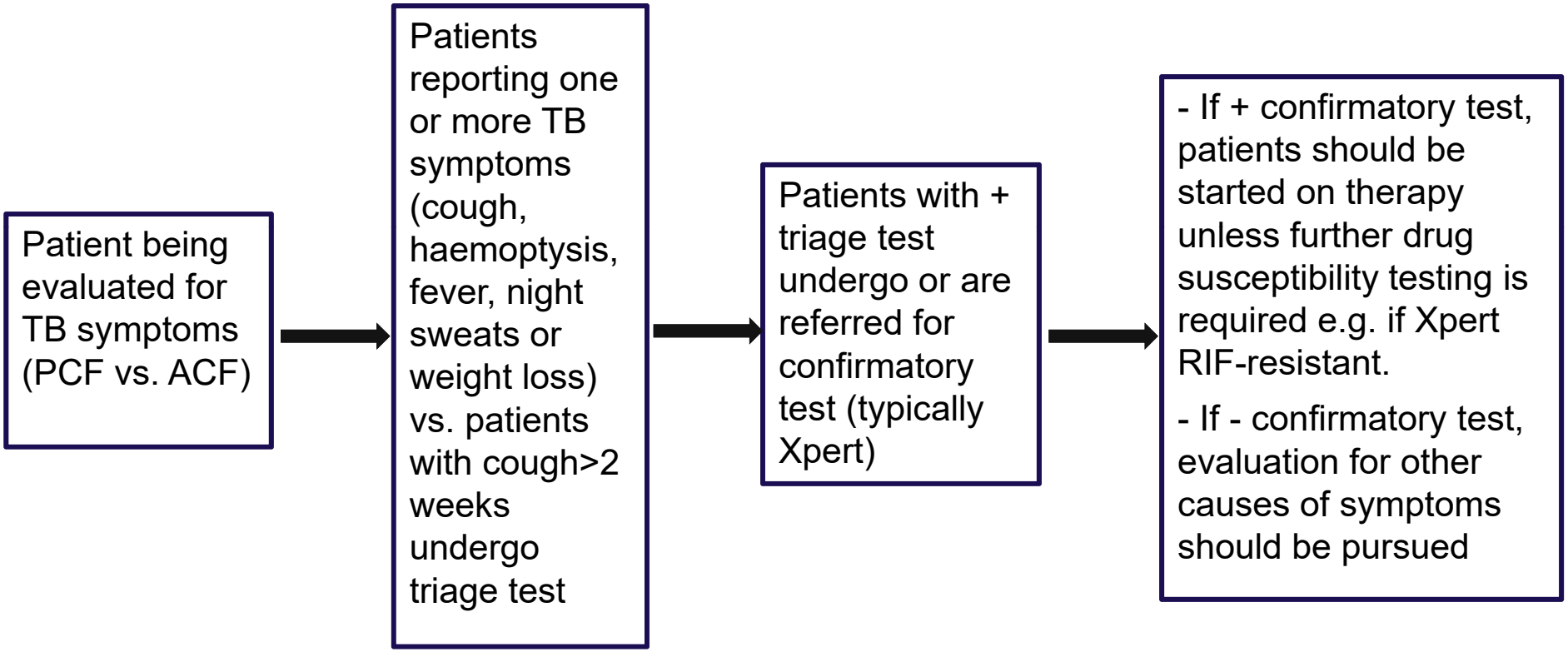
- Optimal specificity >80%
- Minimal specificity >70%

Triage Test: Role

- Facilitate earlier diagnosis by increasing the number of patients with TB symptoms who undergo TB testing
- Improve PPV of follow-up testing
- Reduce the patient and health system costs by decreasing the number of necessary follow-up tests, which will typically involve more expensive molecular diagnostics such as Xpert

- Primarily for use at lower levels of healthcare system
- PPV will vary according to prevalence

Triage Test: Clinical Pathway



Location, Location, Location: where are TB services in HBCs?

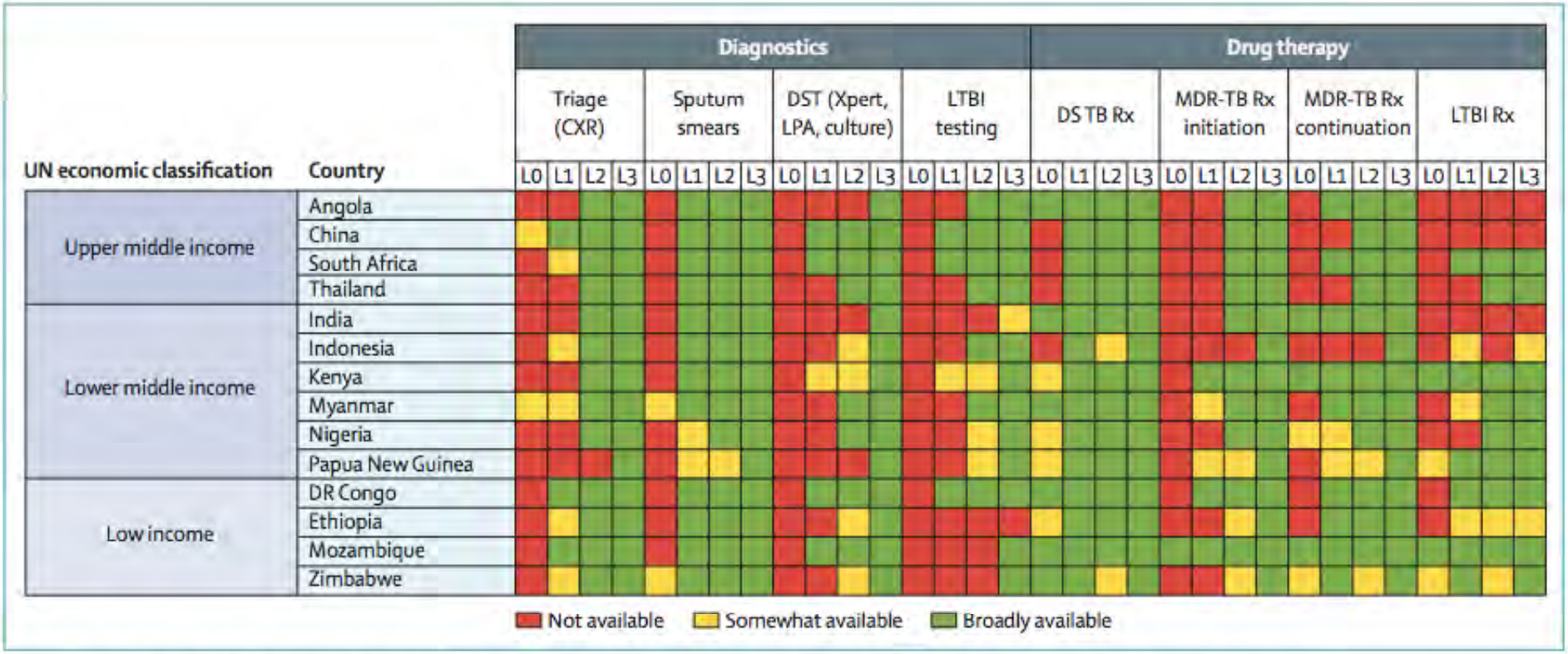
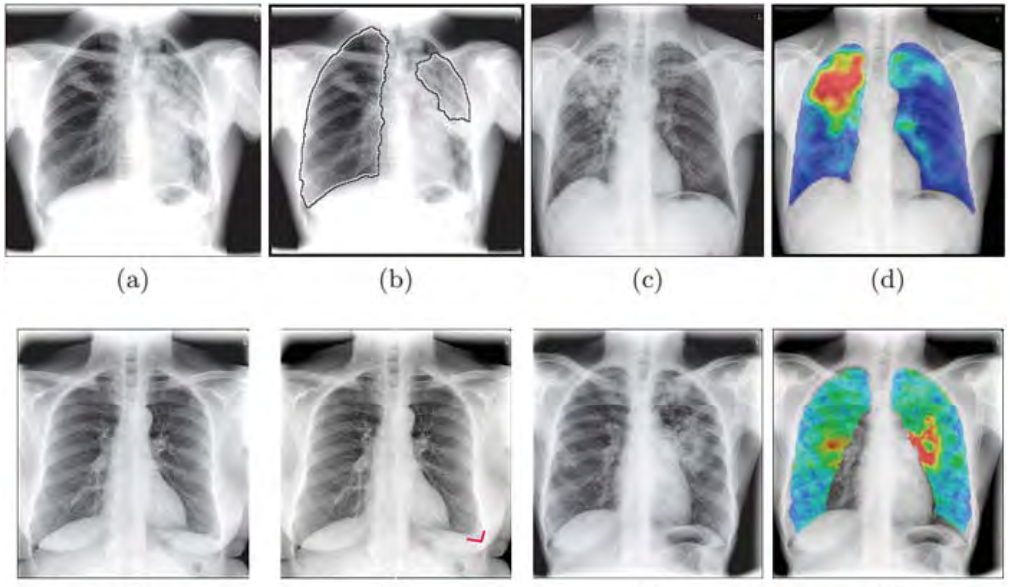


Figure 1: **Availability of tuberculosis diagnostic and treatment services across various health-care levels in 14 highest burden countries**
CXR=chest radiography. LTBI=latent tuberculosis infection. DS=drug sensitive. DST=drug sensitivity testing. MDR-TB=multidrug-resistant TB. L0=care by community or village health workers or at health posts. L1=microscopy centres or primary health centres. L2=district hospitals or community health centres. L3=reference or tertiary hospitals. TB=tuberculosis.



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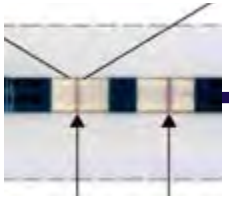
Triage Test: Clinical populations/settings

- Key initial study population for the evaluation of triage tests will be adults with symptoms of PTB (need for reference standard which is challenging in children)
- Populations of interest: paucibacillary/smear-negative TB, extrapulmonary TB (test would need to be non-sputum based) and paediatric TB
- Patient enrolment & testing should ideally be performed in the primary settings of intended use i.e. L0-L2
- N.B. prevalence at L0 lower -> need higher specificity
- TT may be based on host markers which may vary

Triage Test: Evaluation

- Ideally culture as reference standard, consider Xpert
- For impact (vs. DTA) studies, results of triage testing followed by confirmatory testing e.g. with Xpert should be compared to confirmatory testing alone or other algorithms
- Triage tests may detect early or subclinical TB, which may be culture negative -> needs adequate follow up
- Should consider using clinical or composite reference standard or latent class analysis
- Other comparators e.g. human readers for CXR? CRP?



Triage Test: Other considerations

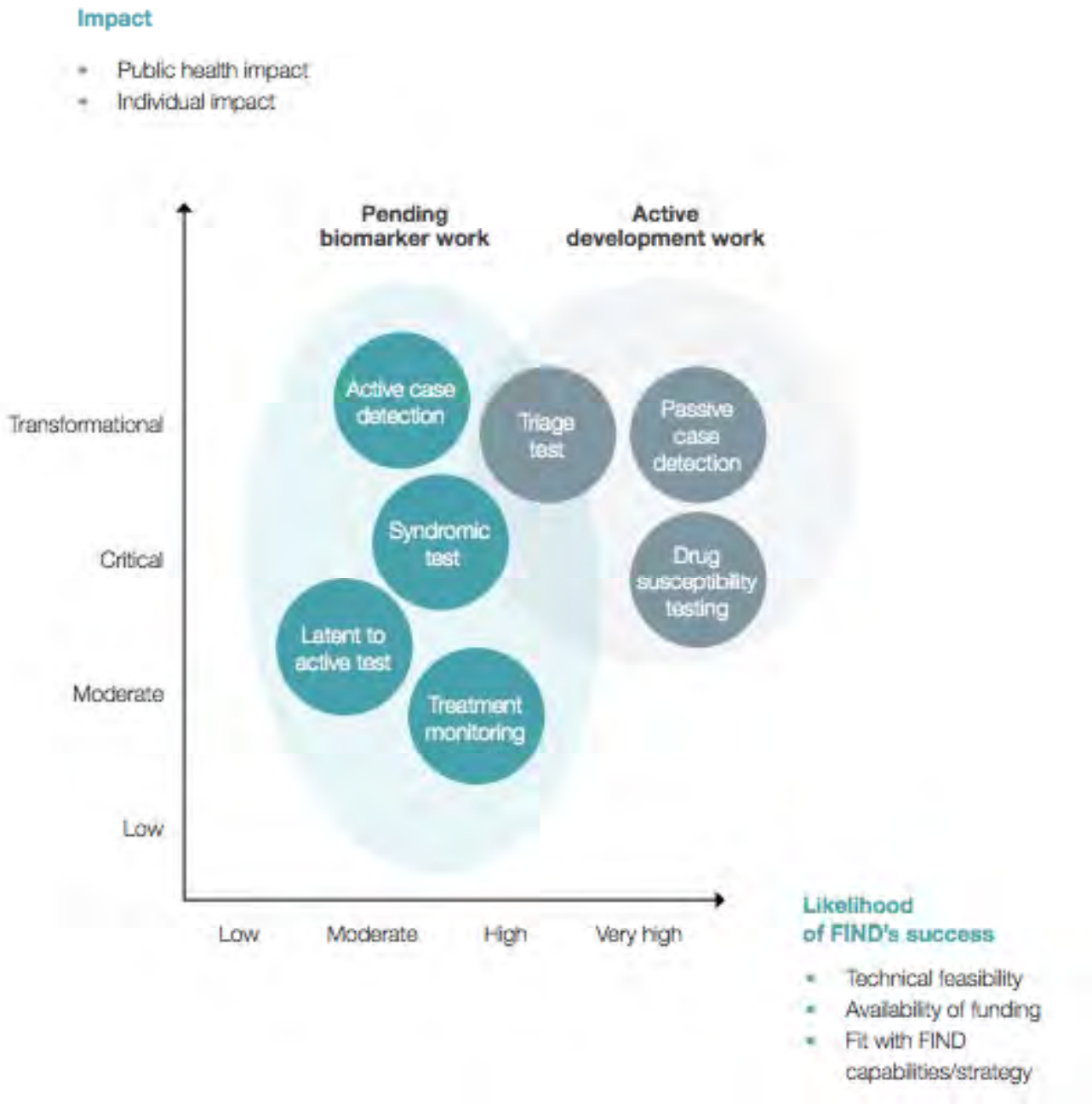
- Sample type- ideally non sputum based
- Specimen flow- ideally integrated sample preparation, no precise timing required,disposable, low maintenance
- Evaluation on banked specimens may aid development but needs to demonstrate pre-analytic stability

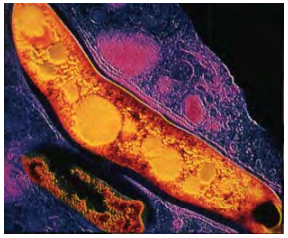
- Test development may involve machine learning e.g. CAD versus ROC curve analysis of biomarker signatures e.g. breath testing

Triage Test: Limitations

- Reliant on symptom screening
- Test performance limitations – false negatives that may still warrant confirmatory testing or empiric therapy, false positives result in high volume of confirmatory tests needed
- Implementation is critical – no test is a magic bullet and impact relies on functional systems of care i.e. linkage to confirmatory testing -> results -> Rx initiation
- Importance of implementation studies to evaluate process indicators and other benefits (costs, access)

TB Diagnostic Pipeline





Triage test questions?

- Current tests e.g. CXR -> ↑sensitivity but ↓specificity
- Where in the testing pathway should triage test be placed?
  - Triage at community health post level vs. PHCs?
  - Triage for patients in healthcare facilities?
  - Screening for asymptomatic patients e.g. PLHIV?
- Who is the target user? CHWs, nurses, doctors?
- What sort of tests can be used in different settings e.g. widespread applicability of CAD4TB?
- What should follow up strategy be? How to ensure?

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Table 6. Revised target product profile (TPP) for a community-based triage or referral test to identify people suspected of having TB, using input from a Delphi survey and discussions at a consensus meeting, 2014

Characteristic	Optimal requirements	Minimal requirements
Scope		
Goal	To develop a test that can be used during a patient's first encounter with the health-care system to identify patients with **any symptoms of or risk factors for active TB**, including patients coinfected with HIV, those who do not have TB and those who need referral for further confirmatory testing	To develop a test that can be used during a patient's first encounter with the health-care system to identify patients with **any symptoms of or risk factors for active pulmonary TB**, including patients coinfected with HIV, those who do not have TB and those who need referral for further confirmatory testing
Target population	Adults and children with signs and symptoms of **active TB at any site** in countries with a medium prevalence to a high prevalence of TB as defined by WHO[a]	Adults and children with signs and symptoms of **active pulmonary TB** in countries with a medium prevalence to a high prevalence of TB as defined by WHO[a]
Target user of the test[b]	Community health workers and informal providers who have had a minimum of training	Health workers trained to the level of auxiliary nurses
Setting (level of the health-care system)	Community level or village level or higher levels of the health-care system	Health posts and primary-care clinics or higher levels of the health-care system
Diagnostic sensitivity[b]	Overall sensitivity should be > 95% when compared with the confirmatory test for pulmonary TB[c] no lower range of sensitivity was defined for extrapulmonary TB[d]	Overall sensitivity should be > 90% compared with the confirmatory test for pulmonary TB[c]
Diagnostic specificity[b]	Specificity should be > 80% compared with the confirmatory test	Specificity should be > 70% compared with the confirmatory test
Operational characteristics		
Sample type	Non-sputum samples (such as urine, oral mucosal transudates, saliva, exhaled air or blood from a finger-stick)	Sputum; non-sputum samples are preferred (such as urine, oral mucosal transudates, saliva, exhaled air, or blood from a finger-stick; imaging technology

Manual preparation of samples (steps needed after obtaining sample)	Sample preparation should be integrated or manual preparation should not be required (excluding waste disposal); precise timing and measuring should not be required	2 steps (excluding waste disposal); precise timing and measuring should not be required
Time to result[b]	< 5 minutes	< 30 minutes
Instrument and power requirement	None	Small, portable or hand-held device (weighing < 1 kg); should have an option for battery power or solar power
Maintenance and calibration[b]	Disposable, no maintenance required	Preventative maintenance should not be needed until after 1 year or 1 000 samples; only simple tools and minimal expertise should be required; an alert to indicate when maintenance is needed should be included; the device should be able to be calibrated remotely, should calibrate itself, or no calibration should be required
Operating temperature and humidity level	Between +5 °C and +50 °C with 90% humidity	Between +5 °C and +40 °C with 70% humidity
Result capturing, documentation and data display	An instrument-free test with visual readout and with the ability to save results using a separate, attachable reader	The test menu must be simple to navigate; the instrument should have an integrated LCD screen, a simple keypad or touch screen, and the ability to save results using either the instrument or a separate reader
Internal quality control	Internal controls should be included for processing the sample and detecting TB	Internal control included only for processing the sample
Pricing		
Price of individual test[b] (costs of reagents and consumables only; after scale-up; ex-works [f	< US$ 1.00	< US$ 2.00