

# **Implementation of Xpert MTB/RIF: controversial issues**

Think Tank organized and sponsored  
by the South Africa/US and Brazil/US  
ICOHRTA



INTRODUCTION

# **XPRT MTB RIF: OVERVIEW OF PERFORMANCE AND GUIDELINES**

# Diagnostic challenges in TB

	Smear microscopy	Culture
Sensitivity	Moderate Poor in HIV-infected individuals and children	Good (gold standard)
	Very low in extrapulmonary specimen	
Specificity	High	High (gold standard)
Turn around time	About 2 hours	2 to 6 weeks Liquid faster than solid
Detection of resistance	No	Yes
Laboratory infrastructure	Basic	BSL 3
Cost	Low	High

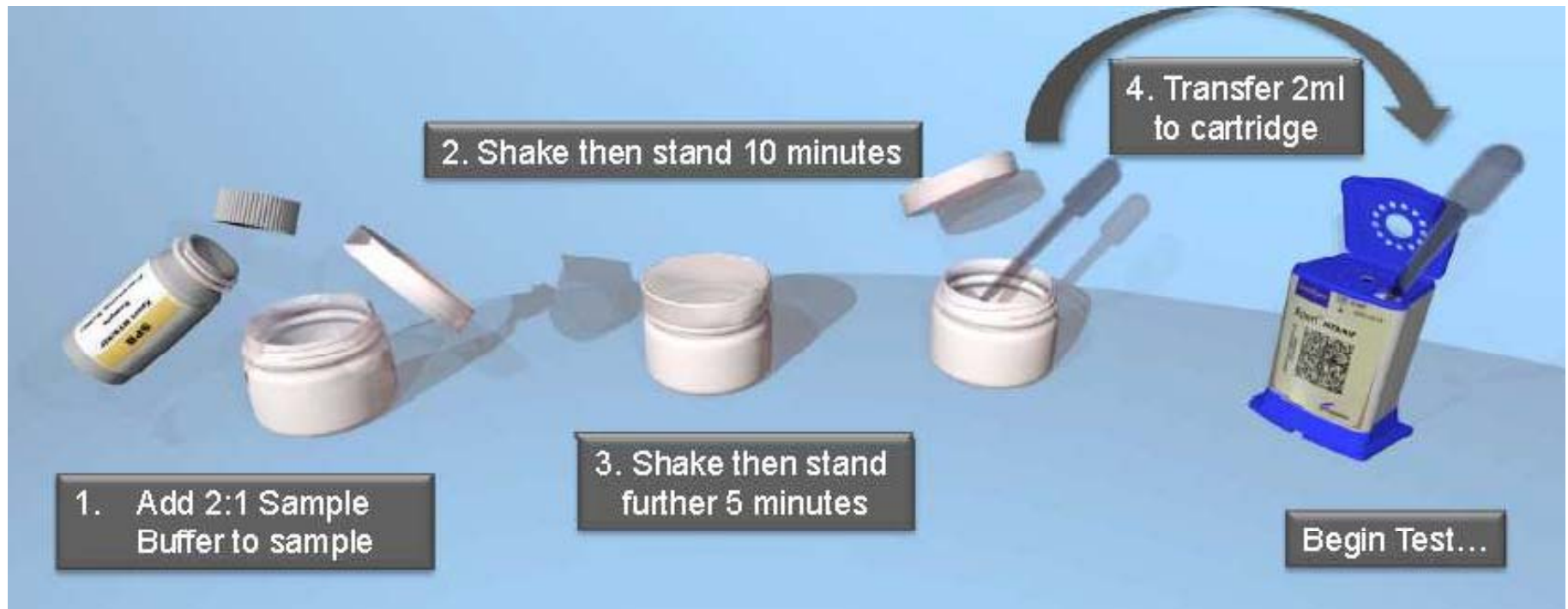
# Xpert MTB/RIF: promise of a dramatic change

- Use of new technologies to use for neglected disease
- Highly automated PCR technology for diagnosis of TB
  - Rapid
  - Simple
  - Robust
  - Sensitive and specific
  - Diagnosis of drug sensitive and drug resistant TB
  - Works on sputum and likely also other specimen

# Assay performance

- Sensitivity for smear positive culture-positive PTB in adults:
  - 99.8% (95% CI: 99.0–100)      3 assays
  - 98.2% (95% CI: 96.8–99.0)      1 assay
- Sensitivity for smear negative culture-positive PTB in adults
  - 90.2% (95% CI: 84.9–93.8)      3 assays
  - 72.5% (95% CI: 42.4–79.9)      1 assay
- Specificity in adults without TB
  - 98.1% (95% CI: 96.6–98.9)      3 assays
  - 99.2% (95% CI: 98.1 –99.6)      1 assay

# Simple



# For “every” setting



GeneXpert

Xpert  
MTB/RIF



5      20      80      Samples per shift      500-1000

# Recommendations

1. Xpert MTB/RIF should be used as the initial diagnostic test in individuals suspected of having MDR-TB or HIV-associated TB.

(Strong recommendation)

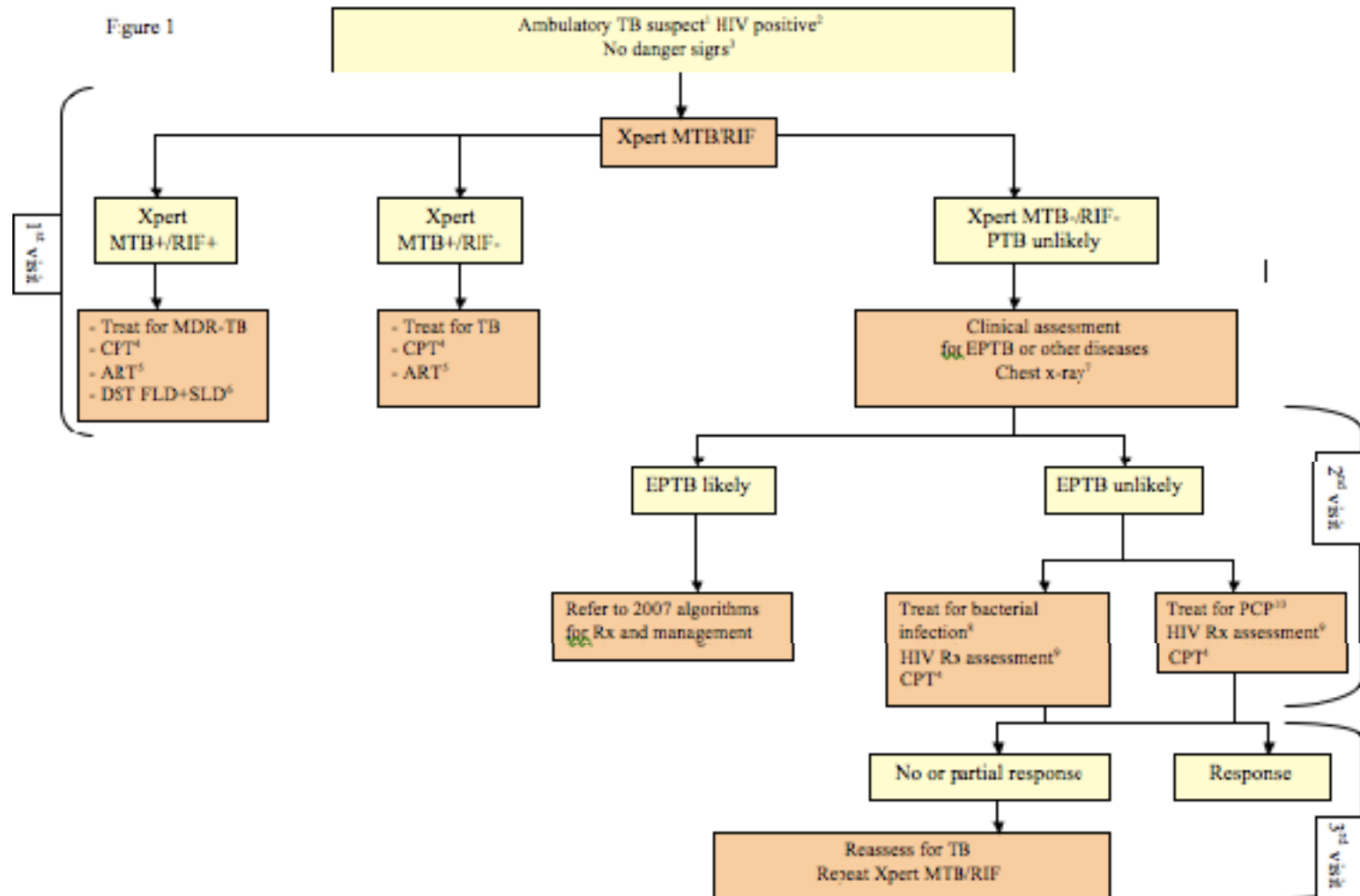
2. Xpert MTB/RIF may be considered as a follow-on test to microscopy in settings where MDR-TB or HIV is of lesser concern, especially in further testing of smear-negative specimens.

(Conditional recommendation acknowledging major resource implications)

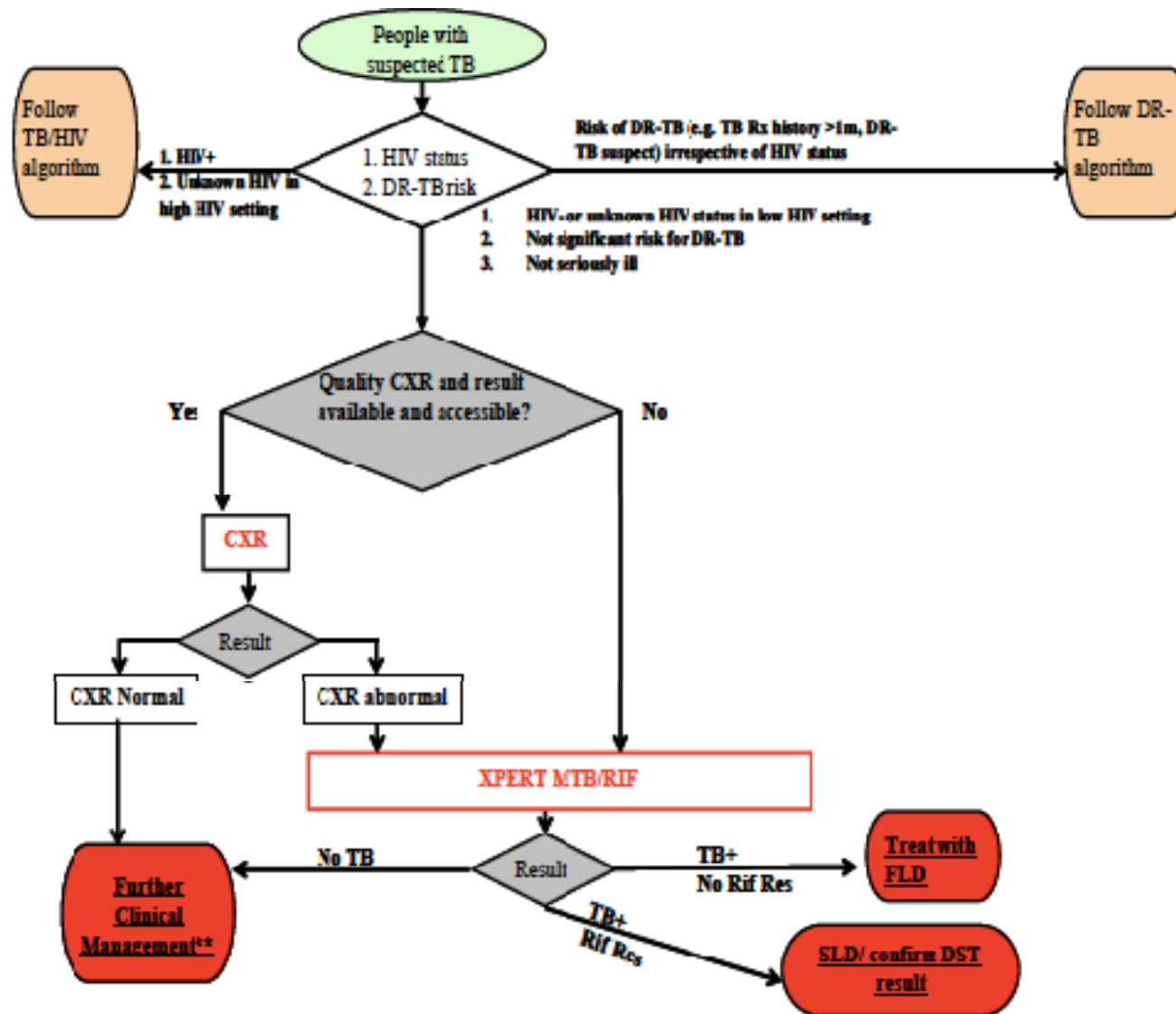
# Guidelines

- HIV positive, critically ill
  - HIV positive, ambulatory
  - HIV negative at high risk of MDR-TB
  - HIV negative at low risk of MDR -TB
- 
- High and low HIV burden setting
  - High and low TB burden setting
  - High and low MDR-TB setting
- 
- On-site: assay at health care clinic or
  - Off site: assay at (reference) laboratory

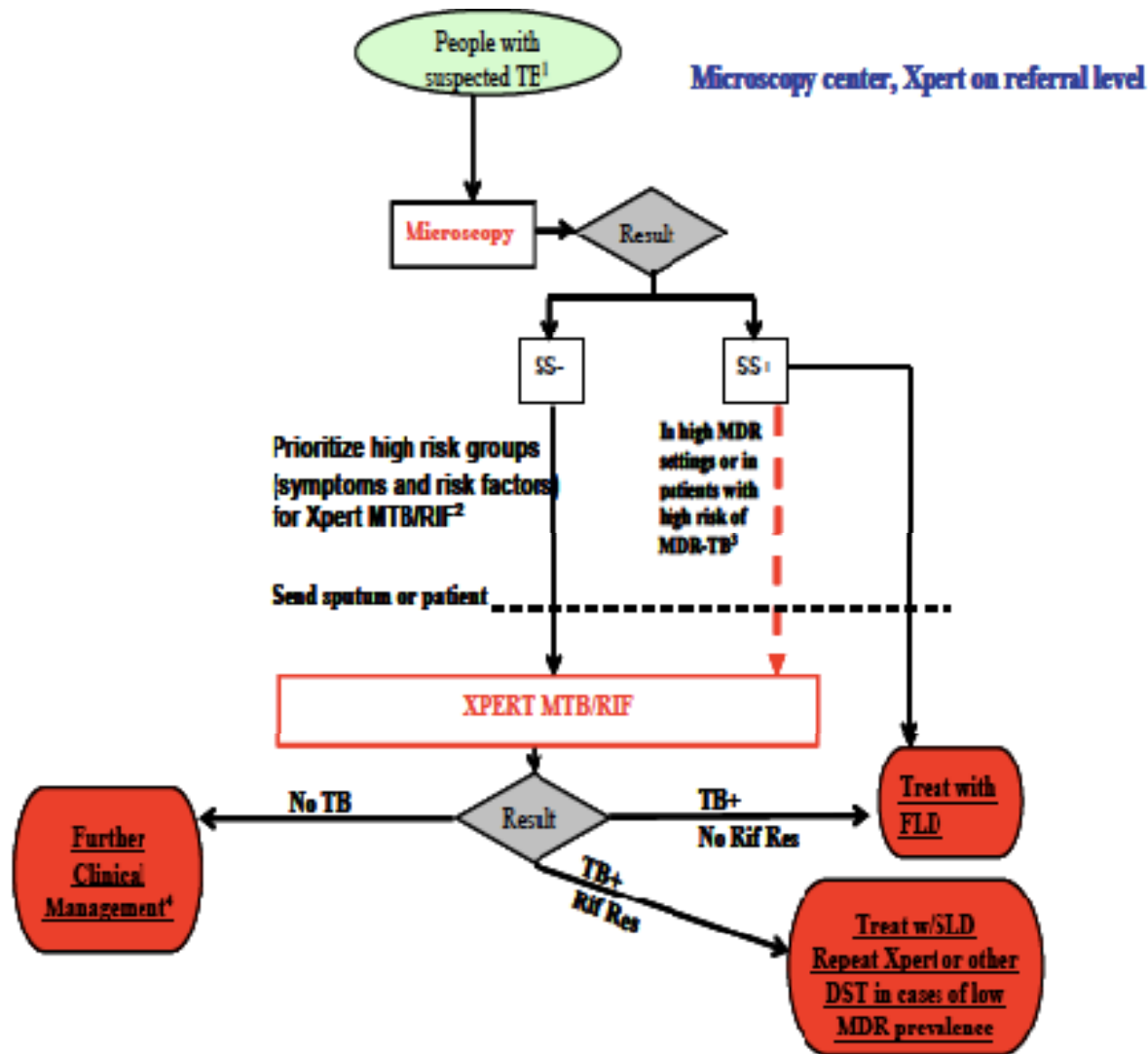
# Algorithm HIV pos, ambulatory



# Algorithm HIV neg



# Xpert off-site, at referral lab





CONTROVERSY 1

**WHEN IMPLEMENTING XPERT MTB/RIF,  
SMEAR MICROSCOPY CAN BE ABANDONED**

# Xpert allows us to abandon smear microscopy: no added value of smear microscopy when access to Xpert

- Superior sensitivity for pulmonary TB
- Equal or superior for extrapulmonary TB (pleural fluid, cerebrospinal fluid, fine needle aspirate of gland)
- Equal or superior specificity (no NTM)
- Diagnosis of RIF resistance in addition to MTB
- Equal indication of level of infectiousness
- Not operator dependent

# Smear microscopy infrastructure needs to remain

- Cheap
- 100 years of experience
  - Smear microscopy exists
  - is widely implemented
  - M&E systems are developed for a smear microscopy-centered diagnosis
- More than half of TB patients are smear microscopy positive
- Works where there is no electricity
- Can be used to monitor response to treatment
- Less sensitive to instrument failure and stock out of reagent (cartridges)

CONTROVERSY 2

**A NEGATIVE XPERT MTB/RIF RESULT DOES  
NOT REQUIRE FURTHER DIAGNOSTIC  
INVESTIGATIONS**

# Stop diagnostic process if Xpert neg

- Public health approach: because of limited resources, select most cost-effective approach (low prevalence of TB in suspects with one negative Xpert assay)
- Second assay will have little impact on patient management (health care workers will treat TB empirically even if Xpert assay is negative)

# Xpert is one test in diagnostic algorithm

- Limited sensitivity (72%) of first assay, increases to 90% with 3 assays
- Perceived inadequacy of single test diagnostic process by patients
- Perceived inadequacy of single test diagnostic process by health care workers
- Improve quality of surveillance by increasing bacterial confirmation

CONTROVERSY 3

**IMPLEMENTATION OF XPRT MTB/RIF WILL  
MAKE A SIGNIFICANT CONTRIBUTION TO  
THE DIAGNOSIS OF PEDIATRIC TB IN  
RESOURCE POOR SETTINGS**

# Xpert will make a difference for pediatric TB

- Collecting a sputum in kids is difficult; access to Xpert will motivate health care workers to collect sputum samples in them
- Could reduce cost compared to current complex, multi-visit diagnostic process
- Xpert allows rapid diagnosis of TB in children (lower sensitivity than culture but faster)
  - Could reduce empiric TB treatment
  - Could reduce mortality
- HIV positive children may benefit as much as HIV negative children (different from adults)

# Xpert will make no significant impact on pediatric TB

- Collection of a sputum (or gastric aspirate) is difficult, especially in young kids (population with highest incidence of TB)
- Sensitivity may be too low (about 30% of children with TB are culture positive)
- Little impact on clinical management (health care workers will start even if Xpert is negative)
- Unclear if Xpert will work well on gastric aspirates

# Organization of think tank

- **AIM:** to identify operational research questions and implementation science question to help resolve the controversies in different settings
- **APPROACH:**
  - 3 groups for discussion on each of the controversies.
  - Reporting
  - 3 new groups: second round of discussion to add new elements
  - Wrap up