Wisconsin State Laboratory of Hygiene

UNIVERSITY OF WISCONSIN–MADISON

Use of the Cepheid GeneXpert® to Release Patients from Airborne Isolation

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Wisconsin State Laboratory of Hygiene

A. We have a GeneXpert ® in our lab and use the MTB/RIF assay

B. We have a GeneXpert ® in our lab but do not use the MTB/RIF assay

C. We don't have a GeneXpert ®

D. MTB WHAT?????????

Removing Patients from AII

- Traditionally used 3 sputum smears collected early morning
  - Took a long time: average 5-7 days in isolation
  - Not sensitive 50-80%
  - Not specific 70-90% (depending on NTM and TB prevalence)
- Current guideline
  - 3 sputums collected 8-24 hr apart, with at least one being an early morning specimen

Problems with Isolation

- Average 5-7 days in isolation for TB
- Limited number of isolation rooms
- Patients seen less by HCWs
- 8 fold increase in adverse effects
- Have a negative perspective of their care
- Delays in getting procedures performed
- Most patients admitted into isolation do not have TB

FIND
foundation
for innovative new diagnostics

GeneXpert ® System

Cepheid, Sunnyvale, CA

RT-PCR, < 2 hours

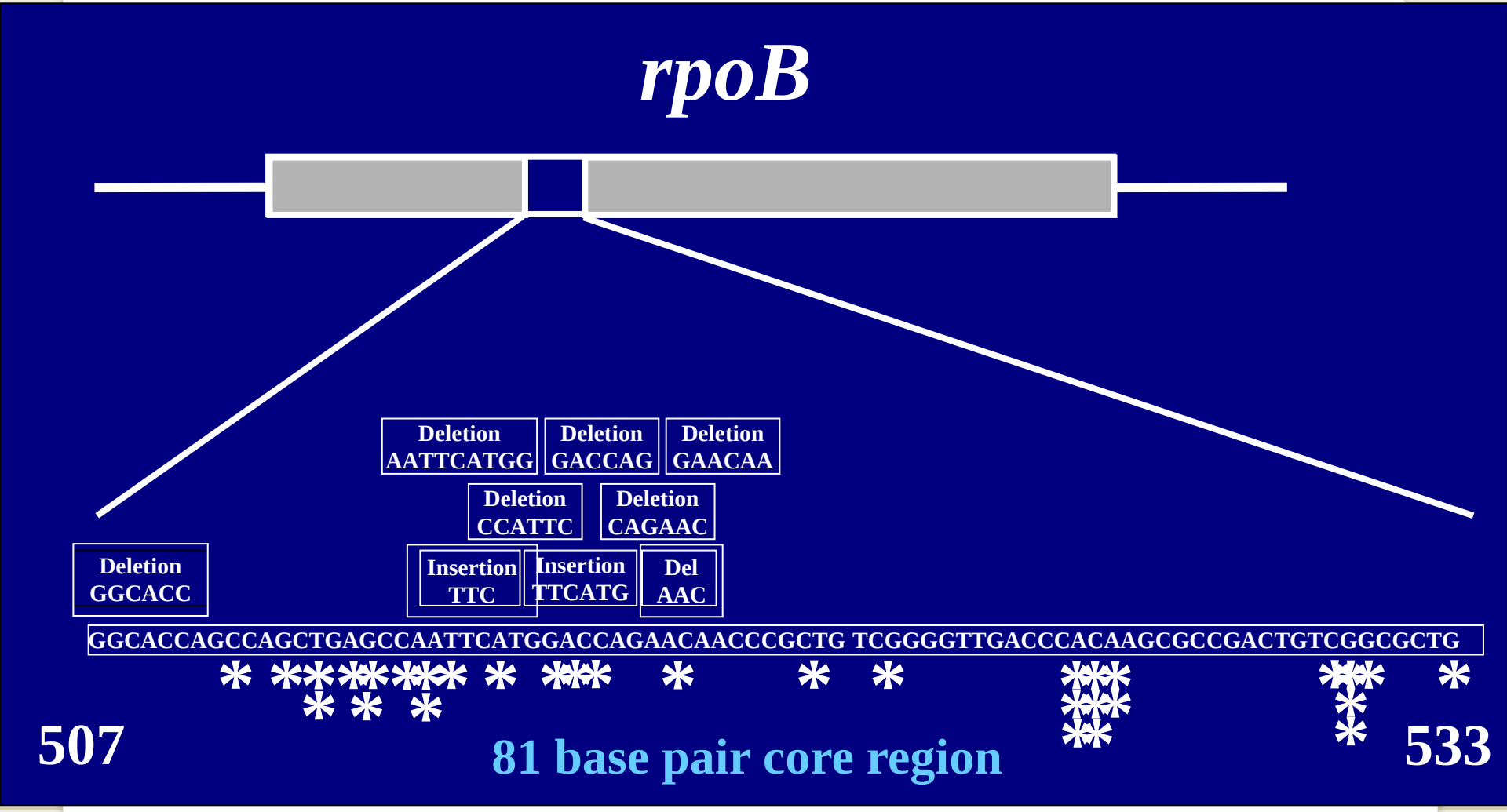
GeneXpert ® MTB/RIF Assay

- Automated system for identification of *M. tuberculosis* complex and detection of rifampin resistance
- Decontamination, digestion, DNA extraction, amplification, and detection in a single cartridge
- Integrated positive control assures that a negative result is not due to NAA inhibitors in the specimen
- Results in ~2 hours
- Minimal hands on manipulation- technically simple
- Platform is random access

GeneXpert

- Target: rpoB gene
- Nested PCR and molecular beacon technology
- Same segment of the rpoB gene is used for detection of both M. tb complex and rifampin resistance
- PCR amplifies a small region relevant to rifampin resistance
- Uses 5 probes to assess for mutations

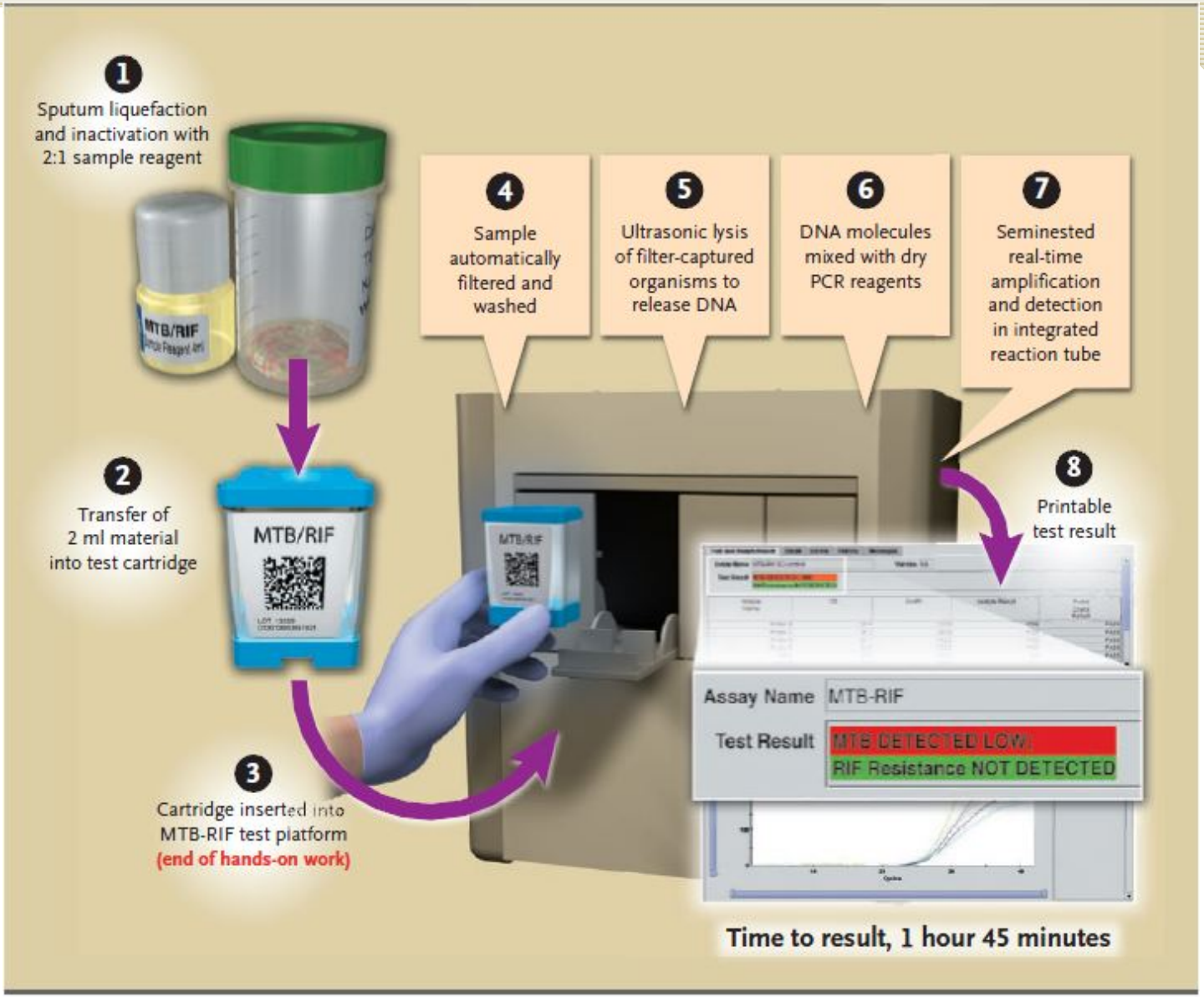
Genetics of Rifampin Resistance in *M. tuberculosis*



Adapted from Ramaswamy & Musser. 1998. Tubercule Lung Dis 79:3

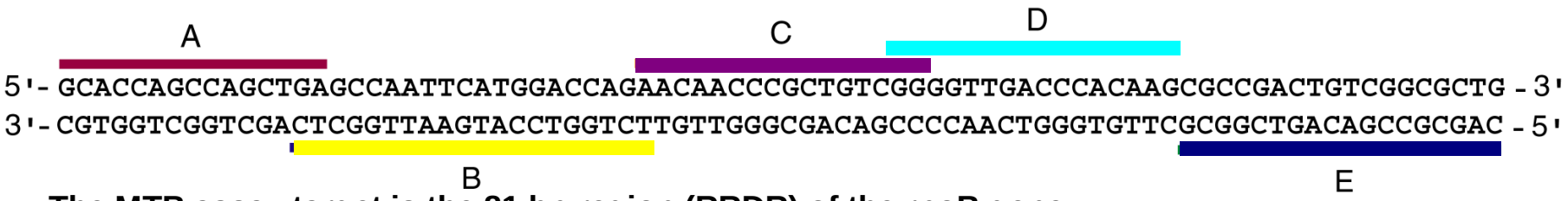
Specimen Requirements

- Quality specimen and adequate volume are critical
- Expectorated or induced sputum
- Specimen requirements may vary among laboratories
  - One specimen for both Xpert and smear/culture, 5-10 ml
    - Allows interpretation of Xpert in conjunction with AFB smear result
  - Two specimens
    - One for Xpert, 1-2 ml
    - Separate specimens for smear/culture

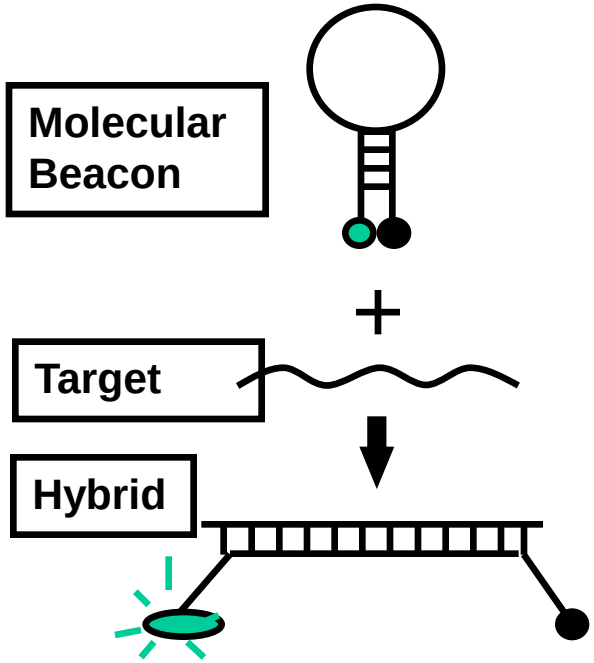


finddiagnostics.org

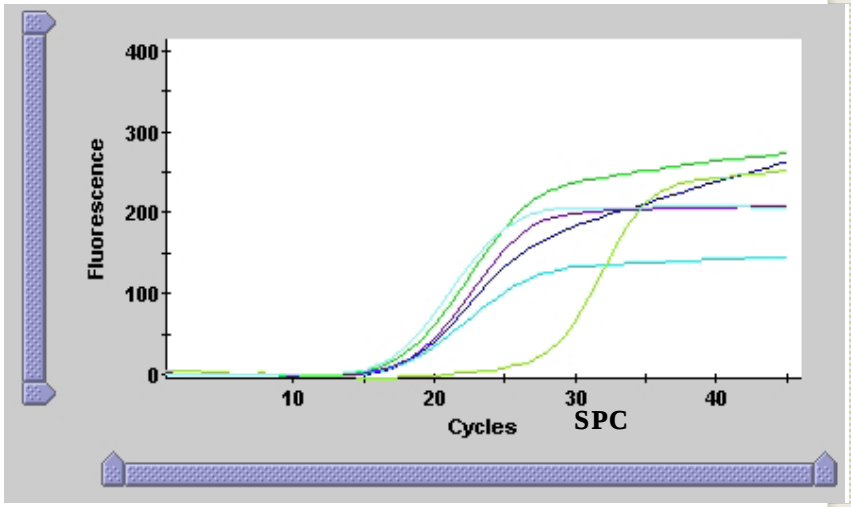
MTB/Rif Assay design



The MTB assay target is the 81 bp region (RRDR) of the rpoB gene.



Each probe is labeled with a different fluorophore, permitting simultaneous detection of the presence of wild type.



Example of Rif-Sensitive Profile – 5 probes are positive

Cepheid GeneXpert ® Assay Performance

- Limit of detection – **131 CFU/ml**
- *M. tuberculosis* viability – **minus 8 log**
- 107 clinical specimens/suspicion of TB – Vietnam
  - 100% - 29/29 AFB smear + / Culture +
  - 84.6% - 33/39 AFB smear - /solid Culture +
  - **71.7%** - 38/53 AFB smear - / solid & broth Culture

Helb et al. JCM 48:229-237 (2010)

Reporting

- MTB Detected
- MTB Not Detected
- Invalid
  - Presence or absence of MTB could not be determined due to failure of the control
- Rifampin resistance detected
- Rifampin resistance not detected
- Rifampin resistance indeterminate

Reporting

- May include interpretive comments
  - e.g A result of MTB not detected indicates infectious TB is not likely. Make the decision to discontinue airborne infection isolation in conjunction with clinical data.
- Who to report to?
  - Health care provider
  - Infection preventionist
  - TB Control Program
  - Local Public Health

Turn-around Time Expectations

- Will vary with how laboratory is structured and staffed
  - Xpert system available onsite and raw sputum tested----2-4 hr
  - Xpert system offsite and raw sputum tested
    - Factor in transport time plus 2-4 hr
  - Xpert performed in the Mycobacteriology lab using processed sediment ----5 – 24 hr

FDA News Release

New data shows test can help physicians remove patients with suspected TB from isolation earlier

Morbidity and Mortality Weekly Report

Revised Device Labeling for the Cepheid Xpert MTB/RIF Assay for Detecting *Mycobacterium tuberculosis*

Division of Microbiology Devices, Office of In Vitro Diagnostics and Radiological Health, Center for Devices and Radiological Health, Food and Drug Administration

Nucleic Acid Amplification Testing and A.I.I. Decisions

- In February, 2015, the FDA approved a change in the package insert for the ***GeneXpert*** ® to reflect expanded claims related to A.I.I.*

  Specifically:

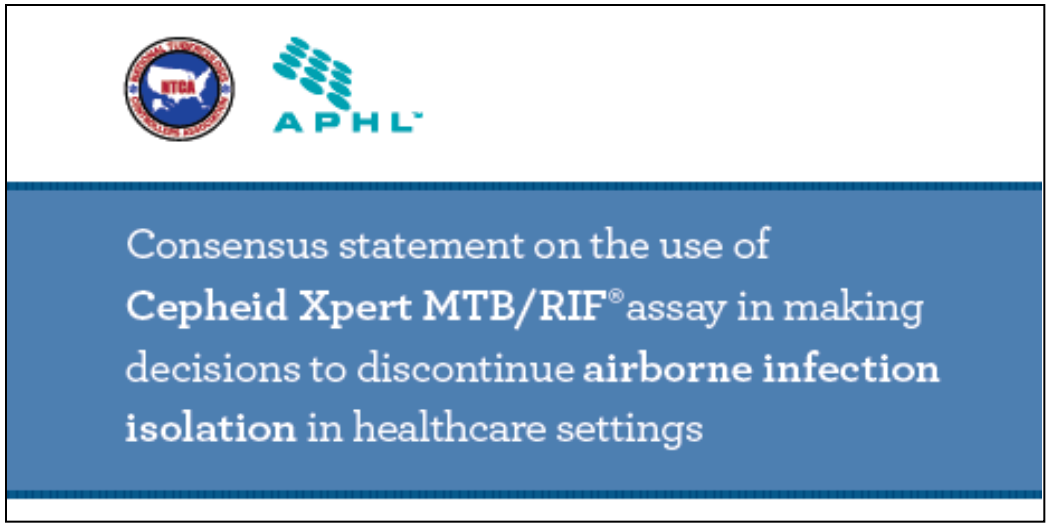
  … results using this assay on "either one or two sputum specimens" can be used as an alternative to examination of serial acid-fast stained sputum smears to aid in the decision to discontinue A.I.I. for patients with ***suspected*** *pulmonary TB.*

* CDC. MMWR, 2/26/2015

Sensitivity of TB PCR, initial specimens on culture-positive TB patients

	Smear Positive	Smear Negative	Total
Respiratory	172/178 (96.6%)	17/27 (62.9%)	189/205 (92.1%)
Non-respiratory	18/18 (100%)	1/6 (16.6%)	19/24 (79.1%)
Total	190/196 (96.9%)	18/33 (54.5%)	208/229 = 90.8%

9/2010 to 6/2015



Purpose:

To provide guidance on the use of the Xpert to discontinue airborne infection isolation (A.I.I.) for persons with suspected, infectious pulmonary tuberculosis (TB)

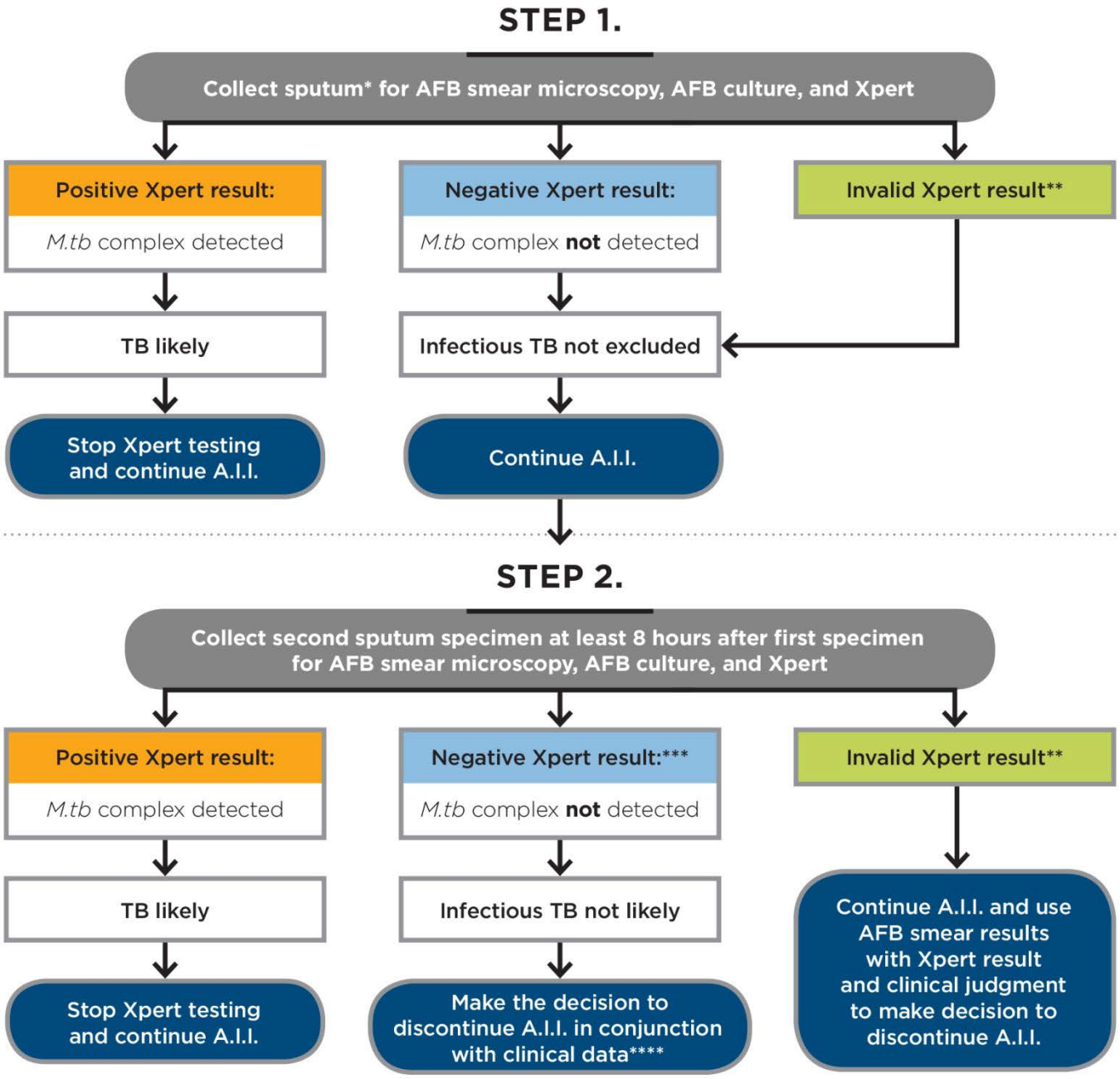
http://www.tbcontrollers.org/docs/resources/NTCA_APHL_GeneXpert_Consensus_Statement_Final.pdf

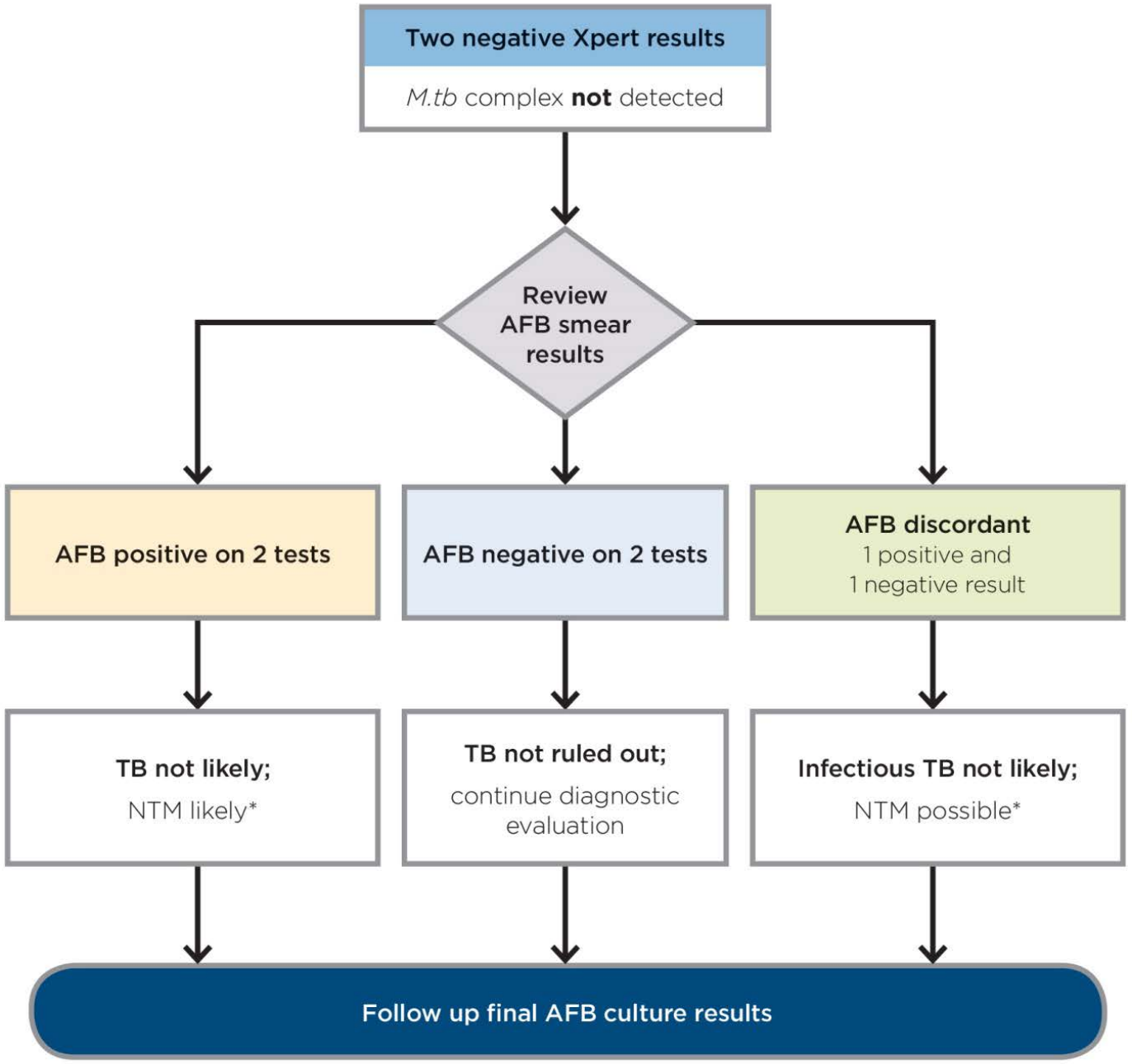
The Statement: What it *IS*

- Recommendations on how to interpret the GeneXpert ® MTB/RIF results
- A document
  - stressing the difference between diagnosis of TB and infectiousness of TB
  - providing easily followed instructions/protocols for sputum induction
  - containing a customizable flowchart for use in hospital policies and procedures manuals or as a decision-making tool
- A reminder of the importance of working with public health TB programs and the public health labs

The Statement: What it is *NOT*

- It is ***NOT*** a diagnostic algorithm
  - sputum smears and cultures are essential for identification of the organism, drug susceptibility testing, and genotyping
- NAA testing ***should not be used to monitor response to treatment or to release a newly confirmed TB patient from A.I.I.***
- It is ***NOT*** an endorsement of Xpert or of any specific product
  - reflects new FDA approval of NAA technology that applies to the Cepheid *Xpert MTB/RIF®* system *only* and for this specific indication
- It is ***NOT*** a rationale for delaying the start of empiric treatment when TB is suspected

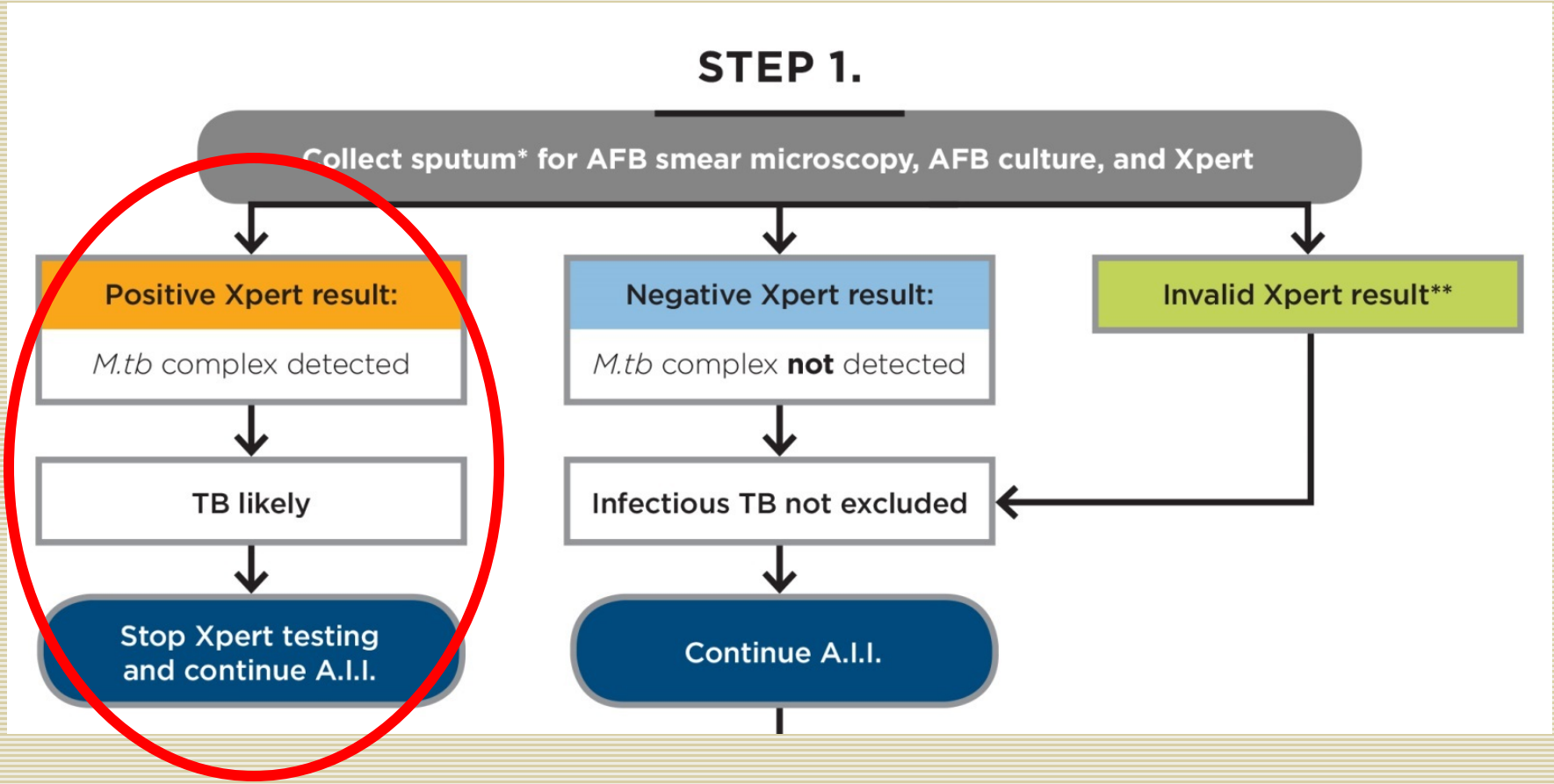

STEP 1.
Collect sputum* for AFB smear microscopy, AFB culture, and Xpert
Positive Xpert result:
M.tb complex detected
TB likely
Stop Xpert testing and continue A.I.I.
Negative Xpert result:
M.tb complex not detected
Infectious TB not excluded
Continue A.I.I.
Invalid Xpert result**
STEP 2.
Collect second sputum specimen at least 8 hours after first specimen for AFB smear microscopy, AFB culture, and Xpert
Positive Xpert result:
M.tb complex detected
TB likely
Stop Xpert testing and continue A.I.I.
Negative Xpert result:***
M.tb complex not detected
Infectious TB not likely
Make the decision to discontinue A.I.I. in conjunction with clinical data****
Invalid Xpert result**
Continue A.I.I. and use AFB smear results with Xpert result and clinical judgment to make decision to discontinue A.I.I.


Two negative Xpert results
M.tb complex **not** detected
Review AFB smear results
AFB positive on 2 tests
AFB negative on 2 tests
AFB discordant
1 positive and 1 negative result
TB not likely;
NTM likely*
TB not ruled out;
continue diagnostic evaluation
Infectious TB not likely;
NTM possible*
Follow up final AFB culture results

Case 1

- 90 yr old man from the Philippines
- History of TB many years ago
- Hemoptysis with no other TB symptoms
- GeneXpert ® Positive

- Would you continue A.I.I.?
  - A. YES
  - B. NO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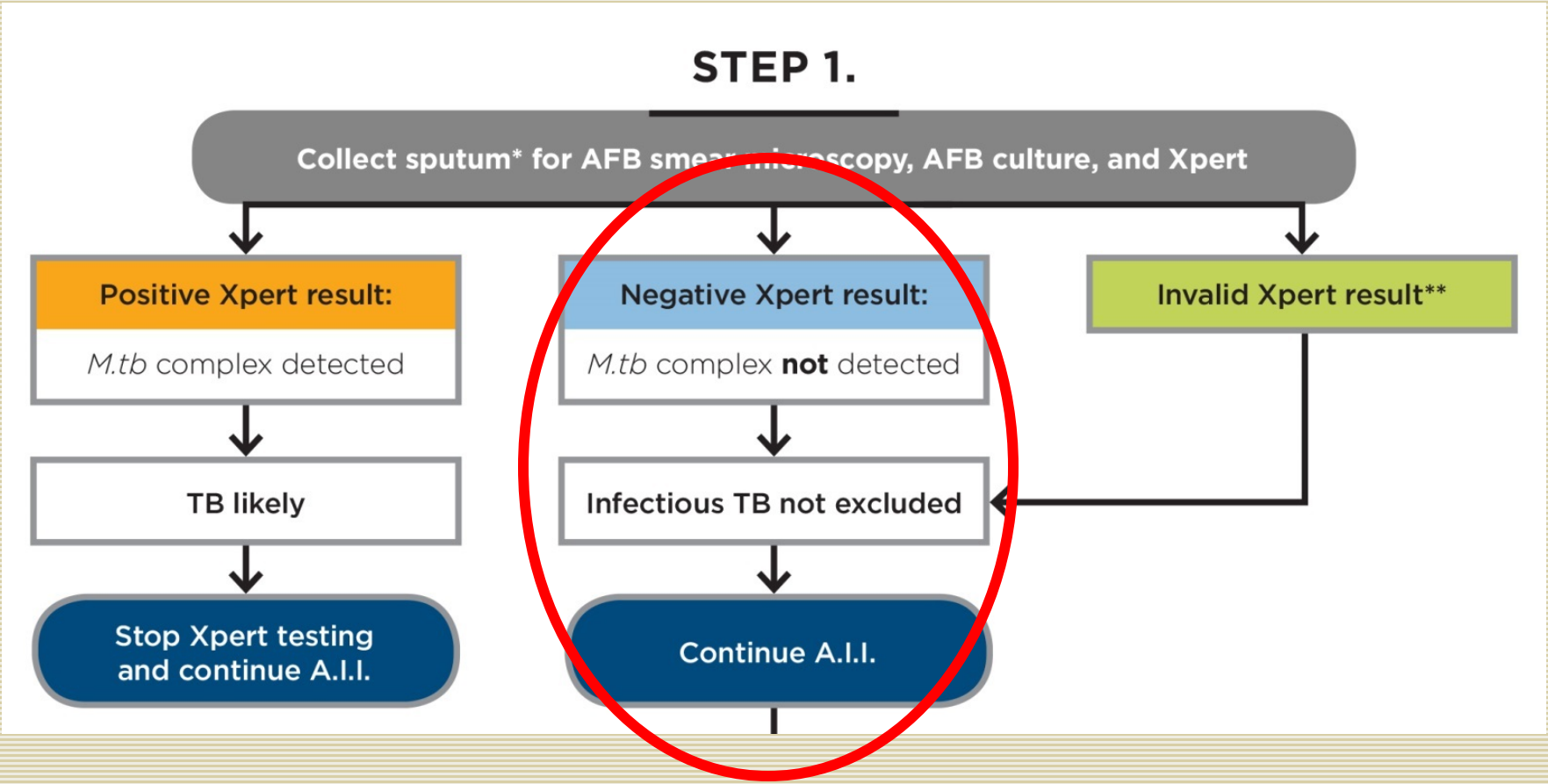
Continue A.I.I.
Invalid Xpert result**

Case 2

- 20 year old from Vietnam
- IGRA negative
- Calcifications in LUL consistent with granulomatous disease
- GeneXpert ® negative on one sputum
- Next step
  - A. Remove from isolation
  - B. Collect a 2nd sputum
  - C. Send him home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Continue A.I.I.
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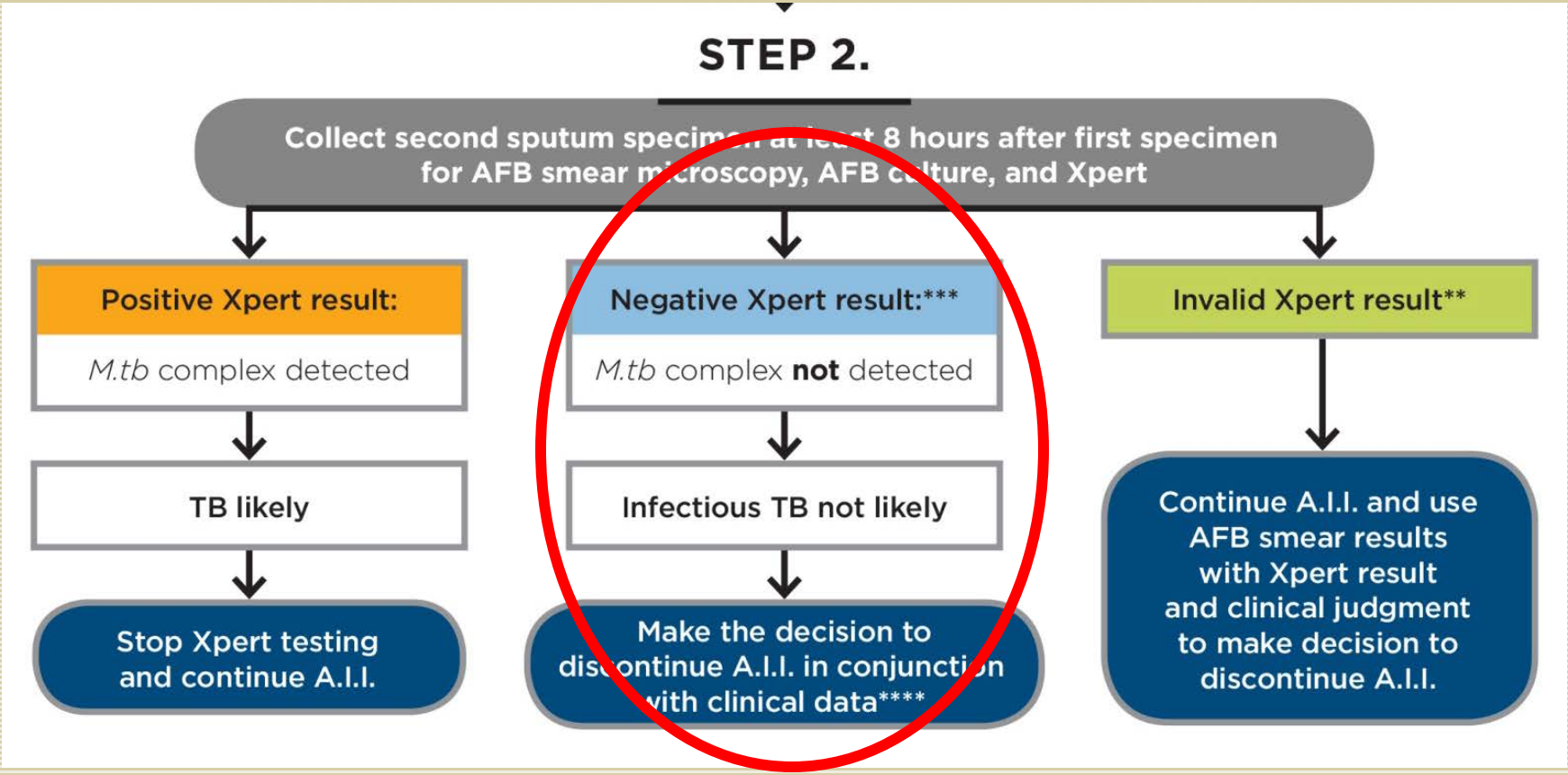
Case 2

- 2nd Xpert NEGATIVE

- Discontinue isolation
  - YES
  - NO


STEP 2.
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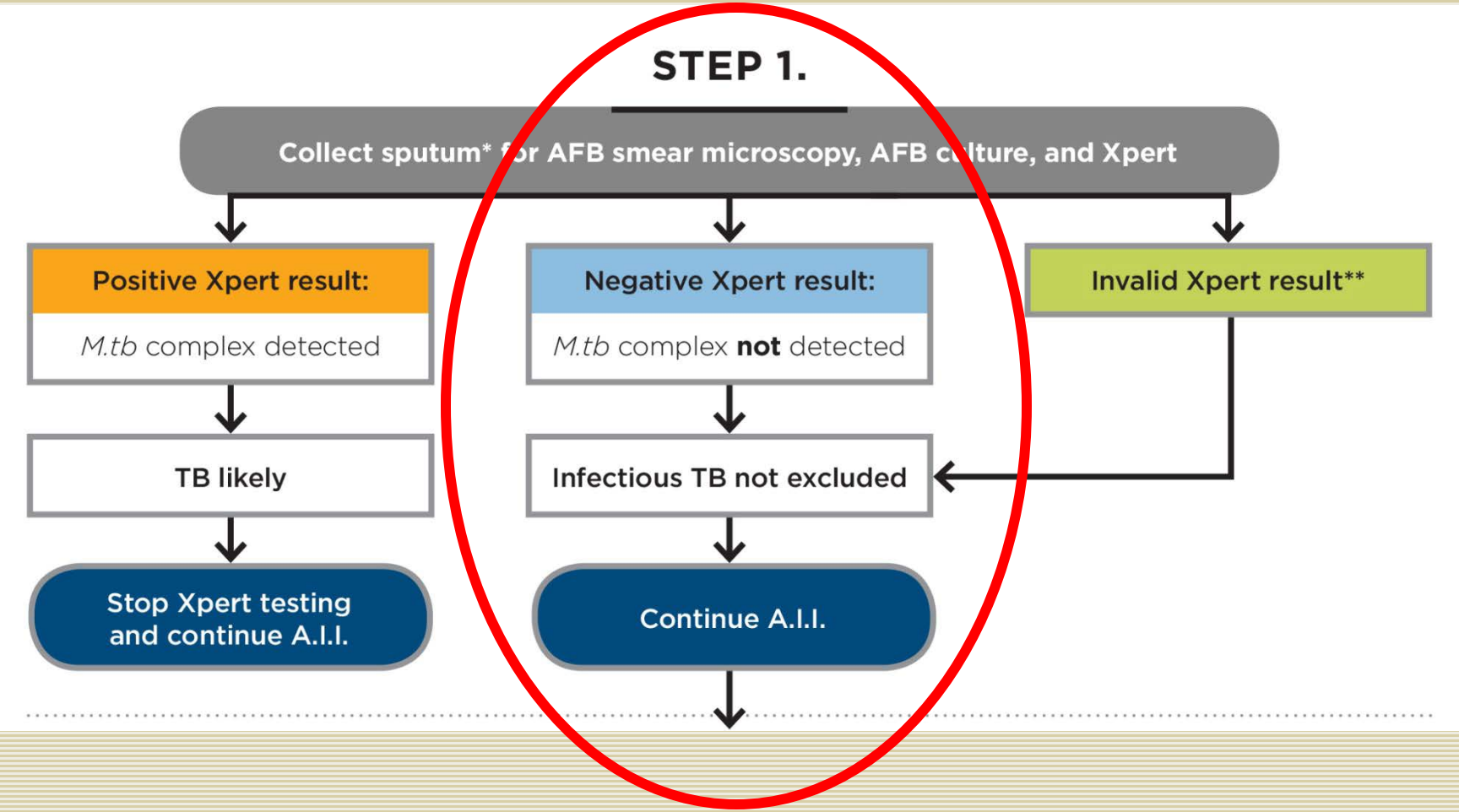
Invalid Xpert result**
Continue A.I.I. and use AFB smear results with Xpert result and clinical judgment to make decision to discontinue A.I.I.

Case 3

- 17 year old male from China
- IGRA positive
- CXR with LUL calcification consistent with granuloma disease
- Nonproductive cough
- Xpert negative
- Next step
  - A. Remove from isolation
  - B. Collect a 2nd sputum
  - C. Send him home

Case 3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TB likely
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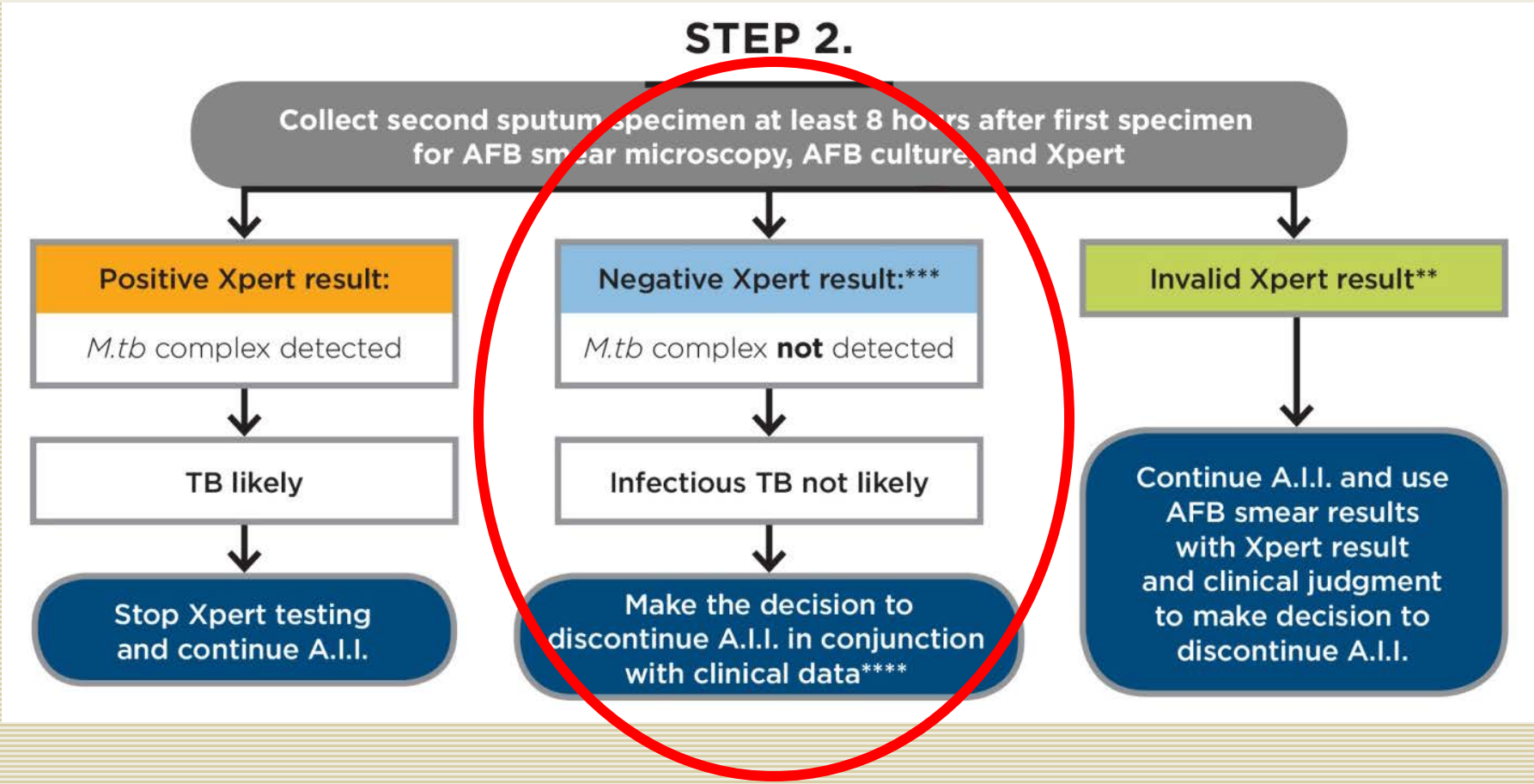
Negative Xpert result:
M.tb complex not detected
Infectious TB not excluded
Continue A.I.I.
Invalid Xpert result**

Case 3

- Second Xpert negative
- Discontinue Isolation?
  - Yes
  - No

Case 3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Invalid Xpert result**
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Case 3

- What if he had hemoptysis instead of dry cough?
- What if it was winter time and everyone in dorm had a cough?

Summary

- The Consensus Statement addresses use of GeneXpert ® for release from A.I.I.
- It is not meant as a diagnostic algorithm
- Must be used in conjunction with patient's clinical data and risk factors
- Suspect TB patients are reportable to public health

Acknowledgments

***The A.I.I. Working Group*:**

Emily A. Anderson
Heidi Behm
Maria Dalbey
Phil Griffin
Kenneth C. Jost
Quratulain Kizilbash
Diana Nilsen
Randall Reves
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