Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

November 18, 2021

DEPARTMENT MEMORANDUM
No. 2021 – 0501

TO : **BANGSOMORO AUTONOMOUS REGION IN MUSLIM MINDANAO MINISTER OF HEALTH; ALL DIRECTORS OF CENTERS FOR HEALTH DEVELOPMENT (CHD); AND OTHERS CONCERNED**

SUBJECT : **Use of the Xpert MTB/XDR Assay for the Rapid Detection of Drug-resistant Tuberculosis (DRTB)**

I. BACKGROUND

The landscape of TB diagnosis continually evolves with the development of new molecular platforms, making early detection of DRTB possible. Just recently, a new nucleic acid amplification test (NAAT), the **Xpert MTB/XDR** assay, was added into the roster of rapid diagnostic tools endorsed by the World Health Organization (WHO).[1]

The Xpert MTB/XDR test, developed by Cepheid (USA), is the first low complexity NAAT that detects presence of *Mycobacterium tuberculosis* (MTB), and resistance to Isoniazid (INH), Ethionamide (ETH), Fluoroquinolones (FQ), and second-line injectable (SLI) drugs. With its low complexity, it can be scaled up in peripheral laboratories, and can give a result in less than 90 minutes. Thu s, its use can improve access to rapid anti-TB drug susceptibility testing (DST).

Given these, and with support from the WHO, **use of the Xpert MTB/XDR assay will now be integrated into the TB diagnostic algorithm as an alternative to Line Probe Assay (LPA) for the rapid detection of DRTB.** All concerned are advised to observe the guidelines hereafter in implementing its use.

II. OPERATIONAL GUIDELINES

A. Site Selection

The Xpert MTB/XDR assay shall be implemented in identified TB laboratories based on the following criteria:

1. High expected demand for Xpert MTB/XDR testing (based on number of "*Rifampicin resistance detected*" results by Xpert MTB/RIF assay in the region)
2. Geographic accessibility, and availability of specimen referral mechanism (to maximize number of referring health facilities that can be catered to)

[1] World Health Organization. (7 July 2021). *WHO operational handbook on tuberculosis. Module 3: Diagnosis - Rapid diagnostics for tuberculosis detection 2021 update.*

3. With adequate engineering and biosafety requirements (similar with Xpert MTB/RIF assay at the minimum)
4. Availability of laboratory personnel who can be trained to perform the test

Initial sites identified to implement the Xpert MTB/XDR assay, and their respective catchment areas are outlined in *Annex 1*. All health facilities providing TB services within the catchment areas of any of the identified laboratories shall request for the Xpert MTB/XDR test instead of LPA based on *Section III* of this document. They shall implement the specimen referral in coordination with the zoned laboratory, and concerned regional coordinators. All other health facilities not catered to by any of the identified laboratories shall continue their practice of requesting for LPA according to the NTP *Manual of Procedures (6th Edition)*.

Note: If the identified laboratory will not be able to perform the Xpert MTB/XDR assay (e.g., supply challenges), then the affected health facilities shall revert to the use of LPA until the concerned laboratory is able to resume Xpert MTB/XDR testing.

B. Capacity building

The NTRL-RITM is responsible in developing and implementing the **training and competency assessment program** for laboratory personnel who will be performing the Xpert MTB/XDR assay.

C. Equipment installation

One 10-color GeneXpert instrument required for Xpert MTB/XDR testing shall be installed in each of the identified laboratories. It must be placed in a room where ambient temperature **not exceeding 30°C** is maintained. The NTP and NTRL-RITM will be coordinating the delivery and installation of the machines with the identified laboratories, and concerned CHDs.

D. Supply management (test cartridges and reagents)

Xpert MTB/XDR assay cartridges and reagents shall be allocated and delivered to all identified laboratories. Supply management for these supplies shall be subsumed into the current system for Xpert MTB/RIF (and Ultra) assay. For instance, Xpert MTB/XDR test cartridges and reagents, as with those for Xpert MTB/RIF (and Ultra), must be stored at **2-28°C.**

E. Quality assurance

Quality of Xpert MTB/XDR testing shall be assured through the following:

1. Routine calibration, and preventive maintenance of 10-color GeneXpert instrument
2. Timely monitoring of laboratory performance indicators (i.e., error/invalid/no results rate, cartridge utilization rate)
3. Regular participation to proficiency testing to be provided by NTRL-RITM
4. On-site visits by the city/provincial health offices, CHD, NTRL-RITM, NTP, and partners.

F. Recording and reporting

The Xpert MTB/XDR assay shall be incorporated into the current laboratory recording and reporting system of the NTP, using newly developed/updated forms *(Annex 2)*. This includes utilization of the Integrated TB Information System (ITIS). Xpert MTB/XDR test results shall be released within the desired turnaround time of **three days** from the date of specimen collection.

G. Monitoring and evaluation

The NTP and NTRL-RITM, together with the CHDs, shall regularly monitor and evaluate the implementation of the Xpert MTB/XDR assay vis-à-vis the *Philippine TB Strategic Elimination Plan (PhilSTEP)*.

III. TECHNICAL GUIDELINES

A. Reason for examination

In accordance with the WHO's recommendations, the Xpert MTB/XDR assay will be used as a **follow-on test for detecting additional drug resistance**, as follows:

1. The Xpert MTB/XDR assay will be used as a **baseline examination** for patients with **bacteriologically confirmed (BC) pulmonary RRTB and other DRTB**[2] before initiation of DRTB treatment (*Annex 3a)*.

   Notes:
   a. For **clinically diagnosed** (CD) pulmonary RRTB/other DRTB, use **LPA**.
   b. For BC or CD **extrapulmonary (EP)** RRTB/other DRTB, refer case to the **Regional TB Medical Advisory Committee (R-TB MAC)**.

2. For **patients with BC pulmonary TB (PTB) undergoing DRTB treatment**, the Xpert MTB/XDR test should be requested again in any the following scenarios (*Annex 3b)*:
   a. Culture still MTB-positive at the fourth month of treatment;
   b. Culture reversion during treatment; and/or
   c. MTB-positive culture during post-treatment follow-up.

   Note: The MTB-positive culture isolate shall still be referred for LPA.

3. The Xpert MTB/XDR assay should also be requested for **patients with BC-PTB who are non-converters of drug-susceptible TB (DSTB) regimen and remain Rifampicin (RIF) susceptible by Xpert MTB/RIF (or Ultra) test** (*Annex 3c)*.

   Note: If Xpert MTB/RIF (or Ultra) test shows **RIF resistance**, then Xpert MTB/XDR assay shall also be requested following the reason stated in item no. 1.

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[2] National Tuberculosis Control Program. (2020). *Manual of Procedures* (6th ed.). Manila: Department of Health. (page 28)

B. Specimen handling

Acceptable specimen types for Xpert MTB/XDR assay are listed in *table 1* below.

Table 1: Acceptable specimen types and conditions for Xpert MTB/XDR assay.

Specimen type	Minimum volume	Temperature	Viability period
Sputum	1 mL	2-8°C	7 days from collection
Leftover SR-treated sputum*	2 mL	2-8°C	4 hours from addition of SR
		Up to 35°C	2.5 hours from addition of SR

**Leftover sputum treated with the sample reagent (SR) from Xpert MTB/RIF (or Ultra) test*

If the patient is a **presumptive DRTB,** and the laboratory is capable of doing both Xpert MTB/RIF (or Ultra), and Xpert MTB/XDR tests, then **reflex Xpert MTB/XDR testing** may be done immediately after Xpert MTB/RIF (or Ultra) testing if it shows a *"RIF resistance DETECTED"* result (*Annex 3a*).

1. If there is sufficient volume of leftover SR-treated sputum after loading the Xpert MTB/RIF (or Ultra) cartridge, the leftover SR-treated sample should be stored properly while waiting for the test result. If it shows RIF resistance, then the stored leftover SR-treated sputum may be used for reflex Xpert MTB/XDR test.

   In such scenario, the referring health facility will receive both the Xpert MTB/RIF (or Ultra), and Xpert MTB/XDR test results together. The Xpert MTB/XDR test shall be considered as baseline examination already (no need to recollect specimen for Xpert MTB/XDR or LPA), and its result shall be used in deciding for the most appropriate DRTB regimen for the patient. Still, two specimens should be collected for culture and phenotypic DST (pDST) prior to treatment initiation.

2. If there is no available leftover SR-treated sputum after an Xpert MTB/RIF (or Ultra) test showing RIF resistance, the referring health facility will only receive that test result (no Xpert MTB/XDR test result). This will prompt the health facility to collect one specimen for Xpert MTB/XDR testing (no need for LPA), and two specimens for culture and pDST.

C. Results reporting and interpretation

The Xpert MTB/XDR test detects the presence of MTB, as well as resistance to anti-TB drugs. Results shall be reported, and interpreted as follows:

1. For **MTB**, results can be *"detected"*, *"not detected"*, *"error"*, *"invalid"*, or *"no result"*. These are interpreted as with Xpert MTB/RIF (and Ultra) assay.
2. For **each drug** (except ETH), resistance may be reported as *"detected"*, *"not detected"* or *"indeterminate"*. Results are interpreted similarly with LPA.
   a. For **INH** and **FQ,** the Xpert MTB/XDR also gives out *"low INH/FQ resistance detected"* results.
   b. For **ETH**, there will be no *"indeterminate"* results.

D. Repeat testing

1. The Xpert MTB/XDR test shall be repeated in any of the three scenarios below:
    a. For *"error"*, *"invalid"*, or *"no result"*, the leftover SR-treated specimen may be retested using a new cartridge, provided that conditions in *table 1* under *section B* are satisfied. Otherwise, a new specimen may be collected for repeat Xpert MTB/XDR assay.
    b. For *"MTB not detected"*, or *"indeterminate"* resistance result to any drug, recollect sputum for retesting.
2. For patients with DRTB requested to undergo **baseline examination** by Xpert MTB/XDR assay, specimen for retesting must be collected **before treatment initiation, or within two weeks from the start of treatment.** Otherwise, the health facility shall continue the original treatment regimen while waiting for the pDST result, and review the regimen accordingly once the pDST result becomes available.
3. In most cases, the **second result shall be considered final.** However, a third Xpert MTB/XDR test using a new specimen may be warranted in certain scenarios. *Table 2* below summarizes the decision based on retest result.

Table 2: Decision based on repeat Xpert MTB/XDR test result.

Initial result	Retest result	Decision
"Error", "invalid", or "no result"	Valid *"MTB DETECTED"* result with NO *"indeterminate"* resistance to any drug	Consider retest result as final.
	"Error", *"invalid"*, or *"no result"*	
	"MTB not detected"	Recollect sputum for third test
	"Indeterminate" to any drug	
"MTB not detected"	Valid *"MTB DETECTED"* result with NO *"indeterminate"* resistance to any drug	Consider retest result as final
	"MTB not detected"	
	"Indeterminate" to any drug	Recollect sputum for third test
	"Error", *"invalid"*, or *"no result"*	
***"Indeterminate"* to any drug**	Valid *"MTB DETECTED"* result, regardless of drug resistance result	Consider retest result as final
	"MTB not detected"	Recollect sputum for third test
	"Error", *"invalid"*, or *"no result"*	

E. Handling of inconclusive results

1. In case the **repeat Xpert MTB/XDR test result is still inconclusive** (i.e., *"error"*, *"invalid"*, *"no result"*, *"indeterminate"*), **or *"MTB not detected"***, the initial treatment regimen assigned shall be continued while waiting for pDST result.
2. In case of **discrepant resistance results between the initial and repeat Xpert MTB/XDR tests, or between Xpert MTB/XDR and pDST results,** treatment regimen shall be revised based on reported drug resistance results, and in consultation with the R-TB MAC.

All concerned CHD TB coordinators are hereby directed to disseminate these guidelines to the identified laboratories, zoned health facilities providing TB services, and others concerned for implementation which will be monitored by the NTP and NTRL-RITM.

For compliance.

By authority of the Secretary of Health:

MARIA ROSARIO S. VERGEIRE, MD, MPH, CESO II
OIC Undersecretary of Health
Public Health Services Team

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ANNEX 1

SPECIMEN REFERRAL AND HEALTH FACILITY ZONING SCHEME FOR THE XPERT MTB/XDR ASSAY

Name of laboratory	Catchment regions
National Tuberculosis Reference Laboratory – Research Institute for Tropical Medicine	NCR – National Capital Region III – Central Luzon IV – CALABARZON
Ilocos Training and Regional Medical Center	CAR – Cordillera Administrative Region I – Ilocos Region II – Cagayan Valley
Western Visayas Medical Center	VI – Western Visayas VII – Central Visayas VIII – Eastern Visayas
Zamboanga City Medical Center	IX – Zamboanga Peninsula X – Northern Mindanao XI – Davao Region XII – SOCCSKSARGEN XIII – Caraga BARMM – Bangsamoro Autonomous Region in Muslim Mindanao
Davao Tuberculosis Reference Laboratory	

Notes:

- Other regions not mentioned shall refer specimens for LPA instead of Xpert MTB/XDR assay to the original LPA laboratory where they are zoned to.
- For Zamboanga City Medical Center, and Davao Tuberculosis Reference Laboratory, they will be catering to Mindanao regions, but regional assignments will not be restrictive. Referring health facilities are advised to send specimens for Xpert MTB/XDR to the more accessible laboratory between the two in coordination with the concerned laboratory, and regional coordinators.

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ANNEX 2

Form 2a. Laboratory Request and Result Form

To be filled out by Health Worker

Name of Requesting Facility/Unit: _____ Date of Request: _____

Facility Contact Information: _____ Requesting Physician: _____

Patient's Full Name: _____ Age: _____ Sex: [ ] M [ ] F

Province/City: _____ Patient's Contact No.: _____

Reason for Examination: [ ] Diagnosis [ ] Baseline [ ] Follow-up TB Case No.: _____

History of Treatment: [ ] New [ ] Retreatment Month of treatment: _____

Test Requested:

[ ] Xpert MTB/RIF	[ ] Truenat MTB Plus [ ] Truenat MTB-RIF	[ ] TB LAMP	[ ] Smear Microscopy[a]
[ ] Xpert MTB/XDR	[ ] Line Probe Assay	[ ] TB Culture	[ ] Phenotypic DST

[a] *Is Paragonimiasis considered?* [ ] Yes [ ] No

Type of Specimen: [ ] Sputum [ ] Other (specify): _____ Repeat Collection? [ ] No [ ] Yes Reason: _____

Date:

Specimen	Date Collected	Date Dispatched to Laboratory
1		
2		

Remarks: _____
(i.e. pre-collection details; existing medical conditions, medications taken prior to screening, and/or known risk factors)

Prepared by: _____ Designation: _____
Signature over printed name

To be filled-out by Medical Technologist/Microscopist/Xpert Technician

Name of Laboratory: _____

Specimen Received by: _____ Date and Time Specimen Received: _____

Specimen Volume and Quality: _____ [ ] Accepted [ ] Rejected, reasons: _____

Laboratory Serial Number: _____ Date Specimen Examined: _____

DIAGNOSTIC TESTS			RESULTS	
[ ] Xpert MTB/RIF [ ] Xpert MTB/RIF ULTRA				
Smear Microscopy	Paragonimiasis *		1	2
	TB	Reading	1	2 **
		Lab Diagnosis		
TB LAMP				
[ ] Truenat MTB Plus [ ] Truenat MTB-RIF Dx				

* *Results for Paragonimiasis: P – if Paragonimus ova only are seen, T – if AFB only are seen, Co-I – if BOTH ova and bacilli are seen, Neg – No ova and No bacilli are seen*

** *Specimen 2 is not applicable for follow-up*

Performed by: _____
Signature over Printed Name

Verified by: _____
Signature over Printed Name

Noted by: _____
Signature over printed Name

Date and Time Released: _____

A separate result form for Xpert MTB/XDR, LPA, Culture, and DST will be issued

Form 2f. Xpert MTB/XDR Result Form

TB Case Number: _____ Date of Request: _____
Name of Requesting Facility/Unit: _____ Requesting Physician: _____
Patient' Full Name: _____ Name of Laboratory: _____
Age: _____ Sex: [ ] M [ ] F

Reason for Examination: [ ] Diagnosis [ ] Baseline [ ] Follow-up; month: _____
Type of Specimen: [ ] Sputum [ ] Others (specify): _____
Date Specimen Collected: _____ Date and Time Specimen Received: _____
Laboratory Serial Number: _____ Specimen Volume and Quality: _____

***M. tuberculosis* Complex Result:**

First Line Drug		Second Line Drug	
Name of Drugs	Result	Class of Drugs	Result
Isoniazid (H)		**Fluoroquinolones (FQ)**	
Ethionamide (Eto)		**Amikacin (Amk)**	

Remarks: _____ Date and Time Released: _____

Performed by:	Verified by:	Noted by:
_____	_____	_____
Signature over Printed Name	*Signature over Printed Name*	*Signature over Printed Name*

Form 3c. Laboratory Register for Line Probe Assay and Xpert MTB/XDR

Laboratory Serial Number	Date Specimen Collected	Date and Time Specimen Received	Collection Unit Code	Patient's Full Name (SURNAME, Given Names, Name Extension, Middle Name)	Age	Sex (M/F)	History of Treatment (N/R)	Reason for Examination			Type of Specimen	Type of Test		LPA and Xpert MTB/XDR Result						Signature of Laboratory Staff	Remarks
								Diagnosis	Baseline	Follow-up		LPA	Xpert MTB/XDR	MTB	First Line Drug			Second Line Drug		Date and Time Released	
															RIF	H	Eto/Pto	FQ	SLI		

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Report 1e. Quarterly Report on Xpert MTB/XDR

(Source of Data – Form 3c. Laboratory Register for Line Probe Assay and Xpert MTB/XDR)

Laboratory Name:			Quarter / Year	
Region:			Date Submitted:	
Prepared by:	*Name:*	*Signature:*	Designation:	
Approved by:	*Name:*	*Signature:*	Designation:	

Case Finding:

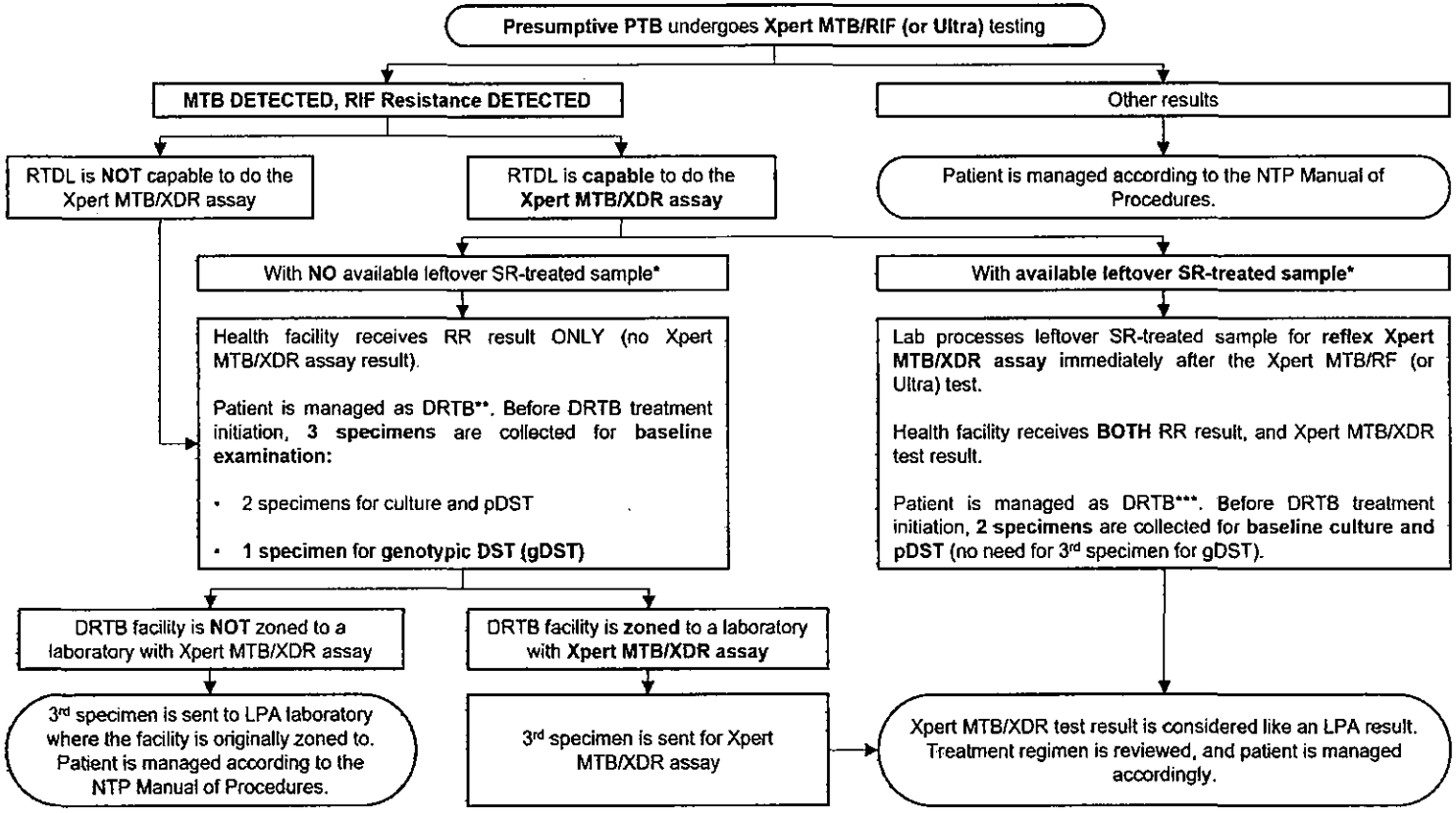
Cases Examined	History of Treatment		TOTAL	
	New	Retreatment	No.	%
1. No. of cases examined for **Xpert MTB/XDR.**				
2. No. of **M. *tuberculosis* cases detected**				
2.1 Total number of TB cases with resistance detected to **Isoniazid (H)** only				
2.2 Total number of TB cases with resistance detected to **Ethionamide (Eto)** only				
2.3 Total number of TB cases with resistance detected to **Fluoroquinolone (FLQ)** only				
2.4 Total number of TB cases with resistance detected to **any 2nd Line Injectable** (Amk, Km, and/or Cm) only				
2.5 Total number of TB cases with resistance detected to **both H and Eto** only				
2.6 Total number of TB cases with resistance detected to **both H and any 2nd Line Drugs** (FLQ and SLI) only				
2.7 Total number of TB cases with resistance detected to **both Eto and any 2nd Line Drugs** (FLQ and SLI) only				
2.8 Total number of TB cases with resistance detected to **both FLQ and SLI** only				
2.9 Total number of TB cases with resistance detected to **all 1st Line and 2nd Line Drugs** (H, Eto, FLQ, and any SLI)				
2.10 Total number of TB cases susceptible to **all 1st Line and 2nd Line Drugs**				
2.11 Total number of TB cases with **resistance indeterminate to all drugs, except Eto**				
3. No. of **M. *tuberculosis* cases not detected**				
4. Total number of TB cases with **Invalid/Error/No result.**				
5. No. of test with **Initial** results				
6. Total cartridges used				

Remarks: _____

_____

DIAGNOSTIC ALGORITHMS INCORPORATING THE XPERT MTB/XDR ASSAY

Algorithm 3a. Use of the Xpert MTB/XDR assay in the baseline examination of BC pulmonary RRTB



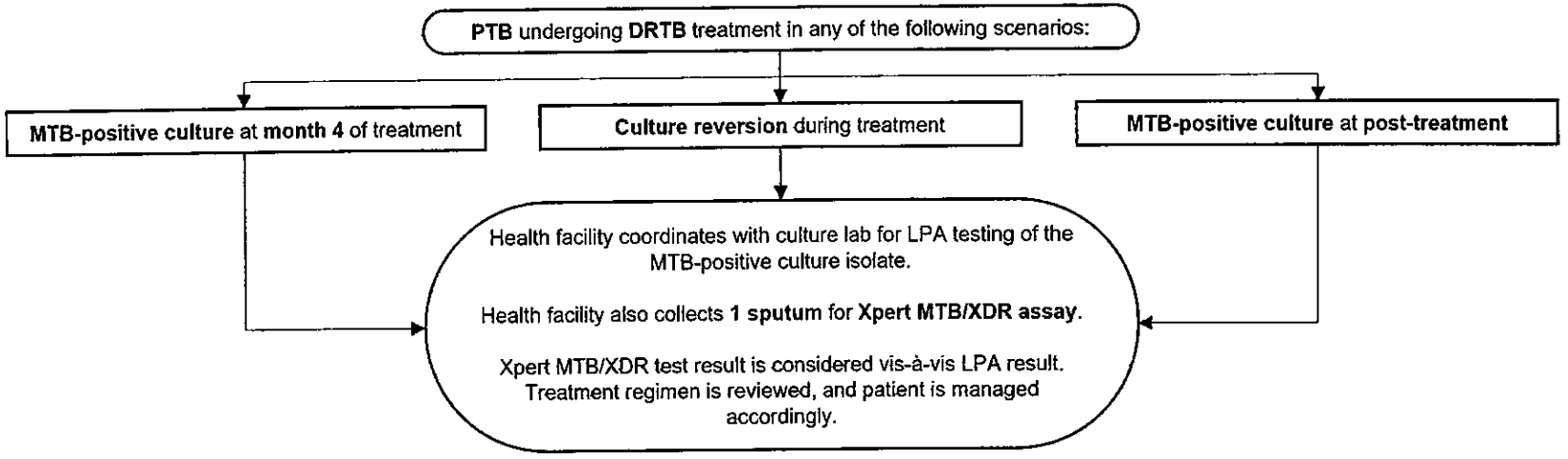
Notes:

* 2 mL of leftover SR-treated sample is required for reflex Xpert MTB/XDR assay. It must have been stored at 2-8°C for up to 4 hrs., or up to 35°C for up to 2.5 hrs. after addition of SR during Xpert MTB/RIF (or Ultra) processing.

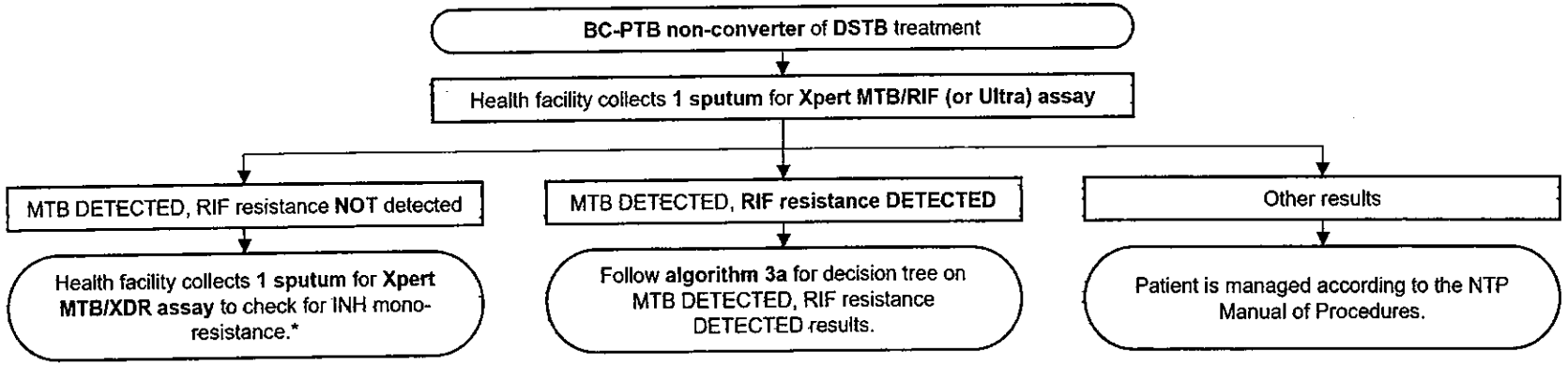
** If the patient will not be initiated on DRTB treatment in the original health facility, then the patient must be referred to the DRTB treatment facility.

*** If the patient will be referred to another facility for DRTB treatment, then the Xpert MTB/XDR test result must be properly endorsed by the original health facility to the DRTB treatment facility as this will already serve as the baseline gDST result, hence no need to collect specimen for LPA or another Xpert MTB/XDR test.

Algorithm 3b. Use of Xpert MTB/XDR assay in PTB undergoing DRTB regimen



Algorithm 3c. Use of Xpert MTB/XDR assay in BC-PTB non-converter of DSTB treatment



Note:
* Guidance for INH mono-resistant regimens will be issued accordingly.