

Revised National Guideline on using WHO recognized rapid molecular diagnostic test (GeneXpert), for diagnosis of Tuberculosis in Sri Lanka

Introduction

GeneXpert (Xpert MTB/RIF) assay is a cartridge based rapid molecular diagnostic test which is used for rapid and simultaneous detection of *Mycobacterium tuberculosis* and presence of rifampicin resistant strains directly on patient samples. It is recommended by the World Health Organization for bacteriological confirmation of Tuberculosis and for detection of rifampicin resistant TB. The test has been validated mainly on respiratory specimens with 99% specificity and 88% sensitivity for detection of pulmonary TB.

The National Programme for Tuberculosis Control and Chest Diseases (NPTCCD) of the Ministry of Health, Sri Lanka currently recommends the use of Xpert MTB/RIF test to improve the TB case detection as well as for the rapid detection of drug resistant forms of TB in Sri Lanka.

The test has been validated and used at the National TB Reference Laboratory (NTRL), Welisara since 2013. The facilities for testing has been expanded from 2017 with improving capacity at NTRL and establishing testing facilities at other laboratories (29 sites) at provincial level (**Annex 1**).

1. Indications for Xpert MTB/RIF test

NPTCCD recommends the use of Xpert (MTB/RIF) test for 2 sets of indications.

A. Xpert MTB/RIF as the initial diagnostic test

GeneXpert test (Xpert MTB/RIF) should be performed as the initial diagnostic test in the following groups of patients (culture +/- microscopy for AFB can be done as additional tests)

- A1.** Presumptive TB meningitis
- A2.** Critically ill patients in whom TB is suspected (PTB/EPTB)
- A3.** Presumptive TB in paediatric patients (age 14 years or less)
- A4.** TB testing on people living with HIV
- A5.** Presumptive PTB during pregnancy and peri-partum period
- A6.** Presumptive PTB in patients with evidence of immune suppression
- A7.** Presumptive EPTB patients in whom tissue or fluid aspiration from affected site is possible
- A8.** All presumptive MDR TB patients (refer annex 2 for presumptive MDR groups)

B. Xpert (MTB/RIF) as a follow –on test

Microscopy for Acid Fast Bacilli (AFB) will continue to be the initial diagnostic test in patients with presumptive pulmonary TB (PTB) **except** in patients belonging to groups **A2-A6** above.

Xpert (MTB/RIF) test will be used as a follow on test in the following groups of patients

- B1.** Patients with negative sputum AFB smears but having clinical features suggestive of PTB or chest radiography or Mantoux testing (smear negative PTB)

C. Universal Drug Susceptibility (DST) testing

Universal DST is defined as providing DST for at least Rifampicin for all patients with bacteriologically confirmed TB.

C1- Patients with Smear positive PTB (currently this service is available in all pilot districts- Kegalle, Gampaha, Kalutara, Kandy, Rathnapura, Kurunagala, Badulla, Monaragala) and will be expanded to other districts in a phased-out manner by 2021.

C2- Patients with Smear positive PTB in districts obtaining services from ITL (Intermediate TB Laboratories)

2. Use of AFB Microscopy & Mycobacterial Culture services

AFB microscopy are available in most centers (District Chest Clinic Laboratory /Microscopy Center /Hospital Microbiology Laboratory performing AFB microscopy) with a shorter turnaround time but should not be used to exclude TB due to low sensitivity.

3. Types of specimens to be sent for Xpert (MTB/RIF) testing

1. Sputum/other respiratory specimens (bronchial wash, broncho-alveolar lavage, endotracheal aspirates, induced sputum etc.)
2. All specimens from presumptive paediatric TB cases (e.g. early morning gastric aspirates should be collected from young children who cannot cough out sputum)
3. Extra-pulmonary (EPTB) specimens e.g. **CSF**, other fluid/pus aspirates, biopsy and tissue.

Unsuitable specimens for Xpert (MTB/RIF) testing- blood stained specimens, urine, faeces.

Pleural fluid is a suboptimal sample for bacteriological confirmation of pleural TB. These samples could be sent for mycobacterial cultures.

4. Specimen collection (Refer to National Manual for Tuberculosis Control for details)

- Sterile, screw capped transparent (preferably disposable) containers should be used.
- Containers should be labelled on the side (not on lid) with patient identification (name, age, gender and registration number) and sending site (ward/clinic) identification
- Advise patients to provide two well expectorated sputum specimens one for culture and one gene Xpert (2-3ml), preferably an early morning sample. Appropriate infection control precautions should be followed.
- Appropriate specimens (1ml or more) from presumptive EPTB cases should be collected using aseptic techniques.
- Special request form² (TB 06 - available at District Chest Clinics) should be completed, signed by the requesting physician and sent to the laboratory with the specimen.

Transport & storage of specimens

Specimens should be transported to the relevant laboratory (see below) under cold conditions (2-8°C) as soon as possible (may be stored at 2-8°C up to 5 days).

Leaking or unlabeled specimens should not be accepted.

Safe (preferably 3 layer) packaging suitable for transport of biological specimens should be used.

5. Xpert(MTB/RIF) test performance & validation

Testing and technical validation of results should be performed by trained Medical Laboratory Technologists and clinical validation and authorization of results should be done by Consultant Microbiologists of NTRL /Hospitals/ offering off-site consultancy to ITLs.

Reporting of results

- Results should be available within 24hours.
- All rifampicin resistance Xpert MTB/RIF should be informed to NTRL within 24hours over the phone and repeat sample should be sent for confirmation of the results

6. Recording and reporting

- All GeneXpert performing laboratories- Register of usage of GeneXpert should be maintained (**Annex 4**)
- GeneXpert Monthly Summery (**Annex 5**) should be sent to Consultant microbiologist- NTRL with a copy to DTCO of the respective district
- Quarterly report should be sent by DTCO to NPTCCD (**Annex 6**)

Interpretation of results, Referral for management and Reporting

MTB = *M.tuberculosis*; RR = rifampicin resistance; ATT = Anti TB Treatment; DCC= District Chest Clinic

Result	Action
MTB detected; RR detected	Patient needs to be reassessed for starting second line ATT. Inform Consultant Respiratory Physician and District TB Control Officer and refer to nearest DCC; Inform Consultant Microbiologist of NTRL and send another sputum sample to NTRL for confirmation of rifampicin resistance. Complete TB notification.
MTB detected; RR not detected	Patient needs first line ATT; refer to nearest DCC or branch clinic; Complete TB notification
MTB detected; RR indeterminate	Patient has TB but needs further testing to determine susceptibility to rifampicin. Request a repeat specimen.
MTB not detected	No evidence of TB in the specimen. Further investigations are required if patient is likely to have TB based on clinical grounds or other investigations.
Invalid or error	Needs repeat testing

Annexures

1. GeneXpert facilities at central and provincial level
2. Groups of patients with presumptive PTB belonging to **10 presumptive drug resistant TB categories**
3. Request form for TB culture and/or Xpert (MTB/RIF) test (TB 06 form)
4. Gene Xpert monthly summery
5. Quarterly report on Utilization of GeneXpert for Diagnosis of TB and MDR TB

Annexure 1- GeneXpert facilities at central and provincial level

National TB Reference Laboratory, Welisara (NTRL) (to offer services mainly to Colombo, Gampaha & to other districts as required)

Intermediate TB laboratories (ITL performing both Xpert & cultures) at

District Chest Clinic, Kandy

Provincial General Hospital, Rathnapura

Teaching Hospital, Karapitiya

Teaching Hospital, Jaffna

Hospital Microbiology laboratories

National Hospital of Sri Lanka, Colombo

Lady Ridgway Hospital for children- Borella

Prison Hospital –Welikada

Colombo South Teaching Hospital- Kalubowila

District Chest Clinic – Borella

Colombo Municipal Council

District General Hospital- Hambanthota

District General Hospital -Matara

District General Hospital -Nuwara Eliya

District General Hospital -Matale

District General Hospital- Monaragala

Teaching Hospital –Kegalle

District General Hospital- Puttlam

District General Hospital- Polonnaruwa

District General Hospital –Vavuniya

District General Hospital- Mannar

District General Hospital- Mullativ

Teaching Hospital, Batticaloa

Ashroff Memorial Hospital-Kalmunai

District General Hospital- Ampara

District General Hospital- Trincomalee

Teaching Hospital, Kurunegala

Provincial General Hospital, Badulla

Teaching Hospital, Anuradhapura

National Institute of Health Science -Kaluthara

Annexure 2 - Groups of patients with presumptive PTB belonging to 10 presumptive drug resistant TB categories

Category A: High risk cases for drug resistance

- A.** Symptomatic contacts of MDR-TB patients or those asymptomatic contacts screened with CXR and found to have changes suggestive of TB
- B.** First line regimen failures and non-converters/delayed sputum conversion
 - i. Patients who continue to remain sputum smear positive after 3 months of retreatment with First Line Drugs (FLD) or failures of retreatment with FLD
 - ii. Patients who continue to remain sputum smear positive after 2 months of new treatment regimen with FLD or failures of new treatment regimen with FLD
- C.** Patients with history of treatment interruptions
- D.** All other previously treated TB patients

Category B: Patients with moderate or low risk of drug resistance but in whom the risk of mortality or chance of spread of resistant bacillus to contacts is high

- E.** Patients with TB/HIV co-infection,
- F.** Institutionalized persons e.g.: - prisoners
- G.** Drug addicts
- H.** Healthcare workers
- I.** Those who return from abroad with active TB.
- J.** TB patients treated outside the National TB Programme (NPTCCD).

Annexure 3 -Request form for TB culture and/or Xpert (MTB/RIF) test (TB 06 form)

National Programme for Tuberculosis Control and Chest Diseases

TB 06

REQUEST FORM TB CULTURE, DRUG SUSCEPTIBILITY AND MOLECULAR TESTING National TB Reference Laboratory, Welisara

Specimen		Date of Collection			Lab Use Only	Serial No		
Sputum	Other (Specify)	dd	mm	Yy	Date of Receipt		Lab No.	
					dd	mm	yy	Culture
								DST

Last Name of the Patient (In Block Letters)

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First Name/Initials of the Patient (In Block Letters)

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Date of Birth			Sex		Contact Number	NIC/ID of Patient/Parent/Guardian
yyyy	mm	dd	M	F		

Name of Sending Institution	Ward/ Clinic	BHT/Clinic No	Forwarding DCC	Standard Card No.	District TB NO	Report to be Sent to

Patients Address:		Residential District:	
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Test/s Requested	Culture & DST		Xpert (MTB/RIF)	
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Indication	For Diagnosis		Follow Up CAT I		Follow Up CAT II		Follow Up CAT IV		Other (Specify)	
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Probable Diagnosis	PTB Smear positive		PTB Smear negative		EPTB		Site/s	
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Treatment History	New		Previously Treated		Known MDR		Known MOTT		History Unknown	
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If Previously Treated	First Relapse		>1 Relapse		Rx After Failure		Rx After Loss to Follow Up		Other (Specify)	
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Details of Treatment

Past ATT (Indicate periods of treatment)	Cat I/Cat II/Cat IV
Present ATT (on the date of specimen collection)	Not on ATT / On ATT (indicate regime & starting date) Cat I /Cat II /Cat IV

Current Sputum Smear Status of Follow Up Patients	Duration of Treatment	Does the patient belong to a Presumptive MDR group?
Positive		Yes
Negative		No

Presumptive MDR category: [please write the relevant letter in the column] - (A) Contacts of MDR-TB patients, (B) previously treated patients, (C) Non-converters / delayed sputum conversion, (D) Patients with history of repeated treatment interruptions, (E) TB patients treated outside the NTP, (F) Patients with TB/HIV co-infection, (G) Institutionalized patients, (H) Healthcare workers, (I) Those who return from abroad with active TB, (J) Others (High Risk Behaviour like substances Abuses).

Previous Cultures Done

Lab Serial No.	ABST No.	MDR No.	Year	Result

Other Relevant Clinical Details (e.g. HIV /Other Causes of Immune Suppression/X Ray/Mantoux)

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Signature of Medical Officer:.....

Name:

Designation: HO/ MO/DTCO/SHO/REG/SR/VP/VS/.....

Please Refer to Lists Given to District Chest Clinic for the Following

- *Indications for Culture - List 1*
- *Indications for Xpert MTB/RIF - List 2*
- *Presumptive MDR Groups –List 3*

Laboratory Use Only

Lab Serial No:

Smear	Positive 3+		Positive 2+		Positive 1+		Positive scanty		Negative	
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Culture	Positive		Negative		Contaminated		Other	
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Identification	MTB		Atypical		Other (Specify)	
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Results of Sensitivity Test

Result	Streptomycin	Isoniazid	Rifampicin	Ethambutol
Sensitive				
Resistant				

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MLT /NTRL

Date :

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Consultant Microbiologist/NTRL

Date :

Annexure 4

Gene Xpert Monthly Summary

Laboratory: -

Month :-

Year :- 2019

Total No. of patients referred	Referred from Health institutions	
	Referred from DCC	
Total Tests Done		
MTB Detected	Total	
	RR	
	RR N/D	
	RR Ind	
MTB N/D		
Error		
Invalid		
Repeat		

Cartridge Lot	Expiry Date

Stock available at the end of the month	Expiry Date

	Name	Designation
Prepared By		
Approved By		

Total Pulmonary Specimens		AFB Smear +	AFB Smear -	Smear Result not Known	Total	
	Total					
	RR					
	RR/ND					
	RR/IND					
MTBN/D						
Error						
Invalid						
Repeat						

Total Extra Pulmonary Specimens		
MTB Detected	Total	
	RR	
	RR N/D	
	RR Ind	
MTB N/D		
Error		
Invalid		
Repeat		

Total CSF Specimens		
MTB Detected	Total	
	RR	
	RR N/D	
	RR Ind	
MTB N/D		
Error		
Invalid		
Repeat		

MTB - Mycobacterium tuberculosis

RR/ND - Rifampicin Resistance Not Detected

RR - Rifampicin Resistance Detected

RR/Ind - Rifampicin Resistance Indeterminate

Annexure 5

WHO Recommended Diagnostics (WRD) Register

[illegible]

Presumptive MDR category: [*please write the relevant letter in the column*] - (A) Contacts of MDR-TB patients, (B) Previously treated patients, (C) Non-converters / delayed sputum conversion, (D) Patients with history of repeated treatment interruptions, (E) TB patients treated outside the NTP, (F) Patients with TB/HIV co-infection, (G) Institutionalized patients, (H) Healthcare workers, (I) Those who return from abroad with active TB, (J) Others (High Risk Behaviour like substances Abuses).

Annexure 6- Quarterly report on Utilization of GeneXpert for Diagnosis of TB and MDR TB

Quarter-.....

Chest Clinic-.....

		Column A		Column B		Column C		Column D	Column E
Type of Sample taken for GeneXpert		Presumptive TB patients		New smear positive PTB Patients		Presumptive MDR TB Patients		EPTB patients	Smear negative PTB patients
				Total - <div></div>		Total- <div></div>			
Sputum	Other	No. of patients Tested	No. of patients diagnosed as TB	No. of Patients tested	No. of patients positive	No. of Patients tested	No. of patients positive		

Column A- This column is to identify the number of presumptive TB patients investigated with GeneXpert as initial investigation- People living with HIV, central nervous system TB patients, Paediatric TB cases, Critically ill patients in whom TB is suspected, immunosuppressive patients, presumptive PTB during pregnancy and per partum period,

Column B- This column is to identify the number of new smear positive PTB Patients investigated with GeneXpert (Who has undergone universal DST). Please mention the total number of new smear positive PTB Patients diagnosed in this particular month, in the given box.

Column C- This column is to identify the number of Presumptive MDR Patients (All retreatment cases, Contacts of known drug resistance TB cases, Healthcare workers, Patients who return from abroad with active TB, Prisoners, Drug addicts, Patients treated outside the programme. Please mention the total number of of Presumptive MDR Patients diagnosed in this particular month, in the given box.

Column D- This column is to identify Number of EPTB patients Diagnosed by GeneXpert

Column E- This column is to identify Number Smear negative patients Diagnosed by GeneXpert

PTB-Pulmonary Tuberculosis **EPTB-**Extra Pulmonary Tuberculosis **MRD-** Multi drug resistance