Workshop

Joint SEAR-WPR workshop to plan the accelerated implementation of new WHO TB policies

1-4 APRIL 2025

Hanoi, Viet Nam

WHO Policy Updates: Initial Molecular Testing for TB and Drug-Resistant TB

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2025 TB Diagnostic Policy Updates: 3 Categories

Structural Updates

Consolidated Content on TB Infection & Diagnosis

Added Recommendation Lists & Summaries of Changes

Added a Chapter on Diagnostic Class Determination & Prequalification

Revised Diagnostic Algorithms & Annex Structure

New Testing Classes & Product Endorsements

2 New Classes of Low Complexity Nucleic Acid Amplification Tests (automated and manual)

2 New Interferon Gamma Release Assays for Detection of TB Infection

1 Updated Targeted NGS Solution for Detection of Drug-Resistant TB Updated

Testing Strategy Updates

Recommendations for Concurrent Testing of Multiple Sample Types for Children and People Living with HIV

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WHO Now Recommends Classes of TB Diagnostic Technologies

- The WHO assessment process for TB diagnostics has evolved to focus on evaluating ‘classes’ of TB diagnostic technologies rather than specific products
- Class include diagnostic testing technologies that share the following characteristics:
  - purpose of use (i.e., detection of TB or drug-specific resistance)
  - principle of action
  - infrastructure and human resource requirements
  - complexity of the testing procedure and associated instrumentation
  - reporting method (automated versus manual)
  - setting of use (e.g., reference or peripheral low-complexity, near point-of-care, point-of-care)

WHO Classes of TB Diagnostics Grouped by Purpose

Initial tests for detection of TB *with* drug resistance

Initial tests for detection of TB *without* drug resistance

Follow-on tests for detection of drug resistance

Tests for detection of TB infection

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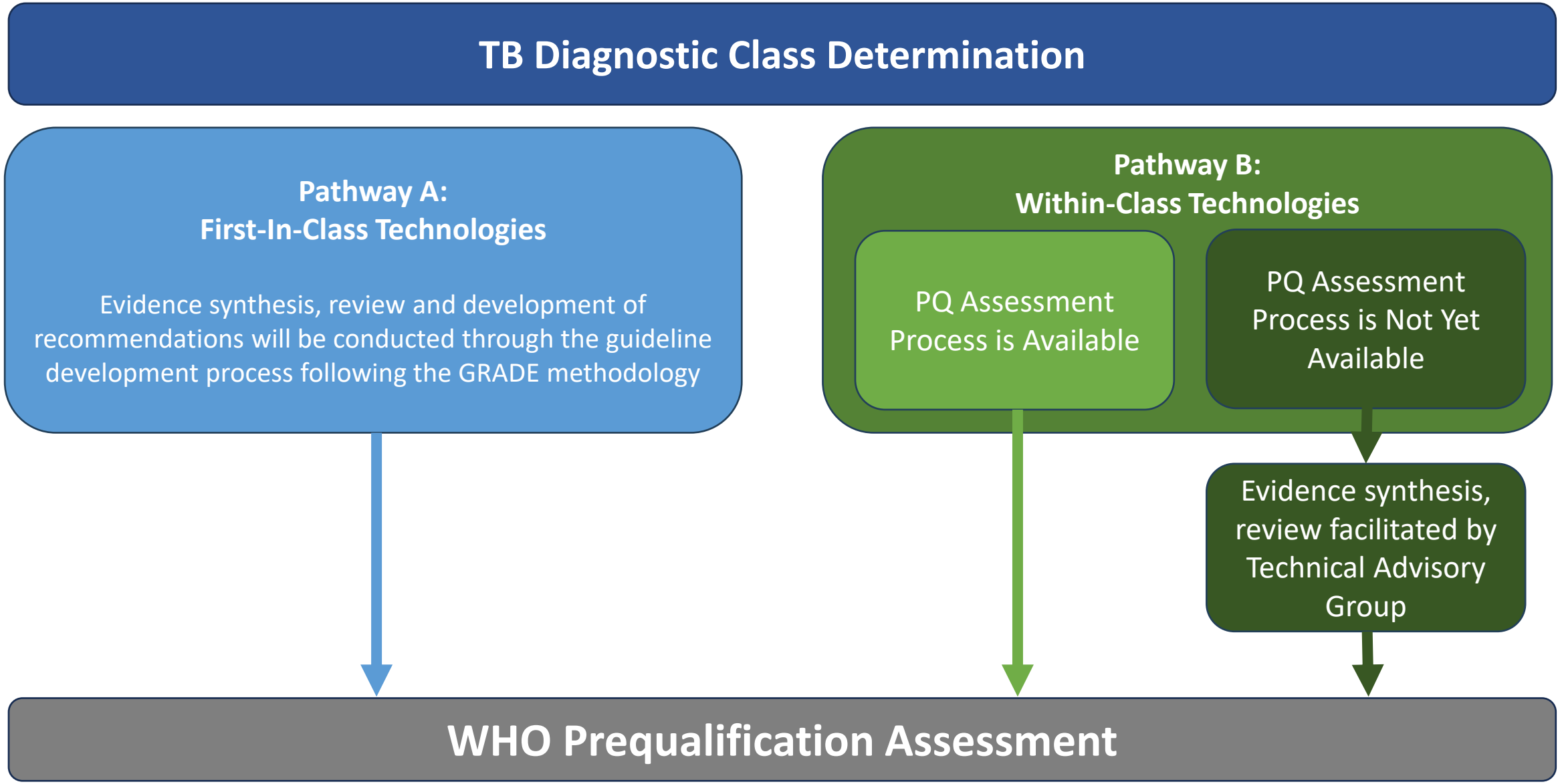
Recommendation Pathways for TB Diagnostics



Technology Class	Included Products
Initial tests for TB diagnosis with drug resistance detection	
NEW	
Initial tests for TB diagnosis without drug resistance detection	
NEW	
Follow-on tests for detection of TB drug resistance	
Tests for TB infection	

New TB Testing Classes

Low Complexity Automated Nucleic Acid Amplification Tests (LC-aNAATs)

Class of LC-aNAATs includes:

- Xpert® MTB/RIF Ultra (Cepheid)
- Truenat® MTB Plus with MTB-RIF Dx (Molbio)
- Instrument-based, require a well-established laboratory network, laboratory infrastructure and trained testing staff

Cepheid GeneXpert

Molbio Truenat

Purpose		Detection of **TB and Rifampicin Resistance**
Principle of Action		Nucleic acid amplification testing
Complexity	Reagents	Most reagents are enclosed in a disposable sealed container to which a clinical specimen is added. The disposable sealed container does not have special storage requirements.
	Skills	Basic technical skills (e.g., basic pipetting, precision not critical)
	Pipetting	**Either no, or only one, pipetting step** in the process
	Testing procedure	• May require an initial manual specimen treatment step before transferring the specimen into the disposable sealed container for automated processing • Automated DNA extraction • Automated real-time PCR
Type of Result Reporting		**Automated**
Setting of Use		**Basic laboratory** (no special infrastructure needed)

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Recommendations for Use of LC-aNAATs for the Detection of TB and RR TB

Population	Assessed Technology	Sample(s)	Purpose and Performance^	Strength of Evidence	Quality of Evidence
Adults and adolescents with signs or symptoms or who screen positive for PTB	Xpert MTB/RIF Ultra Truenat MTB Plus + MTB-RIF Dx	Respiratory samples	Detection of TB	Strong	High
People with bacteriologically confirmed TB	Xpert MTB/RIF Ultra Truenat MTB Plus + MTB-RIF Dx	Respiratory samples	Detection of resistance to rifampicin	Strong	High
People with signs or symptoms of TB meningitis	Xpert MTB/RIF Ultra	Cerebral spinal fluid	Detection of TB	Strong	Moderate
People with signs or symptoms of EP TB	Xpert MTB/RIF Ultra	Lymph node tissue/ aspirate, pleural tissue/fluid, synovial/ peritoneal/ pericardial fluid	Detection of TB	Strong	Low to Very Low

Acronyms: PTB = Pulmonary TB, EP TB = Extrapulmonary TB, RR TB = rifampicin-resistant TB.

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Recommendations for Use of LC-aNAATs for the Detection of TB and RR TB

Population	Assessed technology	Sample(s)	Purpose	Performance^
Adults and adolescents with signs or symptoms or who screen positive for PTB	Xpert MTB/RIF Ultra Truenat MTB Plus + MTB-RIF Dx	Respiratory samples	Detection of TB	*Sensitivity 90.4% (95% CI: 88.0–92.4)* *Specificity 94.9% (95% CI: 93.0–96.3)*
People with bacteriologically confirmed TB	Xpert MTB/RIF Ultra Truenat MTB Plus + MTB-RIF Dx	Respiratory samples	Detection of resistance to rifampicin	*Sensitivity 95.1% (95% CI: 83.1–98.7)* *Specificity 98.1% (95% CI: 97.0–98.7)*
People with signs or symptoms of TB meningitis	Xpert MTB/RIF Ultra	Cerebral spinal fluid	Detection of TB	*Sensitivity 88.2% (95% CI: 83.7–91.6)* *Specificity 96.0% (95% CI: 86.8–98.9)*
People with signs or symptoms of EP TB	Xpert MTB/RIF Ultra	Lymph node tissue/ aspirate, pleural tissue/fluid, synovial/ peritoneal/ pericardial fluid	Detection of TB	*Sensitivity range 33% - 99%* *Specificity range 74% - 99%* *(sample dependent)*

Acronyms: PTB = Pulmonary TB, EP TB = Extrapulmonary TB, RR TB = rifampicin-resistant TB.
^Performance values represent summary sensitivity and specificity systematic review data.

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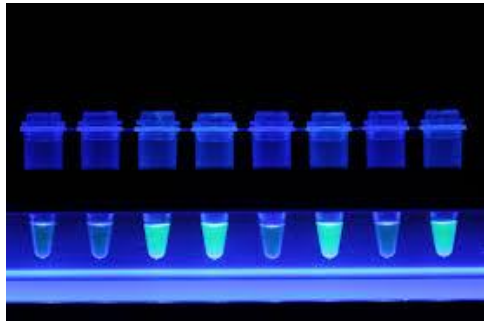
Low Complexity Manual Nucleic Acid Amplification Tests (LC-mNAATs)

Class of LC-mNAATs includes:

- Loopamp™ MTBC Detection Kit (TB LAMP) (Eiken Chemical)
- Basic equipment and UV lamp required for testing and reading; can be implemented at the lowest levels of the laboratory network by trained testing staff.



Eiken Chemical TB-LAMP

Purpose		**Detection of TB**
Principle of Action		Nucleic acid amplification testing
Complexity	Reagents	Most reagents are enclosed in multiple disposable sealed containers not requiring special storage requirements.
	Skills	Basic technical skills (e.g., basic pipetting, precision not critical)
	Pipetting	**Multiple pipetting steps** (maximum of 10) from processed sample to result generation
	Testing procedure	At least three distinct steps: • DNA extraction • PCR amplification • Results visualization
Type of Result Reporting		**Automated or manual**
Setting of Use		**Basic laboratory** (no special infrastructure needed)

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Recommendations for Use of LC-mNAATs for the Detection of TB

Population	Assessed technology	Sample	Purpose	Performance^
Adults and adolescents with signs and symptoms or who screen positive for pulmonary TB	Loopamp MTBC Detection Kit (TB LAMP) (Eiken Chemical)	Respiratory samples	Detection of TB (*Strong recommendation, High quality of evidence*)	Sensitivity 84.1% (95% CI: 78.3–88.6) Specificity 96.1% (95% CI: 94.2–97.4)

^Performance values represent summary sensitivity and specificity systematic review data.

Remark Highlights:

- Applies to all people living with HIV and extrapolated to children for use with respiratory samples (induced sputum and gastric aspirate), with the caveat of low to moderate certainty of evidence and noting concurrent testing with LC-aNAAT and LF-LAM for PLHIV are recommended where available.
- Data on the use of paediatric stool samples were very limited, and there were no data on the use of nasopharyngeal aspirates. The recommendation was, therefore, not extrapolated to these sample types.
- As LC-mNAATs do not provide rifampicin-resistance results, all positive diagnostic tests for TB require follow-up and referral for DST for, at a minimum, rifampicin.

Concurrent Testing for Children and PLHIV

Concurrent Testing as a Strategy for Children & PLHIV

What is It?

- ✓ Multiple samples are taken simultaneously (whenever possible) and tested using one or more test.
- ✓ A positive result on any test is a positive result for the combination.
- ✓ However, the inability to collect one or more specimens at the initial visit, or lack of one of the test types should not delay testing of available specimens and tests but instead trigger specimen collection and testing as soon as possible.

Why Do It?

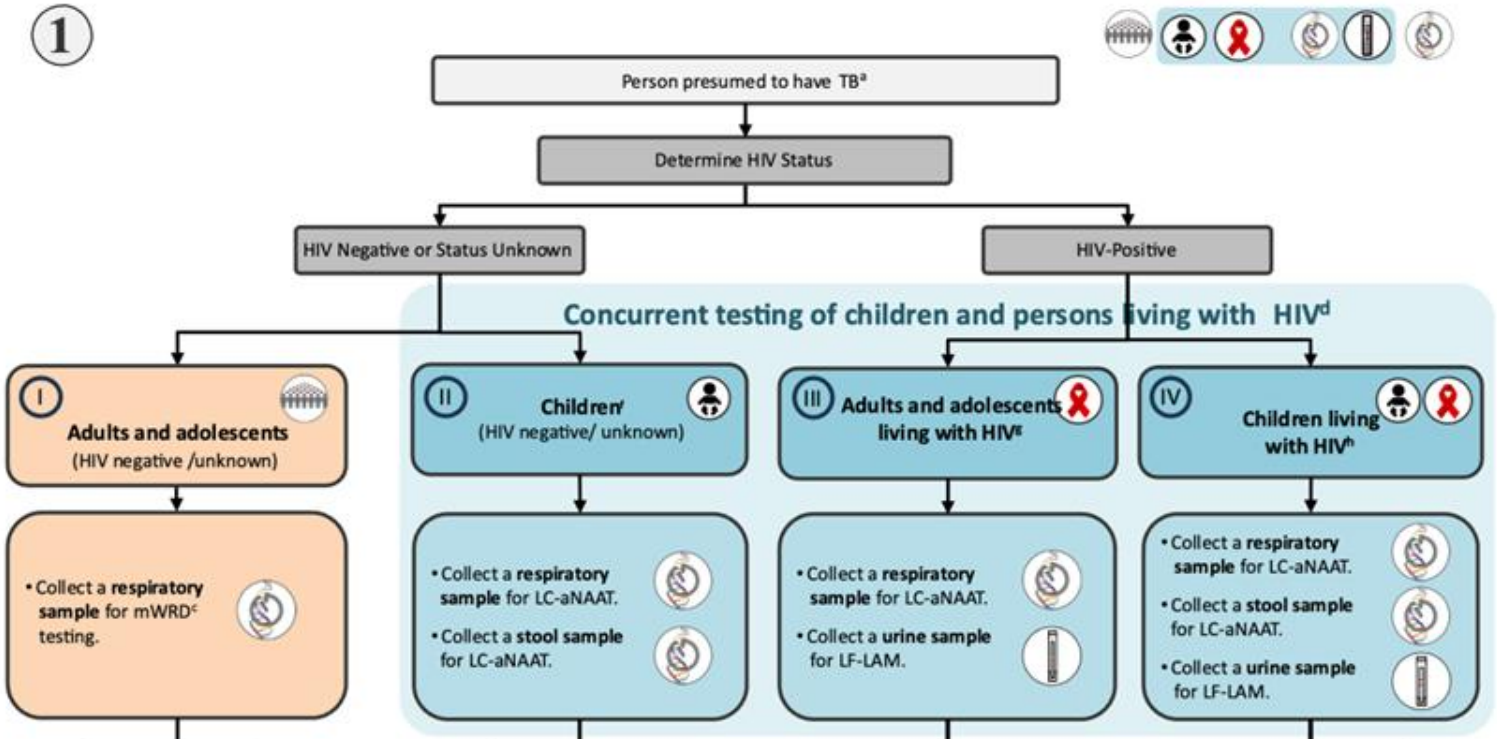
- ➢ There are significant burdens of TB in PLHIV and children, particularly in low- and middle-income countries
- ➢ Diagnostic testing for TB in persons living with HIV and children is challenging, because of:
  - Non-specific clinical presentations, including disseminated TB
  - Often low and varying numbers of mycobacteria in samples
  - Inability to provide sputum samples
- ➢ Implementing concurrent sample testing could:
  - Simplify diagnostic processes using easy-to-collect sample types
  - Shorten the patient journey
  - Improve TB detection rates and health outcomes for these at-risk populations

Concurrent TB Testing Recommendations: Detection of TB

Population	Intervention	Performance	95% Confidence Interval	Strength of Evidence	Quality of Evidence
Adults and adolescents with signs or symptoms of TB, screen positive for TB, are seriously ill or have advanced HIV disease	LC-aNAAT respiratory sample + LF-LAM on urine	Δ Se: 6.7% (I:77.5%; C: 68%)	3.8% to 10.7%	Strong	High
		Δ Sp: - 6.8% (I:89.4%; C: 97%)	-9.5% to -4.7%		
Children	LC-aNAAT respiratory sample + LC-aNAAT on stool	Δ Se: 7.1% (I:79.9%; C: 72.5%)	3.2% to 13.4%	Strong	Low
		Δ Sp: - 1.7% (I:93.4%; C: 95.0%)	-3.8% to -0.6%		
Children living with HIV	LC-aNAAT respiratory sample + LC-aNAAT on stool + LF-LAM on urine	Δ Se: 6.9% (I:77.8%; C: 69.3%)	1.5% to 20.1%	Conditional	Low
		Δ Sp: - 10.2% (I:83.9%; C: 95.4%)	-19.6% to -4.9%		

Technology Assessed: *Xpert MTB/RIF Ultra. No or limited data for Truenat MTB Plus.*
Remark Highlight*: Supersedes prior guidance on use of LF-LAM for TB detection among PLHIV.*

New Algorithm 1 Highlights Populations & Consolidates Tests



WHO Prequalification Process Available for LF-LAM and NAATs

TSS 17 - In vitro diagnostic medical devices used for the qualitative detection of Mycobacterium tuberculosis complex DNA and mutations associated with drug-resistant tuberculosis

TSS 23 - Rapid diagnostic tests to detect mycobacterial lipoarabinomannan (LAM) antigen in urine

Mycobacterium Tuberculosis complex and resistance to first and/or second line anti-TB drugs Tests

Product name	Product code(s)	Manufacturer name	Dossier review	Quality Management System review	Product performance evaluation	Labelling review
BD MAX MDR-TB	443878	Becton, Dickinson and Company, BD Biosciences (USA)	◆	◆	🗁	🗁
Truenat MTB Plus	601130020, 601130005, 601130025, 601130050, 6011301100, and 601130200	Molbio Diagnostics Private Limited	R	◆		
Truenat MTB-RIF Dx	601210200, 601210005, 601210020, 601210100, 601210025, and 601210050	Molbio Diagnostics Private Limited	R	◆		
cobas MTB-RIF/INH	09040617190, 09040625190, 09051953190, 08185476001	Roche Diagnostics GmbH	🗁	S	Alternative laboratory evaluation pathway	🗁
cobas MTB	09040579190, 09040587190, 09051953190, 08185476001	Roche Diagnostics GmbH	R	S	Alternative laboratory evaluation pathway	
Loopamp MTBC Detection Kit	972000, 970000, 971000	Eiken Chemical Co., Ltd.	R	🗁	🗁	
Xpert MTB/XDR	GXMTB/XDR-10	Cepheid AB	R	🗁	Alternative laboratory evaluation pathway	◆

In Vitro Diagnostics Under Assessment | WHO - Prequalification of Medical Products (IVDs, Medicines, Vaccines and Immunization Devices, Vector Control)

- Prequalification Technical Specification Series and Performance Evaluation protocols available for NAATs
- Xpert MTB/RIF Ultra prequalified as the first TB diagnostic
- Prequalification Technical Specification Series available for LF-LAM + Performance Evaluation protocol publication in 2025
- At least 7 additional low and moderate complexity products undergoing evaluation

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Summary and Next Steps

- Two new classes of Low Complexity Nucleic Acid Amplification testing are now recommended for detection of TB (with and without rifampicin resistance detection)
- Concurrent testing of multiple samples is now recommended for persons living with HIV and children
- WHO Consolidated Guidelines and Operational Handbook on TB Diagnosis (Module 3) are planned for publication in Q2 2025
- Dissemination activities will include workshops, webinars, and ad hoc engagements
- Planning for 2025 Guideline Development Group and Technical Advisory Group meetings underway

https://extranet.who.int/tbknowledge

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Guiding Questions for Experience Sharing

1) How many countries are using Low Complexity NAATs (i.e., Xpert MTB/RIF, Xpert MTB/RIF Ultra, or other) on stool for detection of TB among children?

2) How many countries are using urine LF-LAM to diagnose TB among people living with HIV?

3) How could/ will concurrent testing impact case finding efforts for children and persons living with HIV?

4) What are some anticipated benefits and challenges?