Proud to be a Danaher Company.

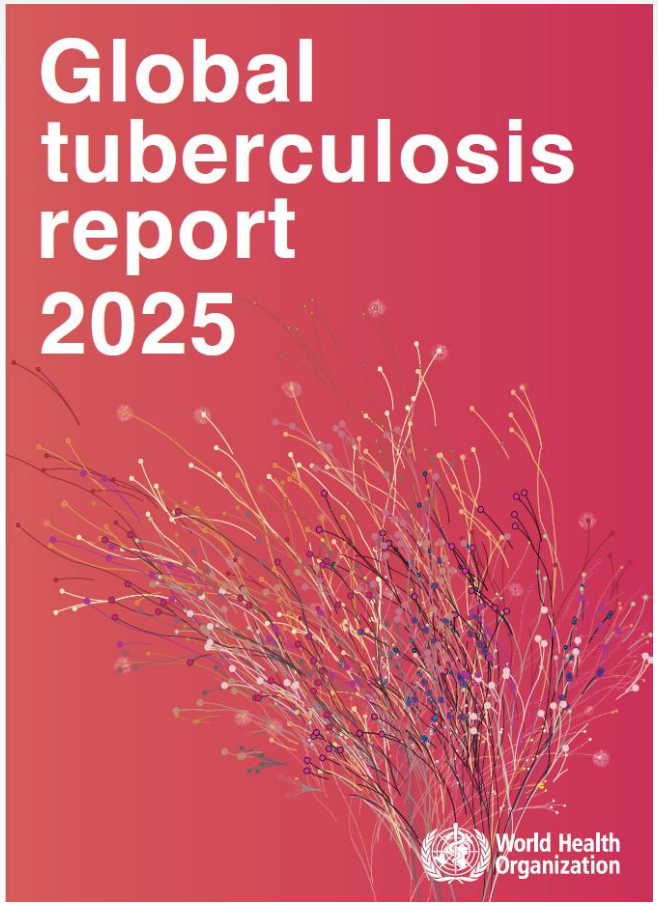
FROM DIAGNOSIS TO ACTION

Xpert® MTB/RIF Ultra + Xpert® MTB/XDR in practical TB diagnostic pathways

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Global Statistics



INDICATOR (2024)	GLOBAL ESTIMATE	KEY IMPLICATION
People who developed TB	10.7 million	TB remains a leading infectious killer globally
TB deaths	>1.2 million	Mortality decline remains too slow for End TB targets
People diagnosed and treated	8.3 million (~78%)	>2 million people with TB missed by health systems
DR-TB patients treated	<40%	Major gap in access to life-saving care
Rapid diagnostic coverage	54%	Improvements made, but access remains uneven



WHO-recommended rapid molecular test was used as the initial diagnostic test for **54% of the 8.3 million people newly diagnosed with TB in 2024**, up from 48% in 2023

1. Global tuberculosis report 2025. Geneva: World Health Organization; 2025. Licence: CC BY-NC-SA 3.0 IGO.

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The Clinical Question Is Not Only “Is TB Present?”

The pathway must also answer: what resistance information is needed now to start the right regimen.

1 **Detect TB**

Sensitive first-line molecular testing
Algorithm 1 in the figure — mWRD, LC-aNAAT or LF-LAM as the initial diagnostic test

2 **Identify RIF resistance**

Immediate signal of RR-TB risk
Branch point after Algorithm 1 — RIF-resistant leads to 2a and 2b, RIF-susceptible to 3

3 **Extend resistance profile**

INH, FQ, ETH and SLID-associated mutations
Algorithms 2a and 2b (RIF-resistant) and Algorithm 3 (RIF-susceptible) in the figure

4 **Act**

Link the result to treatment and further DST
Algorithm 4 in the figure — TB infection testing and TPT on the screen-negative arm

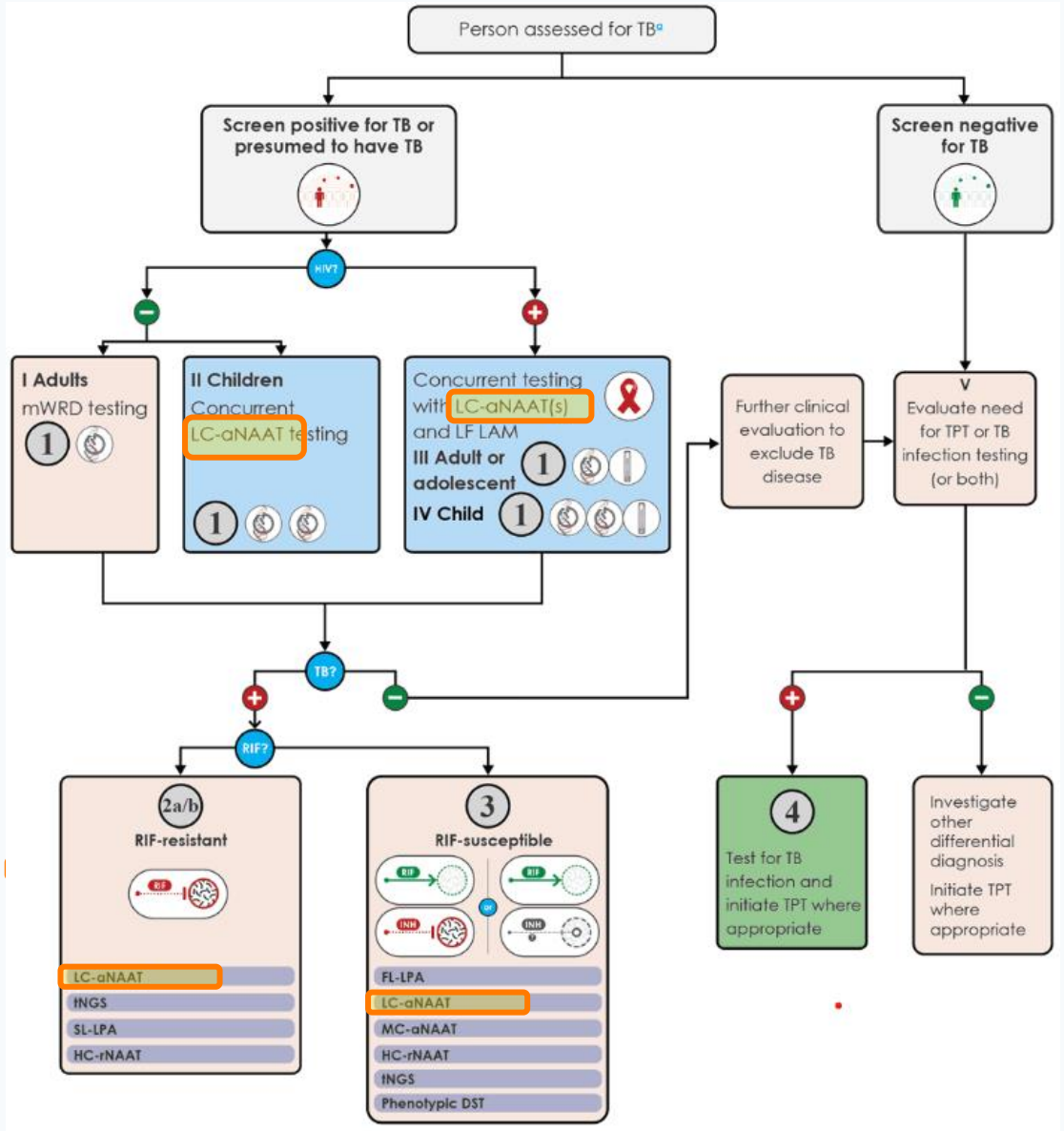


Fig. 6.1, cascade of the four model algorithms. WHO operational handbook on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection, third edition. Geneva: World Health Organization. Licence: CC BY-NC-SA 3.0 IGO.

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A Two-Cartridge Pathway: Different Roles, One Clinical Decision

Use each assay for the question it was designed to answer.

Xpert® MTB/RIF Ultra*

Launched 2017 · WHO recommendation to replace Xpert MTB/RIF · WHO prequalified · Results in less than 80 minutes · 6-color technology

- Detects MTB complex DNA
- Reports semiquantitative MTB categories
- Assesses rifampicin resistance when signal is sufficient
- Supports first-line diagnostic testing across eligible specimen types
- Increased sensitivity from additional IS targets and melt curve analysis
- Limit of detection: 12 CFU/mL



Xpert® MTB/XDR*

Launched 2020 · WHO recommended · Results in 90 minutes · First 10-color test on the GeneXpert system

- Reflex test on an MTB-positive respiratory specimen
- Detects INH, FQ, ETH and SLID-associated resistance mutations
- Qualitative MTB detection, not a bacillary-load assay
- Runs on GeneXpert systems with 10-color modules
- Expands diagnostic scope beyond rifampicin in a single cartridge
- Limit of detection: 136 CFU/mL (unprocessed sputum); 86 CFU/mL (sediment)



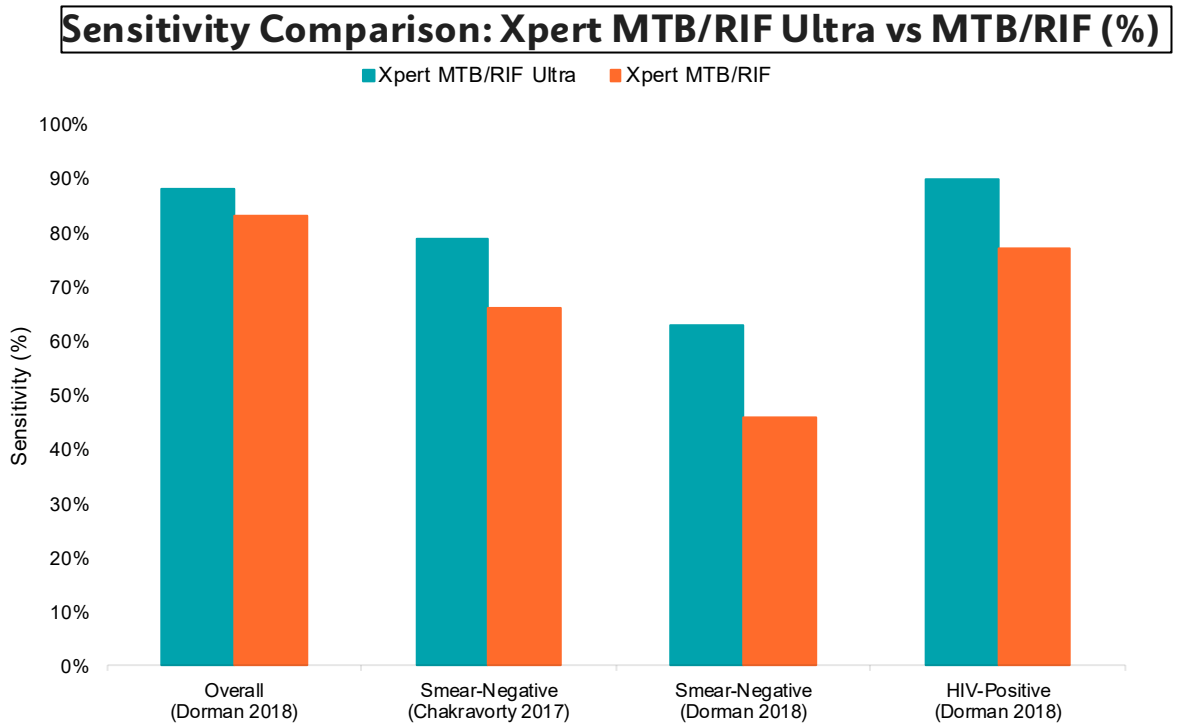
The result sets are complementary, not interchangeable.

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Xpert® MTB/RIF Ultra*- Clinical Performance Breakthrough

Ultra delivers a 13% increase in sensitivity over its predecessor in smear-negative patients while maintaining equivalent specificity, directly addressing the patients most likely to be missed.



Key Study Findings

Chakravorty et al. 2017
LOD 15.6 vs 112.6 CFU/mL (~10× gain); smear-neg sensitivity: 78.9% vs 66.1%; specificity 98.7% both

Dorman SE et al. 2018
Overall 88% vs 83%; smear-negative 63% vs 46% (+17%); HIV-positive 90% vs 77% (+13%)

Evrevin et al. 2020
Reduced diagnostic delay by 18 days in smear-negative patients; cost-effective for TB diagnosis

Clinical Insight
Ultra's "trace" result category enables earlier detection in paucibacillary disease — especially relevant for HIV-positive patients

Charkravorty S, et al. The New Xpert MTB/RIF Ultra: Improving Detection of Mycobacterium tuberculosis and Resistance to Rifampin in an Assay Suitable for Point-of-Care Testing.MBio. 2017 Aug 29;8(4). pii: e00812-17. Accessed Oct 2023. mBio.00812-17.pdf (nih.gov)

Marine Evrevin et al. 2020 https://www.journalofinfection.com/article/S0163-4453(20)30764-7/abstract. Accessed June 2024

Dorman S E .et al, Xpert MTB/RIF Ultra for detection of Mycobacterium tuberculosis and rifampicin resistance: a prospective multicentre diagnostic accuracy study.Lancet Infect Dis. 2018 Jan;18(1):76-84. https://pubmed.ncbi.nlm.nih.gov/29198911/

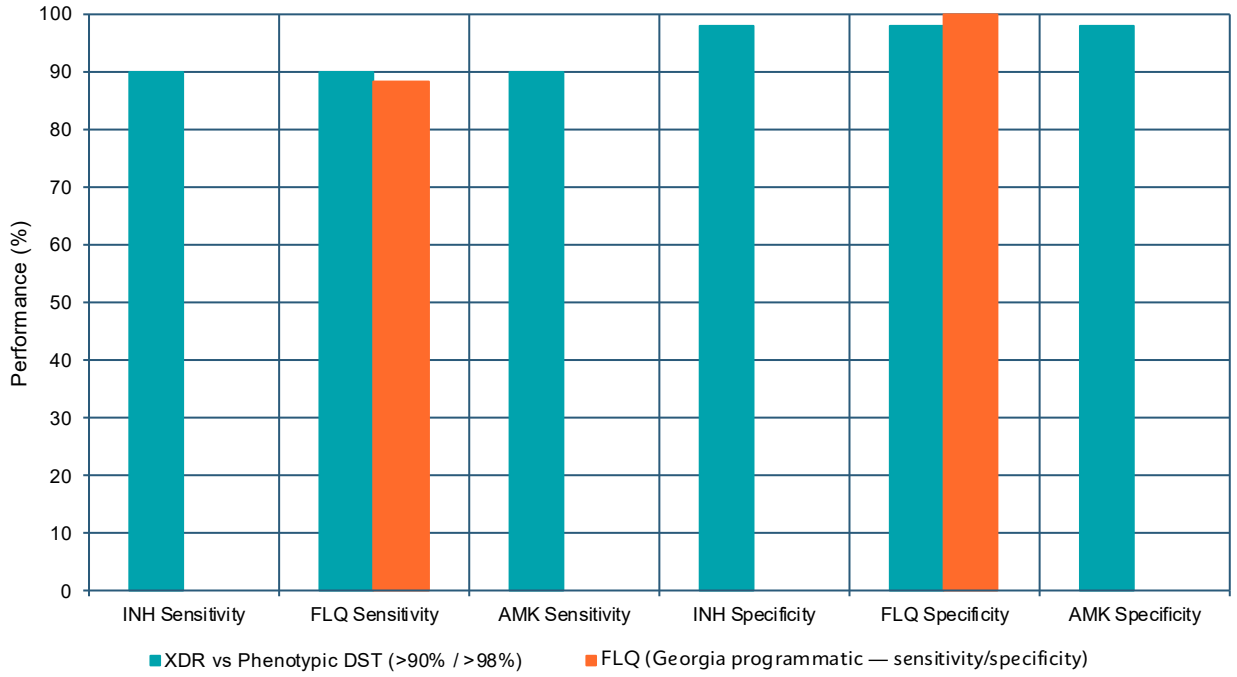
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Clinical Evidence For Xpert® MTB/XDR* — Treatment-Enabling Performance

Published evidence confirms Xpert MTB/XDR delivers high sensitivity and specificity for INH and fluoroquinolone detection, with results in 90 minutes versus days to weeks for culture-based DST.

Xpert MTB/XDR — Sensitivity & Specificity vs Reference Standards (%)



Penn-Nicholson et al. 2022

High performance across a diverse clinical population; decentralizable rapid drug resistance profiling; high relevance given importance of INH and FLQ in current DR-TB treatment regimens.

Katamba et al. 2023 (Uganda)

High sensitivity and specificity for INH and FLQ vs LPA and phenotypic DST. Helps rule out FLQ resistance for MDR/RR-TB patients qualifying for bedaquiline-based regimens. Reduces challenges from complex tests such as LPA and culture-based DST.

Saderi et al. 2022

90 min vs LPA at 48–72 hours minimum in resource-limited settings. Guides dose selection (higher dose) for low-level INH/FLQ resistance.

WHO MDR-TB Treatment Context

Rapid fluoroquinolone resistance information can support regimen selection in accordance with national guidelines and clinical judgment.

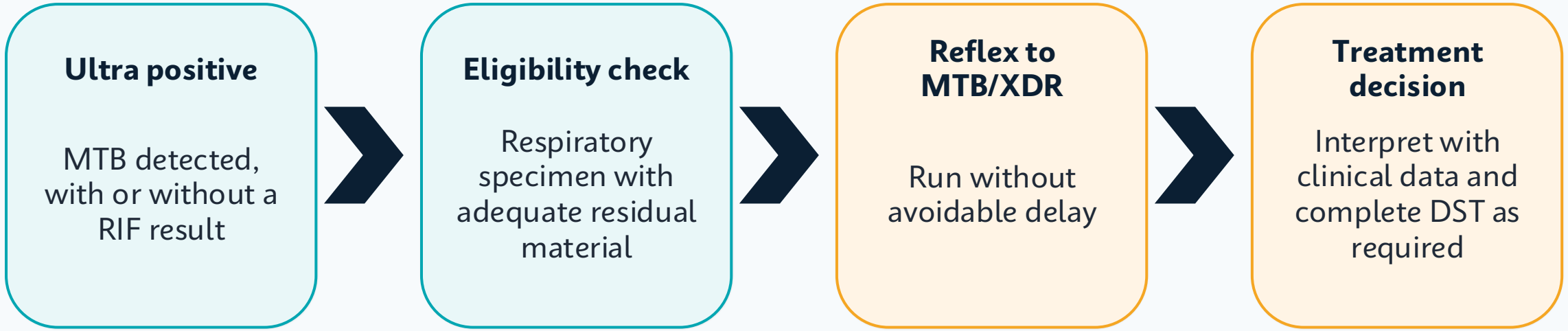
Penn-Nicholson A, Georghiou S, Ciobanu N et al. https://doi.org/10.1016/S1473-3099(21)00452-7, Lancet Infectious Diseases, 2021; 22, 242-249
A Katamba, et al. 2023 https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0284545 Accessed Dec 2023
L Saderi, et al. 2022 https://www.archbronconeumol.org/es-pdf-S0300289622004987 Accessed Dec 2022

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When Should Xpert MTB/RIF Ultra* Be Reflexed?

Minimize handoffs between an MTB-positive result and extended rapid DST.



Test and treat in the same visit is feasible with Xpert technology

Ultra in under 80 minutes and MTB/XDR in 90 minutes, both direct from sputum on the existing GeneXpert network at district level - a resistance-informed regimen decision the same day, without culture or referral.

Default: rapid extended resistance testing for bacteriologically confirmed pulmonary TB, aligned to national policy.

Reference: WHO consolidated guidelines on tuberculosis, Module 3: Diagnosis - rapid diagnostics for tuberculosis detection. Geneva: World Health Organization. National algorithms and product labelling take precedence.
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Why Can Xpert MTB/RIF Ultra* Be Positive While Xpert MTB/XDR* Says “MTB Not Detected”?

Discordance is often a concentration and target-design issue, not a contradiction.

Bacillary load drives what each assay can call

Load category	Ultra	MTB/XDR
High	MTB detected	Resistance result expected
Medium	MTB detected	Resistance result expected
Low	MTB detected	Usually interpretable
Very low	MTB detected	May be indeterminate
Trace	MTB detected	**Often MTB not detected**

Illustrative. As load falls, multicopy MTB targets stay detectable while resistance loci may drop below the amplification threshold.

1. Different analytical sensitivity

Ultra uses multicopy MTB detection targets optimized for very low bacillary burden.

2. Resistance targets need enough amplifiable DNA

A trace or very-low specimen may not provide sufficient target material across the XDR loci.

3. Sampling adds variability

Uneven bacillary distribution, specimen splitting, storage and repeat processing can change the aliquot tested.

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A Practical Response To Xpert MTB/RIF Ultra-Positive Or Xpert MTB/ XDR-Negative Discordance

Protect the patient pathway while preserving specimen integrity.

Confirm	Verify the Ultra result, specimen ID and RIF call.
Assess	Review Ultra category, specimen quality, volume, processing and storage.
Repeat intelligently	Use the best available residual or newly collected sputum according to local procedure.
Do not delay	Manage urgent RR-TB risk using the total clinical and laboratory picture.
Complete DST	Route for additional molecular, sequencing or phenotypic DST as indicated.

Avoid reflexing from a different low-quality specimen simply for convenience.

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What Xpert MTB/XDR* Detects, And What Each Call Means

The assay detects mutations associated with resistance; the result is not a complete phenotypic susceptibility profile.

INH

katG, fabG1, inhA promoter, oxyR–ahpC region

FQ

gyrA and gyrB QRDR

ETH

inhA promoter-associated mutations only

SLID

rrs and eis promoter-associated mutations

Resistance detected

A covered mutation associated with resistance was detected.

Resistance not detected

No covered resistance-associated mutation was detected.

Indeterminate

The assay could not confidently assign the resistance call.

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Why Xpert MTB/XDR* Does Not Report “High / Medium / Low” MTB

Assay outputs follow assay purpose.

Ultra

Primary purpose
Highly sensitive MTB detection + RIF

MTB target architecture
Supports semiquantitative concentration bands

Output
High • Medium • Low • Very Low • Trace

MTB/XDR

Primary purpose
Extended rapid resistance detection

Target architecture
Multiple MTB and resistance-associated loci

Output
Qualitative MTB + resistance calls

Do not derive or manually add a bacillary-load category to an MTB/XDR result.

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Five Implementation Choices Determine Whether Rapid DST Changes Outcomes

Design the pathway around the patient, not the cartridge.

1

Define eligibility

Who receives reflex Xpert MTB/XDR*?

2

Preserve the specimen

Enough well-mixed sputum and clear custody

3

Minimize delay

Same-day or next-step reflex wherever feasible

4

Route results

Results reach the treatment decision-maker

5

Monitor the cascade

Track eligible, tested, successful and acted-on

The KPI is not tests performed. It is patients started promptly on an appropriate regimen.

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Three Take-Home Messages

What to carry out of this session.

1

Xpert MTB/RIF Ultra* is the sensitive front door

MTB detection, semiquantitative category and a RIF call.

2

Xpert MTB/XDR* extends rapid DST

Use as a reflex on an eligible MTB-positive specimen.

3

Workflow determines impact

Preserve specimen, reduce delay, route results and act.

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“ Innovation is about designing diagnostics that consistently produce actionable answers and enable clinicians to act with confidence.”

Dr. Connie Savor
Chief Medical Officer, *Cepheid*

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