Improving TB Management: Clinical Applications and Benefits of the Xpert® MTB/XDR Assay

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Burden of MDR/XDR TB Disease

Gap in Diagnosis Remains

Estimates of TB Disease Burden in 2023	Number (95% CI)
Total TB Mortality	1.25 million deaths (1.13–1.37 million)
Total TB Incidence	10.8 million (10.1-11.7)
TB case notification	8.2 million
MDR/RR-TB incidence	400 000 (360 000–440 000)

Large global gap

Estimated number of people who fell ill with TB - the number of people newly diagnosed = **2.6 million people**

Inadequate use of Rapid Diagnostic tests

Only 48% of the 8.2 million people newly diagnosed with TB in 2023 (up from 47% in 2022 and 38% in 2021 and 33% in 2020.)

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Guidelines for MDR/XDR TB Diagnostics

Xpert® MTB/XDR: WHO Prequalification: 17 October 2025

A New milestone in the global fight against tuberculosis (TB)

This designation affirms the test's compliance with the WHO's rigorous standards for quality, safety, and performance, and enables procurement through international agencies.

CE-IVD. In Vitro Diagnostic Medical Device. May not be available in all countries

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New Recommendations in 2025 (Adult pulmonary TB)

Table A. Recommendations in the WHO consolidated guidelines on tuberculosis. Module 3: diagnosis, fourth edition

Automated

→

→

Manual

→

PLHIV:
concurrent testing with automated NAAT and LF_LAM

→

NEW

1. For adults and adolescents with signs or symptoms of TB or who screened positive[1] for pulmonary TB, low-complexity **automated** NAATs should be used on respiratory samples as initial diagnostic tests for TB, rather than smear microscopy or culture.

   (Strong recommendation, high certainty of evidence)

NEW

2. For people with bacteriologically confirmed TB[2], low-complexity **automated** NAATs should be used on respiratory samples as initial tests for detection of resistance to rifampicin, rather than culture-based DST.

   (Strong recommendation, high certainty of evidence)

NEW

6. For adults and adolescents with signs or symptoms or who screen positive for pulmonary TB, low-complexity **manual** NAATs should be used on respiratory samples as initial diagnostic tests for TB, rather than smear microscopy or culture.

   (Strong recommendation, high certainty of evidence)

Strong recommendations with high certainty of evidence

NEW

7. For adults and adolescents with HIV who have signs or symptoms of TB, screen positive for TB, are seriously ill or have advanced HIV disease, **concurrent testing** using low-complexity automated NAATs on respiratory samples and LF-LAM on urine should be used as the initial diagnostic strategy for diagnosing TB, rather than low-complexity automated NAATs on respiratory samples alone.

   (Strong recommendation, low certainty of evidence)

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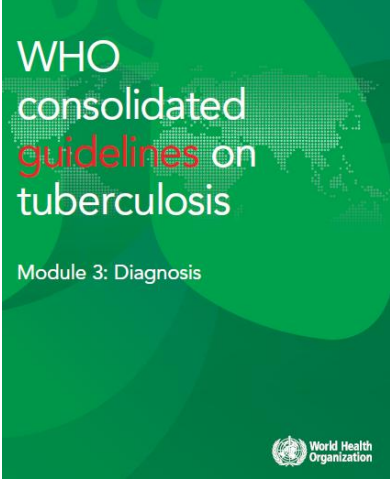# What are the available tools to reach the TB Elimination goals?

Table 1.1.1. Classes and products of TB tests for detection of TB, drug-resistant TB and TB infection included in the current guidelines

Technology class	Included products
Initial tests for TB diagnosis with drug-resistance detection	
NEW: Low-complexity automated nucleic acid amplification tests (NAATs) for detection of TB and resistance to rifampicin	Xpert® MTB/RIF and Xpert MTB/RIF Ultra (Cepheid) Truenat® MTB Plus and Truenat MTB-RIF Dx (Molbio)
Moderate-complexity automated NAATs for detection of TB and resistance to rifampicin and isoniazid	Abbott RealTime® MTB and Abbott RealTime MTB RIF/INH (Abbott) BD MAX™ MDR-TB (Becton Dickinson) cobas® MTB and cobas MTB-RIF/INH (Roche) FluoroType® MTB and FluoroType MTBDR (Hain Lifescience/Bruker)
Initial tests for TB diagnosis without drug-resistance detection	
NEW: Low-complexity manual NAATs for detection of TB	Loopamp™ MTBC Detection Kit (TB LAMP) (Eiken Chemical)
Antigen detection in a lateral flow format (biomarker-based detection) (LF-LAM) for detection of TB	Determine™ TB LAM Ag (Alere/Abbott)

Technology class	Included products
Follow-on tests for detection of TB drug resistance	
Low-complexity automated NAATs for detection of resistance to isoniazid and second-line anti-TB agents	Xpert® MTB/XDR (Cepheid)
Line probe assays (LPAs) for detection of TB drug resistance	GenoType® MTBDRplus v1 and v2; and GenoType MTBDRsl (Hain Lifescience/Bruker) Genoscholar™ NTM+MDRTB II and Genoscholar PZA-TB II (Nipro)
Targeted next-generation sequencing (NGS) tests for detection of TB drug resistance	Deeplex® Myc-TB (GenoScreen/Illumina) AmPORE-TB® (Oxford Nanopore Technologies) TBseq® (Shengting Medical Technology Company)
Tests for TB infection	
Mycobacterium tuberculosis antigen-based skin tests (TBSTs)	Diaskintest® (Generium) Siiltibcy™ (Serum Institute of India) C-TST (Anhui Zhifei Longcom)
Interferon-gamma release assays (IGRAs)	T-SPOT.TB (T-Spot) (Revvity) TB-IGRA (Wantai BioPharm) QuantiFERON-TB Gold Plus (QFT-Plus) (QIAGEN) STANDARD E TB-Feron ELISA (SD BIOSENSOR)[3] LIAISON QFT-Plus CLIA (Diasorin)[3]
Tuberculin skin tests	Tuberculin purified protein derivative (PPD) products

NAAT: nucleic acid amplification test: TB: tuberculosis.

Intended Use of the Xpert® MTB/XDR*!

- The Xpert MTB/XDR test, performed on the GeneXpert Instrument Systems, is a qualitative, nested real-time polymerase chain rection (PCR) in vitro diagnostic test for the detection of extensively drug resistant (XDR) Mycobacterium tuberculosis (MTB) complex. DNA in unprocessed sputum samples, concentrated sediments prepared from sputum, or BD™ Mycobacterial Growth Indicator Tube (MGIT™) culture.

- In specimens where MTB is detected, the Xpert MTB/XDR test can also detect **isoniazid** (INH) resistance associated mutations in the **katG** and **fabG1** genes, **oxyR-ahpC intergenic region** and **inhA** promoter; **ethionamide** (ETH) resistance associated with **inhA** promoter mutations only; **fluoroquinolone** (FLQ) resistance associated mutations in the **gyrA** and **gyrB** quinolone resistance determining regions (QRDR); and **second line injectable drug** (SLID) associated mutations in the **rrs** gene and the **eis** promoter region.

- The Xpert MTB/XDR test is intended for use as a **reflex test for a specimen (unprocessed sputum, concentrated sputum sediments, or MGIT culture) that is determined to be MTB positive.** This test is intended as an aid in the diagnosis of XDR tuberculosis (TB) when used in conjunction with clinical and other laboratory findings.

Manufacturer- Independent Evaluations

Analytical Performance of the Xpert® MTB/XDR* for tuberculosis and expanded resistance detection *(Georghiou et al., Diagnostic Microbiology & Infectious Disease Journal, 2021.)*

1. LoD for MTB

The Xpert MTB/XDR assay demonstrated equivalent limit of detection to Xpert MTB/RIF.

2. Accuracy for INH, ETH, and SLID mutation detection

- 100% of tested INH, ETH, FQ, AMK, KAN, and CAP resistance mutations were detected.
- 78% of *gyrA* A90V, S91P, and D94A mutants detected as 'low FQ resistance' and 100% of *inhA* c-15t mutants as "low INH resistance"

3. Heteroresistance detection

100% detection of resistance with mixtures of 10% INH-R, 25% FQ-R 50% for ETH, AMK and KAN resistance, and 60% for CAP resistance.

Source
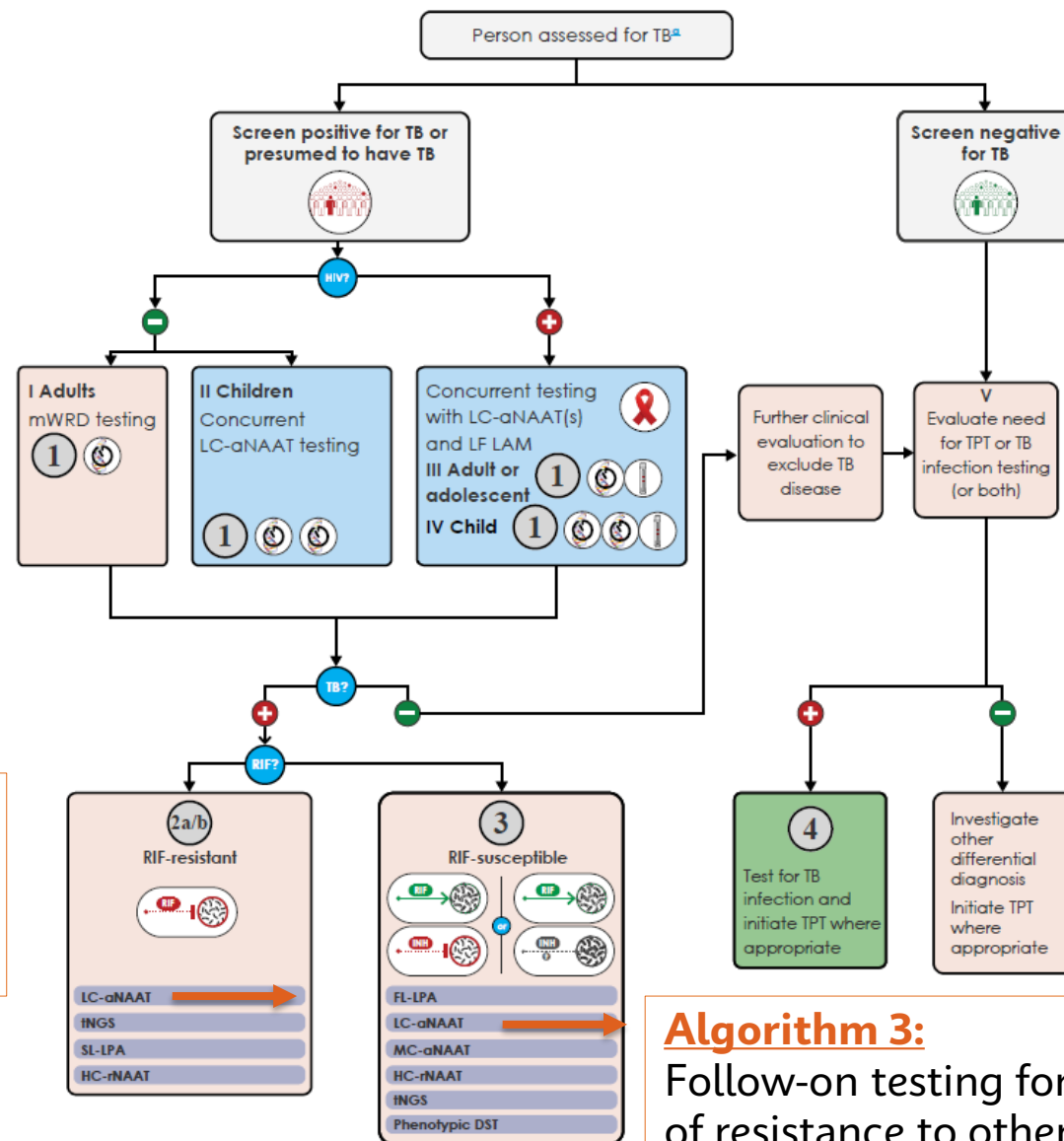1. Georghiou S. B, et al, Analytical performance of the Xpert MTB/XDRR assay for tuberculosis and expanded resistance detection, Diagnostic Microbiology & Infectious Disease, 2021.
https://doi.org/10.1016/j.diagmicrobio.2021.115397

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TB Testing diagnostic algorithm

Algorithm 1: WRDs as initial diagnostic tests for TB

Algorithm 2: DST for second-line drugs for people with MDR/RR-TB

Algorithm 3: Follow-on testing for RIF-S TB at risk of resistance to other drugs

Algorithm 4: Testing for TB infection

Evidence

High Diagnostic Accuracy for INH and FLQ Detection

A Katamba, et al. 2023

PLOS ONE

RESEARCH ARTICLE

Evaluation of Xpert MTB/XDR test for susceptibility testing of *Mycobacterium tuberculosis* to first and second-line drugs in Uganda

Achilles Katamba[1‡*], Willy Ssengooba[2,3,4‡*], James Sserubiri[2,4], Derrick Semugenze[2,4], George William Kasule[5], Abdunoor Nyombi[5], Raymond Byaruhanga[5], Stavia Turyahabwe[5], Moses L. Joloba[2,4,5]

1 Department of Medicine, School of Medicine, Clinical Epidemiology and Biostatistics Unit and Uganda Implementation Research Consortium, Makerere University, Kampala, Uganda, 2 Department of Medical Microbiology, Makerere University, Kampala, Uganda, 3 Lung Institute, Makerere University, Kampala, Uganda, 4 Biomedical Research Center, Makerere University, Kampala, Uganda, 5 Ministry of Health, National Tuberculosis, and Leprosy Programme, Kampala, Uganda

Diagnostic accuracy of Xpert® MTB/XDR test using phenotypic drug susceptibility test as a reference comparator

Drug (n)		R	S	Sensitivity n(%; 95% CI)	Specificity n(%; 95%CI)	PPV % (95%CI)	NPV % (95%CI)
INH (99)	R	58	4	58 (**89.2**; 79.1–95.5)	30 (**88.2**; 72.5–96.6)	**93.5** (84.2–98.2)	**81.1** (64.8–92.0)
	S	7	30				
FQ (100)	R	4	0	4 (**80.0**; 28.3–99.4)	95 (**100**; 96.2–100)	**100** (39.7–100)	**99.0** (94.3–99.9)
	S	1	95				
IAs (100)	R	—	—	N/A	100 (**100**; 96.3–100)	N/A	**100** (96.3–100)
	S	—	100				

Key: INH = Isoniazid, FQ = Fluoroquinolone, IAs = Injectable agents, N = Number, R = Resistant, S = Sensitive, CI = Confidence Interval, PPV = Positive Predictive Value, NPV = Negative Predictive Value, N/A = Not Applicable, * = Xpert® MTB/XDR test indeterminate (n = 1).

https://doi.org/10.1371/journal.pone.0284545.t001

→ **Xpert® MTB/XDR* has high sensitivity and specificity** for INH and FLQ detection compared to LPA and phenotypic DST

→ Xpert MTB/XDR **helps rule out FLQ resistance** for MDR-TB/RR-TB patients qualified **for a Bedaquiline-based regimen**

→ Xpert MTB/XDR **reduces the diagnostic challenges and dependencies** from highly complex tests such as LPA and culture-based DST

A Katamba, et al. 2023 https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0284545 Accessed Dec 2023

A Katamba, et al. 2023 https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0284545 Accessed Dec 2023

* CE-IVD. *In Vitro* Diagnostic Medical Device. May not be available in all countries. Not available in the United States.

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Expanding Drug-Resistant TB Diagnostics: Evidence & Outcomes

Marya Getchell[1*], John Pastor Ansah[2], Dodge Lim[3], Ramon Basilio[3], Francis Tablizo[4], Carmen Corpuz[3] and David Matchar[1,5]

Dynamic modeling (Philippines & Thailand):

- Universal Xpert MTB/XDR testing for all TB cases is cost-effective and offers the highest net benefit. (ICER: $1,808–$5,251 per DALY averted; highest net monetary benefit).

- Targeted testing for previously treated cases is also cost-effective but less impactful.

- tNGS detects more resistance but is not cost-effective for routine use due to its high costs and infrastructure requirements.
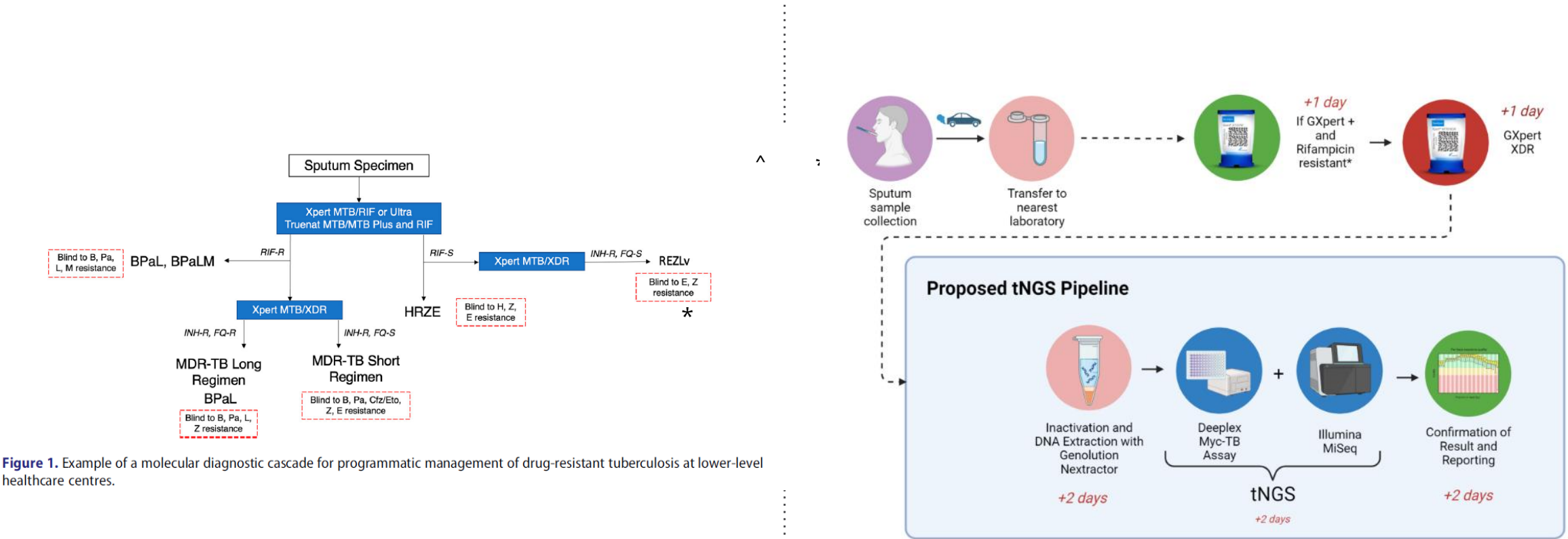
Outcomes:

- **Improved Health Impact:** More DR-TB cases detected and treated, reducing transmission, treatment failure, and mortality.

- **Programmatic Value:** Xpert MTB/XDR is practical, scalable, and compatible with existing GeneXpert infrastructure.

- **Policy Implication:** Supports adoption of Xpert MTB/XDR for all TB cases in high-burden settings; tNGS reserved for high-risk groups as costs decrease.

Xpert MTB/XDR shows to be a cost-effective option for rapid, expanded drug resistance detection in high-burden TB settings

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Example of Diagnostic Cascade for Management of TB

Figure 1. Example of a molecular diagnostic cascade for programmatic management of drug-resistant tuberculosis at lower-level healthcare centres.

Targeted NGS Considerations – TB Diagnostic Alogrithm

Sophia B Georghiou [1,2] Nestani Tukvadze,[3,4,5] Camilla Rodrigues,[6] Shaheed Vally Omar,[7] Andrea Maurizio Cabibbe [8] Marva Seifert,[1] Swapna Uplekar,[1] Nazir Ismail [9] Morten Ruhwald,[1] Anita Suresh,[1] Rebecca E Colman[1,10]

Key Outcomes

High Accuracy: 88–93% of tested samples.

Broad Resistance Detection: tNGS identified resistance to 73–86% of drugs

Recommendation

- **Xpert MTB/XDR** is used as a reflex test for drug resistance in TB cases.
- tNGS (targeted Next-Generation Sequencing) is then employed by centralized laboratories for comprehensive resistance profiling, following preliminary detection by Xpert.
- Integrated workflow enables prompt and tailored treatment decisions

Incorporating tNGS as a follow-up to Xpert MTB/XDR enables faster, more effective TB treatment and safeguards the use of novel therapies.

In Summary

- Rapid diagnostics is needed close the gap in early TB detection and reduce undiagnosed cases.

- Using low-complexity NAAT tests enables fast, accurate identification of TB and drug resistance, supporting timely treatment.

- Integrating molecular tests and targeted sequencing can provide comprehensive resistance profiling and tailored therapy.

- Universal rapid testing shows to be more cost-effective in high-burden settings; reserve advanced sequencing for complex or high-risk cases.

* Footnote source space

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Q&A

Thank You

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