Molecular diagnostic tests for isoniazid-resistant tuberculosis: a scoping review

Thi Mai Nguyen, Emily Lai-Ho MacLean, Xiaomei Zhang, Sophia B Georghiou, Hui Xia, Justin Beardsley, Meru Sheel, Thu-Anh Nguyen, Ben J Marais, Greg J Fox

The paucity of diagnostic tests for isoniazid-resistant tuberculosis is concerning, given its status as the most common form of drug-resistant tuberculosis and a gateway to multidrug-resistant diseases. Molecular drug-susceptibility testing has improved access to timely diagnosis of rifampicin-resistant tuberculosis, but testing for isoniazid-resistant tuberculosis still remains rare. In this Review, we assessed the characteristics of molecular drug-susceptibility testing for detection of isoniazid-resistant tuberculosis, referencing the WHO target product profiles. 9243 citations were screened to select 238 studies published between 2000 and 2024. The diagnostics options have expanded rapidly since 2020, with 27 nucleic acid amplification tests, eight line probe assays, five DNA microarrays, two targeted next-generation sequencing platforms, and two whole-genome sequencing platforms. Most of the evaluated molecular drug-susceptibility tests met diagnostic performance targets but were often complex and costly. Although a few low-complexity nucleic acid amplification tests met key target product profile criteria, additional field validation and greater efforts are needed to ensure optimal feasibility and affordability for low-resource settings.

Introduction

Drug-resistant tuberculosis is a public health threat and a major barrier to the achievement of the WHO End TB strategy targets.[1] Isoniazid-resistant, rifampicin-susceptible tuberculosis is the most common form of drug-resistant tuberculosis, affecting an estimated 7·4% of newly diagnosed and 11·4% of previously treated individuals with tuberculosis globally.[2] The *katG* S315T mutation is the most common isoniazid resistance-conferring mutation and frequently arises before rifampicin resistance across all *Mycobacterium tuberculosis* lineages, geographical regions, and time periods, highlighting isoniazid resistance as a gateway for generation of multidrug resistance (resistance to isoniazid and rifampicin).[3] However, the most widely used front-line tuberculosis diagnostic test (ie, GeneXpert MTB/RIF Ultra) only detects rifampicin resistance, but not isoniazid resistance. Treating individuals with undetected isoniazid resistance using standard first-line regimens is associated with poorer treatment outcomes and increased acquisition of multidrug-resistant tuberculosis as compared with treating those with drug-susceptible tuberculosis, particularly in settings with a high prevalence of isoniazid-resistant tuberculosis.[4] Conversely, individuals with rifampicin-resistant tuberculosis who do not have multidrug-resistant tuberculosis (ie, are isoniazid susceptible) could still benefit from treatment with isoniazid, rather than more costly and poorly tolerated multidrug-resistant tuberculosis treatments. This implication is especially relevant in settings with a high burden of rifampicin monoresistance.[5,6] Therefore, early detection of isoniazid-resistant tuberculosis is crucial to facilitate optimal treatment decisions.[7]

Drug-susceptibility testing can be performed phenotypically or genotypically. Traditionally, diagnosis of isoniazid-resistant tuberculosis relies on culture-based phenotypic drug-susceptibility testing (pDST), which takes 4–6 weeks after microbiological *M tuberculosis* confirmation.[8] The introduction of rapid molecular testing has substantially shortened the time to tuberculosis diagnosis and detection of drug resistance by facilitating the detection of mycobacterial DNA in clinical samples (direct testing) or culture (indirect testing), or both.[9] Additional advantages of rapid molecular testing include high-throughput testing capacity, fewer biosafety requirements, and lower cost as compared with conventional pDST.[10] Molecular drug-susceptibility testing (mDST) can be grouped into five broad classes: line probe assays (LPAs), nucleic acid amplification tests (NAATs), DNA microarrays, whole-genome sequencing, and targeted next-generation sequencing (tNGS).[11] Whole-genome sequencing also serves as an alternative reference standard. Some tests require a separate DNA-extraction step followed by complex manual amplification and hybridisation procedures, which, in turn, require rigorous contamination-control measures and strict spatial separation of work areas. These requirements pose substantial operational challenges for laboratories, particularly in low-resource settings.

Isoniazid resistance is mostly conferred by mutations in the *katG*, *inhA,* and *fabG1* genes or the *oxyR'-ahpC* intergenic region.[12–14] Globally, *katG315* (64·2%) and *inhA-15* (19·2%) mutations are responsible for the vast majority of isoniazid resistance.[12] Since 2008, WHO has endorsed several LPAs and NAATs for rapid detection of isoniazid resistance by screening *katG* and *inhA* promoter mutations.[9] DNA microarray-based assays have been considered a reliable tool for detecting drug-resistant tuberculosis since the 2010s.[15] In 2024, WHO recommended next-generation sequencing, including whole-genome sequencing and tNGS, for rapid and accurate broad-spectrum drug-susceptibility testing.[16] Although whole-genome sequencing provides comprehensive genomic data, tNGS focuses on specific genetic loci.[17]

Lancet Microbe 2026; 7: 101362

Published Online March 20, 2026
https://doi.org/10.1016/j.lanmic.2026.101362

National Health and Medical Research Council (NHMRC) Clinical Trials Centre (T M Nguyen MSc, E L-H MacLean PhD, Prof G J Fox PhD) **and Sydney Infectious Diseases Institute (Sydney ID)** (T M Nguyen, E L-H MacLean, X Zhang PhD, J Beardsley PhD, Prof M Sheel PhD, Prof T-A Nguyen PhD, Prof B J Marais PhD, Prof G J Fox), **Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia; Sydney School of Public Health, The University of Sydney, Sydney, NSW, Australia** (T M Nguyen, Prof M Sheel, Prof T-A Nguyen); **NHMRC Centre for Research Excellence in Tuberculosis (TB CRE) and WHO Collaborating Centre for Tuberculosis, Sydney, NSW, Australia** (T M Nguyen, E L-H MacLean, Prof T-A Nguyen, Prof B J Marais, Prof G J Fox); **Centre for Infectious Diseases and Microbiology-Public Health** (X Zhang) **and Centre for Infectious Diseases and Microbiology** (J Beardsley), **Westmead Hospital, Western Sydney Local Health District, Sydney, NSW, Australia; End TB Dx Consulting, San Diego, CA, USA** (S B Georghiou PhD); **Centre for Tuberculosis Control and Prevention, Chinese Centre for Disease Control and Prevention, Beijing, China** (H Xia PhD); **Department of Microbiology, Hanoi Medical University, Hanoi, Viet Nam** (J Beardsley); **The University of Sydney Vietnam Institute, Ho Chi Minh City, Viet Nam** (Prof T-A Nguyen)

Correspondence to:
Prof Greg J Fox, NHMRC Clinical Trials Centre, Faculty of Medicine and Health, University

In 2024, updated WHO target product profiles (TPPs) outlined minimal and optimal requirements or specifications (hereafter referred to as characteristics) of diagnostic tests for detection of tuberculosis and drug resistance.[18,19] mDST characteristics were described in the TPPs, focusing on performance, scope of use, pricing, and operational characteristics. Existing reviews of mDST for isoniazid resistance have primarily focused on diagnostic accuracy, covering LPAs,[20,21] NAATs,[22–24] whole-genome sequencing,[25] and tNGS.[26] However, no comprehensive review has compared the scope of use, pricing, and operational characteristics. These factors are crucial to identify the suitability and applicability of each mDST, which depend on the available resources, technical capacity, and infrastructure of laboratories and health-care settings of intended use.

This scoping review aimed to systematically compare mDST for detection of isoniazid-resistant tuberculosis with underlying, published performance evaluations across four domains: performance, scope, pricing, and operational characteristics, with reference to the 2024 WHO TPP criteria. The goal is to inform test developers, implementers, and policy makers on the suitability of the latest tests and identify gaps for future innovation.

Methods

This scoping review conformed to the Joanna Briggs Institute guidelines,[27] as documented in a protocol registered with the Open Science Framework,[28] and the PRISMA-ScR checklist (appendix pp 3–4).[29]

Search strategy and selection criteria

We searched four English academic databases (MEDLINE, Embase, Web of Science, and Global Index Medicus WHO), three registries (ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, and International Standard Randomized Controlled Trials Number registry), and three Chinese databases (Chinese National Knowledge Infrastructure, CQVIP Chinese Journals Platform, and Wanfang Data) for studies published from Jan 1, 2000, to Dec 23, 2024 (appendix pp 5–7). We did not apply restrictions on the language of the publication, and we translated non-English publications using Google Translate. A native speaker (XZ) reviewed Chinese publications. We screened reference lists of the included reports to identify additional eligible studies.

Eligibility criteria

We included evaluative studies of manufacturer-developed mDST for isoniazid-resistant tuberculosis. In-house tests and prototypes or previous versions of a test were excluded, given that the latest products might have undergone alterations or improvements from their prototype or previous versions. For studies without a specified GenoType MTBDR*plus* version, version 1.0 was assumed for studies published before 2011, whereas studies published after 2011 were included but not pooled with those explicitly specifying version 2.0. All tests had to have at least one evaluative study providing data on characteristics of interest to be included in this Review. We excluded studies that focused on resistance mechanisms or the epidemiology of isoniazid-resistant tuberculosis, studies that did not use any WHO-approved pDST[30] or whole-genome sequencing, or both, as a reference standard, and studies that used non-molecular assays.

We extracted data regarding key characteristics prioritised by the WHO TPP author team,[18] including performance characteristics (diagnostic sensitivity, diagnostic specificity, analytical sensitivity, analytical specificity, and indeterminate results), scope characteristics (target user and drug resistance tested), pricing characteristics, and operational characteristics (manual sample preparation, time-to-result, power requirements, maintenance, and calibration). Only WHO-approved tests[9] or tests having at least one evaluation entry that met both the diagnostic sensitivity and specificity targets for detection of isoniazid-resistant tuberculosis were included in the data analysis of scope, pricing, and operational characteristics. We did not apply any exclusion criteria regarding patient characteristics or sample size to reduce the risk of removing early-stage studies.

We considered both cross-sectional and cohort studies presenting primary data. We included both laboratory validation and clinical studies, incorporating fresh pulmonary and extrapulmonary samples, stored specimens, and culture isolates. We excluded secondary evidence (eg, reviews) but checked reference lists for potentially eligible studies. For scope, pricing, and operational characteristics, we also consulted manufacturers' documents (eg, instructions for users and package inserts) and reports and product catalogues from WHO and Foundation for Innovative New Diagnostics. If discrepancies arose between the selected studies and the manufacturers' documentation, then we reported both sources and discussed any key differences.

Data extraction

All searched citations were collated in EndNote 21, and duplicates were removed. English titles, abstracts, and full texts, wherever available, were screened by TMN and crosschecked by EL-HM using Covidence. TMN extracted data from the included English studies and XZ from the included Chinese studies using a data-extraction form (appendix pp 8–11); 20% of these studies were then validated by EL-HM. There was high agreement on the extracted results. If multiple studies were identified as using the same cohort to evaluate the same test using the same reference standard, then the overlap was carefully assessed, and the study with the larger dataset or the more recent publication, or both, was retained. We contacted the authors of the studies to request missing or additional data, wherever required.

Data analysis

Some eligible studies reported on more than one test or reference standard. We defined each specific assessment as

of Sydney, Sydney 2050, NSW, Australia
gregory.fox@sydney.edu.au

See **Online** for appendix

an evaluation entry; thus, a single study could contribute more than one evaluation entry, which served as the unit of analysis. Data were synthesised using Excel and visualised using Python. We used the WHO 2024 TPP targets for the characteristics of interest for comparisons in all the evaluations.[18]

We recalculated sensitivity and specificity from the extracted 2×2 tables and compared them with the reported values, wherever data permitted; otherwise, we used the original study-reported values. Indeterminate rates, wherever not reported, were calculated from the sum of results in the 2×2 table and the total number of samples tested. If the rate was 0%, then this finding was recorded; otherwise, the rate was described as not reported, due to potential discrepancies from invalid, no result, or error samples. We stratified performance characteristics by reference standard (ie, pDST, whole-genome sequencing, or a composite reference standard) and specimen type (ie, testing directly on clinical samples *vs* indirect testing on isolates cultured from clinical samples), but not by age or tuberculosis location (pulmonary *vs* extrapulmonary) due to paucity of data.

Pricing characteristics considered only consumables and reagents, as specified in the WHO TPP.[18] We converted costs to US dollars for 2025 using the Xe Currency Converter and adjusted previous year US dollar values to those for 2025 using the US Inflation Calculator. If the year of pricing data was not mentioned, then we used the publication year for adjustment.

Results

Our search identified 9243 potential studies of interest, with 238 studies and 343 evaluation entries included in the final analysis (figure 1). These evaluations covered 44 mDST for isoniazid-resistant tuberculosis, including eight LPAs, 27 NAATs, five DNA microarrays, two whole-genome sequencing platforms, and two tNGS tests (appendix pp 12–22).

Representativeness of the study results

Among the 44 mDST for isoniazid-resistant tuberculosis with published evaluations, two LPAs, five NAATs, and two tNGS tests have received WHO approval. Collectively, the 343 evaluation entries assessed 135 227 samples, primarily from countries with high incidence of tuberculosis,[1] such as India (69 [20·1%] of 343 entries), China (68 [19·8%]), and South Africa (30 [8·8%]; figure 2). The most frequently evaluated test classes were LPA (eight tests, 149 [43·4%] of 343 entries), NAAT (27 tests, 92 [26·8%]), and whole-genome sequencing (two platforms, 62 [18·1%]); all were assessed in diverse global settings. In contrast, DNA microarray (five tests, 32 [9·3%]) and tNGS (two tests, eight [2·3%]) tests were predominantly evaluated in China and India (appendix p 23).

Among WHO-approved tests, GenoType MTBDR*plus* version 2.0, Xpert MTB/XDR, BD MAX MDR-TB, and GenoScreen Deeplex Myc-TB were evaluated in both adults and children, whereas cobas MTB-RIF/INH and Abbott RealTime MTB RIF/INH were evaluated in adults only. Evaluation entries in the three remaining WHO-approved tests (ie, Genoscholar NTM+MDRTB II, FluoroType MTBDR version 2.0, and AmPORE-TB) and most newer tests failed to report the age of participants (appendix pp 12–22). Notably, only one of the 343 evaluation entries specified the inclusion of children, exclusively enrolling children younger than 15 years of age. The tests of interest were primarily evaluated in people with pulmonary tuberculosis (189 [55·1%] of 343) or both pulmonary and extrapulmonary tuberculosis (49 [14·3%]); only 25 (7·3%) of the entries involved individuals with extrapulmonary tuberculosis (appendix pp 12–22).

Different molecular diagnostic test classes

Overall, mDST options for isoniazid-resistant tuberculosis have been growing rapidly; 190 (55·4%) of the 343 entries were evaluated from 2020 to 2024, 124 (36·2%) from 2015 to 2019, 28 (8·2%) from 2010 to 2015, and one (0·3%) from 2005 to 2010 (figure 3).

Eight LPAs were evaluated, with GenoType MTBDR*plus* first receiving WHO approval in 2008 (for GenoType MTBDR*plus* version 1.0) and Genoscholar NTM+MDRTB II in 2015 (figure 3). GenoType MTBDRplus version 2.0 was the most frequently evaluated test, assessed in 122 (35·6%) of the 343 entries. From 2020 to 2024, three newer LPAs were introduced, each with only one reported evaluation entry.

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WHO approved one low-complexity automated NAAT (Xpert MTB/XDR) and four moderate-complexity automated NAATs (cobas MTB-RIF/INH, FluoroType MTBDR version 2.0, Abbott RealTime MTB RIF/INH, and BD MAX MDR-TB),[9] with most evaluations conducted from 2020 to 2024 (figure 3). Among the 92 entries for NAATs available since 2010, MeltPro TB/INH and Anyplex II assays were frequently evaluated, but neither has received WHO approval. 13 newer NAATs were introduced between 2020 and 2024, each represented by one or two entries, except MDR/MTB ELITe MGB Kit, with five entries. No DNA microarrays have received WHO approval, although 32 evaluations of five microarrays have been performed. GeneChip has had multiple evaluations (25 [78·1%] of 32) in China,[11] where it has been widely implemented.[31–42] None of the four other DNA microarrays have been in widespread use.

Given its comprehensive and unbiased assessment of all genomic changes, whole-genome sequencing sometimes contributed to the reference standard. WHO has not formally approved any specific whole-genome sequencing assay or platform. The short-read Illumina platforms, including MiSeq, HiSeq, NovaSeq, and NextSeq, have been more frequently evaluated (54 [87·1%] of 62) than the long-read Oxford Nanopore platform (ONT MinION Mk1B Multiplex, eight [12·9%]). Given the evolving nature of bioinformatics analyses and the ability to incorporate new drug-resistance mutation information, the application of

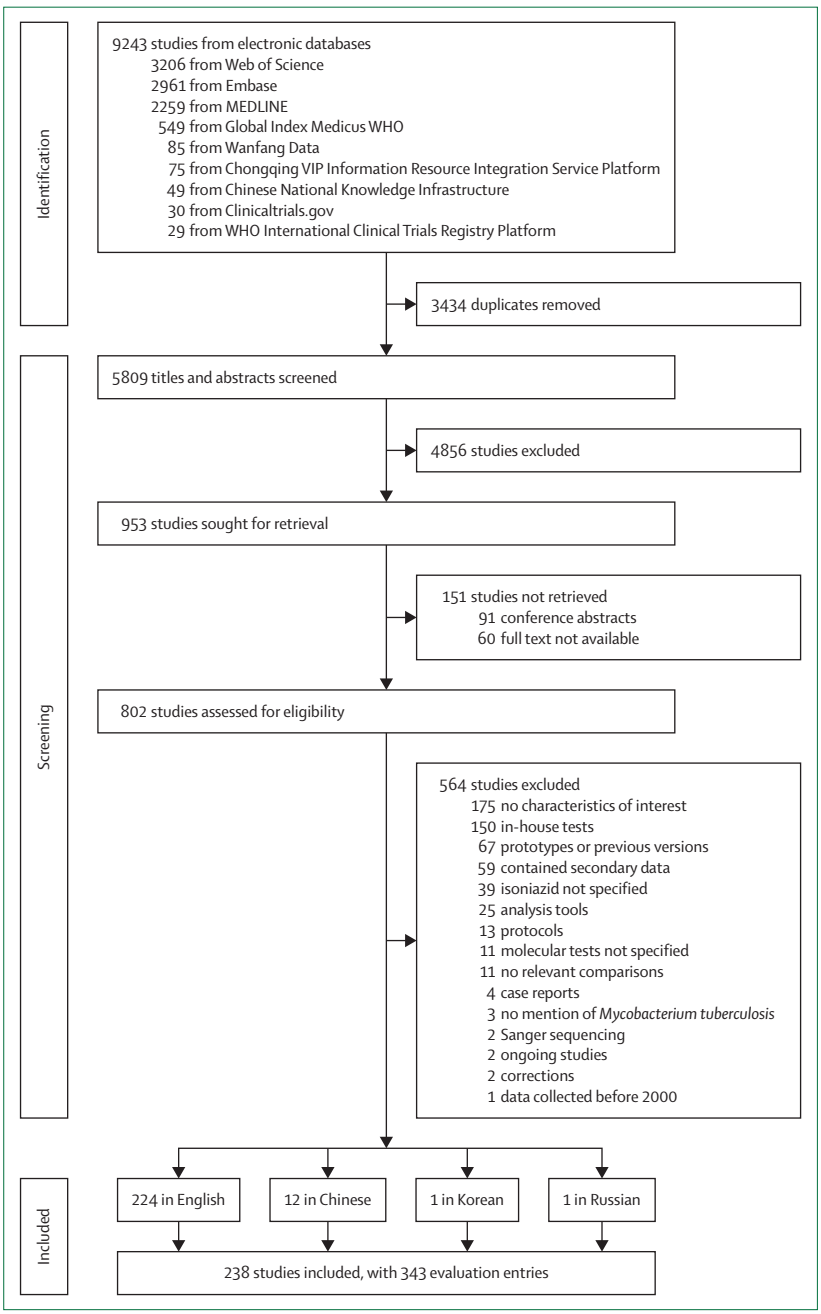


Figure 1: **PRISMA-ScR flowchart for the study selection process**

standard accuracy metrics is complicated. Two tNGS assays have received WHO approval, with GenoScreen Deeplex Myc-TB (seven [87·5%] of eight) being evaluated much more frequently than AmPORE-TB (one [12·5%]).

Diagnostic performance

Among the 323 entries with performance data, 307 (95·1%) reported both sensitivity and specificity. 279 (90·9%) of the 307 entries assessed diagnostic performance against pDST, 20 (6·5%) evaluated analytical performance against whole-genome sequencing (appendix p 24), and eight (2·6%) used a composite reference standard (appendix p 25).

Diagnostic performance against pDST

All entries for diagnostic performance were plotted on receiver operating characteristic plots across five test classes, stratified as WHO-approved tests and tests without WHO approval to date (figure 4). WHO-approved tests showed high diagnostic accuracy. Of the 139 entries for WHO-approved tests, 39 (28·1%) met both targets of 90% sensitivity and 98% specificity for detection of isoniazid-resistant tuberculosis,[18] only 27 (19·4%) achieved the minimum sensitivity target, and 41 (29·5%) met the specificity target (figure 4). GenoType MTBDR*plus* version 2.0, Genoscholar NTM+MDRTB II, and Abbott RealTime MTB RIF/INH performed better using culture isolates than using clinical samples. BD MAX MDR-TB, cobas MTB-RIF/INH, and FluoroType MTBDR version 2.0 were evaluated exclusively using clinical samples. Xpert MTB/XDR showed higher specificity and GenoScreen Deeplex Myc-TB showed superior sensitivity when tested directly on clinical samples than when tested on culture isolates (figure 5).

140 entries evaluated tests that were not yet approved by WHO. In the LPA class, AID TB Resistance LPA (INH/RIF module) and REBA MTB-MDR achieved diagnostic sensitivity and specificity of 80·0–100·0% in both direct and indirect testing (figures 4, 5). Among the 30 entries that met both TPP targets, 12 (40·0%) were NAATs, including Smart Sure MDR-TB Kit,[43,44] STANDARD M10 MDR-TB,[45,46] Conlight TB&DR,[47] and MALDI-TOF-MS.[48] Although MeltPro TB/INH did not consistently meet the targets, it showed good sensitivity (83·3–96·4%) and specificity (84·0–98·3%), performing better on clinical samples than on culture isolates. Among the 43 entries that met only the specificity target, 11 NAATs accounted for 17 entries (39·5%), most commonly the Anyplex assays, which met the specificity target across all entries. The diagnostic performance of GeneChip was evaluated in 24 entries, and despite suboptimal sensitivity (60·4–97·3%), it consistently showed good specificity (81·0–99·6%). XDR-TB TruArray exceeded both targets in its single entry.[49] Other microarrays were assessed in only one to three entries. The whole-genome sequencing Illumina platform contributed 14 (46·7%) of the 30 entries that met both performance targets, including five large-scale entries conducted in China,[50] Singapore,[51] the USA,[52] Australia,[53] and multiple countries combined,[54] all of which were performed on culture isolates.

Performance against whole-genome sequencing and a composite of pDST or sequencing

Compared with whole-genome sequencing, mDST for isoniazid-resistant tuberculosis showed high analytical performance, with nine (45·0%) of 20 entries meeting both the WHO TPP targets of 98% (appendix p 24). Compared

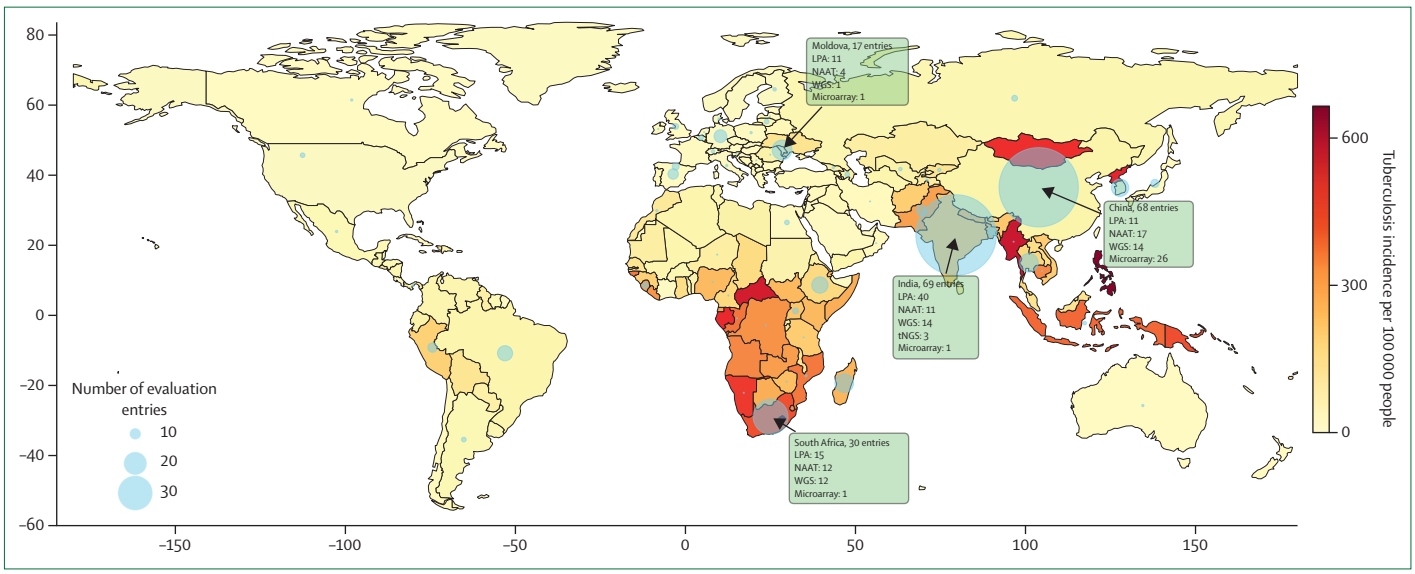


Figure 2: **Geographical locations where evaluations of molecular diagnostic tests for isoniazid-resistant tuberculosis were conducted (2000–24) relative to estimated tuberculosis burden (WHO 2023 estimates)**

The top countries with the highest total number of evaluation entries for molecular diagnostic tests for isoniazid-resistant tuberculosis from 2000 to 2024 are highlighted in green boxes. Some entries evaluated a test across multiple settings but did not report the number of samples for each country. LPA=line probe assay. NAAT=nucleic acid amplification test. tNGS=targeted next-generation sequencing. WGS=whole-genome sequencing.

with a composite pDST or sequencing reference standard, GenoType MTBDR*plus* version 2.0, cobas MTB-RIF/INH, and Xpert MTB/XDR consistently showed optimal specificity despite not always meeting the sensitivity targets (appendix p 25).

Indeterminate rates

The WHO TPP minimum target for indeterminate result rate is less than 10%. Among 13 tests with reported rates, six were approved by WHO and reported wide ranges: GenoType MTBDR*plus* version 2.0, 0·0–14·0%; cobas MTB-RIF/INH, 0·0–13·5%; FluoroType MTBDR version 2.0, 0·0–11·0%; and GenoScreen Deeplex Myc-TB, 0·0–20·0%; with only Genoscholar NTM+MDRTB II and Xpert MTB/XDR reporting consistently less than 10% (appendix pp 12–22).

Scope, pricing, and operational characteristics

The scope, pricing, and operational characteristics of nine WHO-approved tests and 13 additional tests not yet approved by WHO are given in the table, each with at least one entry meeting both the diagnostic performance targets. LPA, DNA microarray, whole-genome sequencing, and tNGS tests required moderate to extensive training for health-care workers, whereas all NAATs required minimal to moderate training, meeting the target for the intended test users. Most tests could only detect isoniazid-resistant and rifampicin-resistant tuberculosis, missing the minimal target for priority of antituberculosis drugs by not detecting fluoroquinolone resistance. Whole-genome sequencing and tNGS met the target, as they could simultaneously detect resistance to a wide range of tuberculosis drugs.

Accurate prices for consumables and reagents were available for only six tests and were generally more than the WHO target of US$10–15 per test (appendix pp 12–22). Notably, Illumina whole-genome sequencing ($211·1–307·6) and GenoScreen Deeplex Myc-TB ($150–240) were far more expensive; however, expert input indicated that the total cost per test dropped to $40–70 in 2025 in China. Prices for consumables and reagents of the GeneChip, Anyplex II MTB/MDR/XDR, and MDR/MTB ELITe MGB Kit were also substantially more than the target. Among the nine WHO-approved tests, five achieved the target price only when purchased through specific centralised channels: GenoType MTBDR*plus* version 2.0, Xpert MTB/XDR, BD MAX MDR-TB, and FluoroType MTBDR version 2.0 through the Stop TB Partnership's Global Drug Facility (GDF); and cobas MTB-RIF/INH through Roche's Global Access Program for low-resource countries. LPAs and NAATs generally involved no more than five manual steps, meeting the minimal target. Some NAATs required only one step. DNA microarrays, whole-genome sequencing, and tNGS were generally more complex than the TPP target.

Time-to-result for GenoType MTBDR*plus* version 2.0 was 6–9 h rather than the 5 h reported by the manufacturer. Other LPAs typically provided results within a day. NAATs and GeneChip generally had a time-to-result under 6 h, meeting the minimal target. Whole-genome sequencing and tNGS had a time-to-result of approximately 48 h when tested directly on sputum, with a much longer

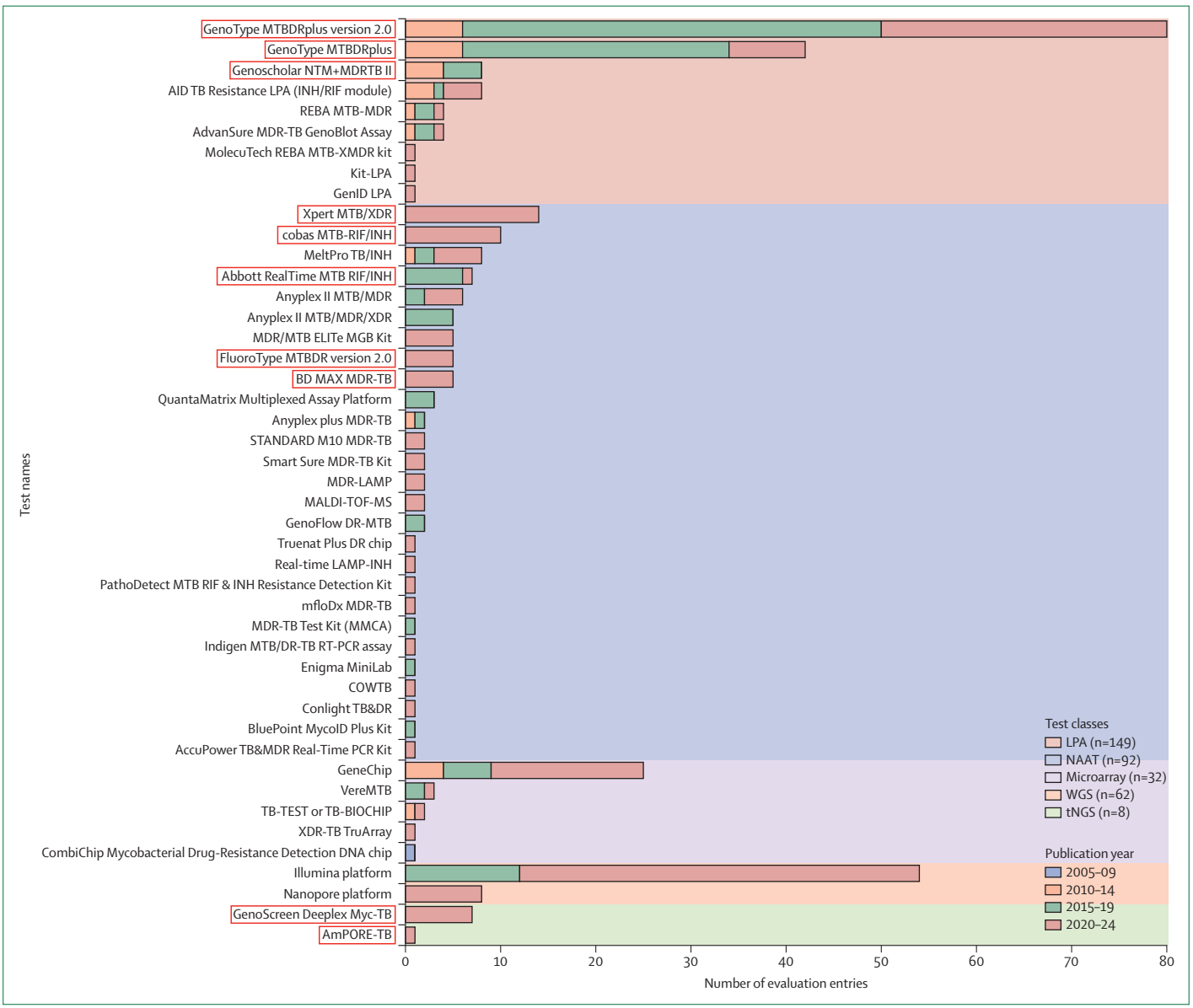


Figure 3: **Evaluation entries assessing molecular diagnostic tests for isoniazid-resistant tuberculosis (2000–24) by test class, test type, and publication year**
WHO-approved tests for isoniazid-resistant tuberculosis detection are highlighted in red boxes. Studies that evaluated the GenoType MTBDR*plus* assay and were published after 2011 but without specifying the assay version are grouped under GenoType MTBDR*plus*. The size of the markers denotes the number of samples tested in each evaluation entry. LPA=line probe assay. NAAT=nucleic acid amplification test. tNGS=targeted next-generation sequencing. WGS=whole-genome sequencing.

time-to-result when performed on culture isolates, given the time required for culturing.[55–57]

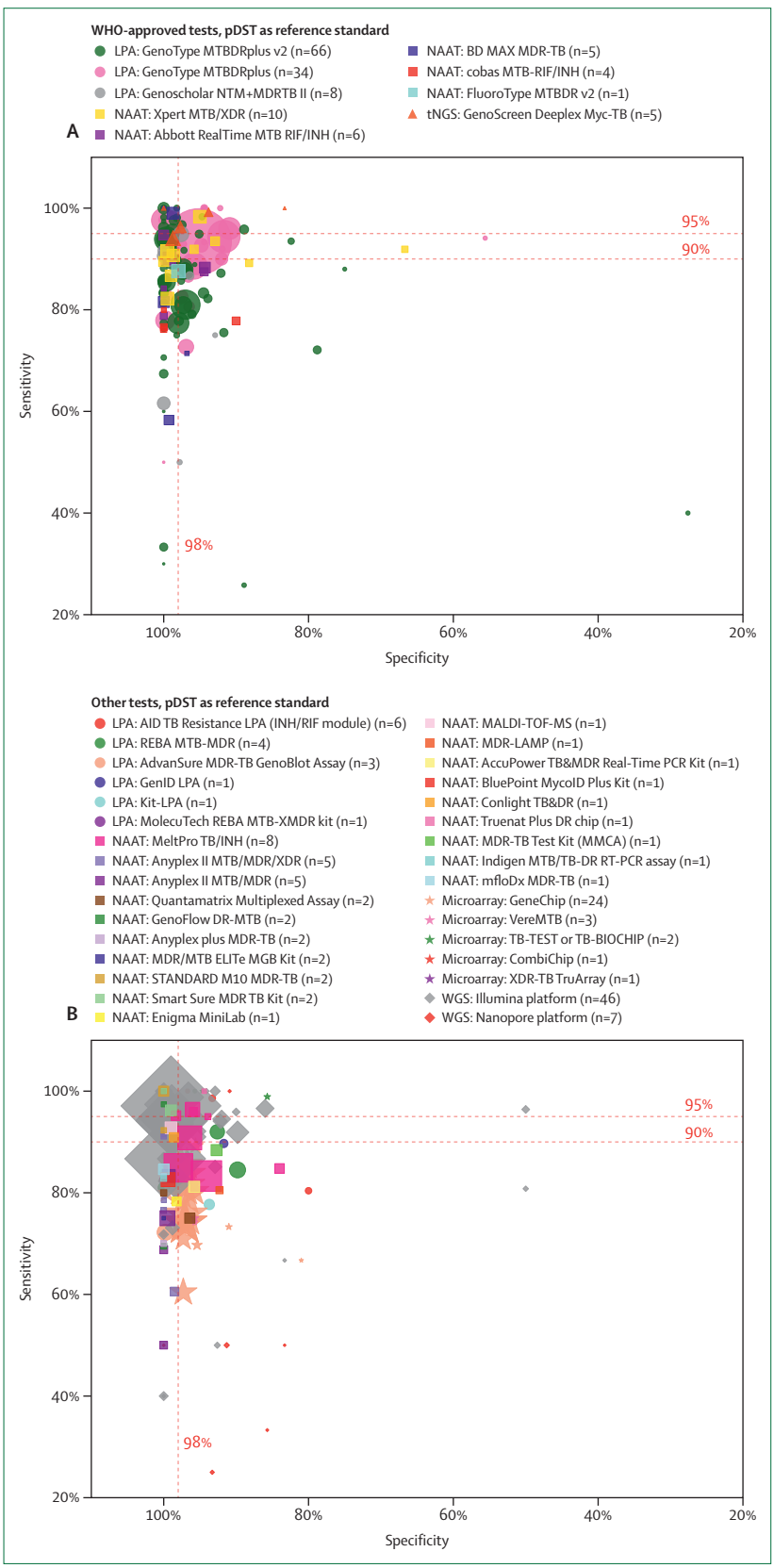
All LPA and NAAT devices used standard electricity, without a built-in uninterruptible power supply or battery-operated options, although uninterruptible power supply support can be added. Routine uninterruptible power supply support was available for some Illumina whole-genome sequencing and GenoScreen Deeplex Myc-TB instruments. AmPORE-TB could be powered via a laptop. XDR-TB TruArray satisfied the targets for power requirements. Annual maintenance and calibration by qualified personnel were required for all LPA, NAAT, and tNGS devices. Illumina whole-genome sequencing devices required more frequent maintenance but met other targets for alerts and remote software updates.

Discussion

Early detection of isoniazid-resistant tuberculosis reduces the time to initiating adequate treatment regimens recommended by WHO, which improves treatment outcomes,[58] thus helping to interrupt transmission and prevent the amplification of multidrug-resistant

tuberculosis. The mDST landscape for isoniazid-resistant tuberculosis has expanded rapidly since 2020. This scoping review included 343 evaluation entries for 44 tests across five test classes, including eight LPAs, 27 NAATs, five DNA microarrays, two whole-genome sequencing platforms, and two tNGS tests. Of these, nine WHO-approved tests showed good diagnostic performance, including two LPAs (GenoType MTBDR*plus* version 2.0 and Genoscholar NTM+MDRTB II), five NAATs (Xpert MTB/XDR, Abbott RealTime MTB RIF/INH, BD MAX MDR-TB, cobas MTB-RIF/INH, and FluoroType MTBDR version 2.0), and two tNGS tests (GenoScreen Deeplex Myc-TB and AmPORE-TB), although some showed a wide range of indeterminate rates. The affordability of WHO-approved LPAs and NAATs was facilitated by the availability of consumables and reagents distributed through the GDF. Eight of the nine tests were better suited for intermediate and central laboratories due to their requirements for moderate to extensive training and complex manual procedures for sample processing. The exception was Xpert MTB/XDR, which required minimal training and only one manual step, thus making it suitable for lower-level laboratories. Several new NAATs, although not yet approved by WHO, showed potential as highly accurate point-of-care diagnostic tools, which should improve detection of isoniazid-resistant tuberculosis in low-resource settings.

Each class of mDST for isoniazid-resistant tuberculosis has specific strengths and limitations, which influence their suitability across different settings. Most LPAs, NAATs, and DNA microarrays target only a fixed set of well characterised mutations associated with isoniazid-resistant and rifampicin-resistant tuberculosis, which has two key drawbacks. First, this narrow focus fails to capture the full genetic diversity of resistance mechanisms, especially in high-burden settings, wherein rare or region-specific mutations might be more prevalent. Second, such focus overlooks resistance to other drugs, most importantly fluoroquinolones. Early detection of fluoroquinolone resistance is essential to guide the design of effective treatment regimens and to preserve the effectiveness of newer drugs.[59] To address this gap, whole-genome sequencing and tNGS can detect both common and rare resistance-conferring mutations across multiple genes, providing a more comprehensive resistance profile.[16] However, both require next-generation high-throughput sequencing instruments and bioinformatics analytical skills, thereby restricting their applicability at the peripheral level. Although whole-genome sequencing offers accessible software tools in which sequencing data can be uploaded for analysis, its adoption remains largely restricted to high-income countries.[51–53,60,61] tNGS offers a more practical solution for field deployment, as it can be performed directly using clinical samples and includes some commercially available, WHO-approved options. By focusing only on clinically relevant genes, which are regularly reviewed and updated in the WHO mutation catalogue, rather than sequencing the entire genome, tNGS reduces the



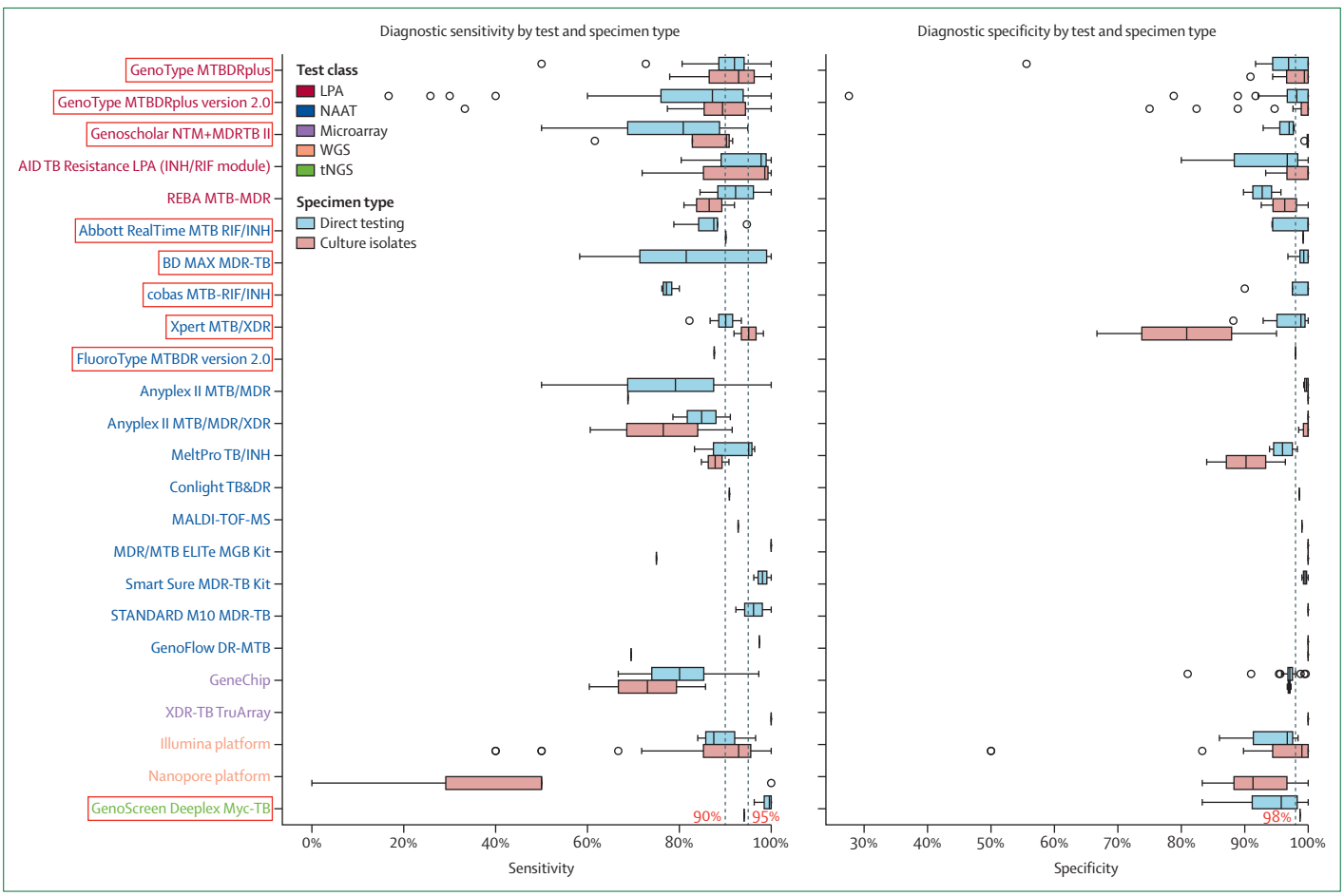


Figure 5: **Subgroup analysis for diagnostic performance by specimen type**
WHO-approved tests for isoniazid-resistant tuberculosis detection are highlighted in red boxes. LPA=line probe assay. NAAT=nucleic acid amplification test. tNGS=targeted next-generation sequencing. WGS=whole-genome sequencing.

sequencing workload and associated computational requirements, thereby enhancing operational feasibility in high-burden, low-resource settings; however, its high cost remains a major barrier to widespread implementation. LPAs and DNA microarrays, despite being potentially suited for these settings, still require complex DNA-extraction processes, restricting their practicality in peripheral laboratories. Despite requiring only a single manual step for sample preparation, four WHO-approved NAATs depend on fairly complex infrastructure and specialised training, making them more suitable for central or intermediate-level laboratories.[62] Additionally, although LPAs and NAATs are available at prices that meet TPP targets through GDF or Roche's Global Access Program, availability is often inconsistent due to supply chain issues or logistical delays,[63] and this price point remains a major financial obstacle in most low-resource settings. Therefore, ongoing efforts are required to advance the development and implementation of affordable, stable, and decentralised diagnostic tools for isoniazid-resistant tuberculosis to enable faster and more accessible diagnosis and treatment in high-burden, low-resource settings. A promising option for near-point-of-care testing was STANDARD M10 MDR-TB, which offered simple, fast, and accurate detection of *M tuberculosis* and its resistance to isoniazid and rifampicin. However, this test, along with many other new tests, has been evaluated in only a few studies and does not have formal approval from regulatory bodies.

Figure 4: **Diagnostic accuracy of molecular diagnostic tests for isoniazid-resistant tuberculosis against any WHO-approved phenotypic drug-susceptibility testing**
(A) Tests approved by WHO. (B) Tests without WHO approval to date. WHO-approved tests for isoniazid-resistant tuberculosis are highlighted in red boxes. Diagnostic performance targets of 90–95% for sensitivity and 98% for specificity are indicated by red dotted lines. White dots indicate outlier values, with each dot representing a datapoint from one evaluation entry. Specimen type differentiates tests performed directly on clinical specimens from those performed on cultured isolates. The clinical specimens were diverse, predominantly sputum, but also included other respiratory samples (eg, pleural fluid and bronchial lavage) and extrapulmonary specimens (eg, pus from abscesses, lymph node aspirates, cerebrospinal fluid, and tissue biopsies) in a few evaluations. LPA=line probe assay. pDST=phenotypic drug-susceptibility testing. NAAT=nucleic acid amplification test. tNGS=targeted next-generation sequencing. WGS=whole-genome sequencing.

	Manufacturer	Diagnostic performance for INH resistance		Target user	Drug resistance tested	Cost per test* (US$)	Specimen preparation steps	Time-to-result (hours)	Power source requirements	Maintenance
		Sensitivity	Specificity							
WHO TPP (minimal target)		90%	98%	Health-care workers with minimal or moderate training	RIF + INH + FQs (LFX and MFX) + BDQ	10–15	≤5 steps	<6 h	Standard electricity plus UPS Option of battery-operated device with the ability to run for one day	Annually User-controlled monitoring Maintenance alert Remote software update
WHO TPP (optimal target)		95%	98%	Health-care workers with minimal training	Minimal + PZA+ LZD + Pa/DLM + CFZ + AMK + DCS + Any additional drugs	≤5	≤1 step	<30 min (<2 h acceptable)	As above	Every 2 years Others as above
Line probe assay (3 tests)										
GenoType MTBDR*plus* version 2.0	Hain Lifescience (Bruker Corporation, Germany)	16·7–100·0%	27·6–100·0%	Health-care workers with moderate or extensive training	INH + RIF	15·7–37·6 (7·8†)	≤5 steps	6–9 (5‡)	Standard electricity No built-in UPS or battery	Once a year by qualified personnel
Genoscholar NTM+MDRTB II	Nipro (Japan)	50·0–94·9%	92·9–100·0%	Health-care workers with moderate or extensive training	INH + RIF	16†	≤5 steps	<1 day‡	As above	Once a year by qualified personnel
AID TB Resistance LPA (INH/RIF module)	AID Autoimmun Diagnostika (Germany)	71·9–100·0%	80·0–100·0%	Health-care workers with moderate or extensive training	INH + RIF	NA	≤5 steps	<1 day (4‡)	As above	Once a year by qualified personnel
Nucleic acid amplification test (14 tests)										
Xpert MTB/XDR	Cepheid (USA)	82·2–98·5%	66·7–100·0%	Health-care workers with minimal training	INH + FQs + SLIDs	14·9†	≤1 step	1·75	As above	Once a year by qualified personnel
Abbott RealTime MTB RIF/INH	Abbott (USA)	78·8–94·7%	94·3–100·0%	Health-care workers with moderate training	INH + RIF	NA	≤1 step	3–12	As above	Once a year by qualified personnel
BD MAX MDR-TB	Becton Dickinson (USA)	58·3–100·0%	96·8–100·0%	Health-care workers with moderate training	INH + RIF	12·9†	≤1 step	<4	As above	Once a year by qualified personnel
cobas MTB-RIF/INH	Roche (Switzerland)	90·0–100·0%	0·0–13·5%	Health-care workers with moderate training	INH + RIF	8·9‡	≤1 step	3‡	As above	Once a year by qualified personnel
FluoroType MTBDR version 2.0	Hain Lifescience or Bruker (Germany)	70·0–100·0%	97·4–100·0%	Health-care workers with moderate training	INH + RIF	6·5†	≤1 step	<5 (2·5‡)	As above	Once a year by qualified personnel
Anyplex II MTB/MDR	Seegene (South Korea)	50·0–100·0%	99·3–100·0%	Health-care workers with moderate training	INH + RIF	NA	≤5 steps	3–9·6	As above	Once a year by qualified personnel
Anyplex II MTB/MDR/XDR	Seegene (South Korea)	60·6–91·5%	98·5–100·0%	Health-care workers with moderate training	INH + RIF + FQs + SLIDs	30·8	≤5 steps	4·5	As above	Once a year by qualified personnel
MeltPro TB/INH	Zeesan Biotech (China)	83·3–96·4%	84·0–98·3%	Health-care workers with moderate training	INH	14‡	≤5 steps	3–3·5	As above	Once a year by qualified personnel
MDR/MTB ELITe MGB Kit	ELITechGroup Molecular Diagnostics (USA)	75·0–100·0%	100·0%	Health-care workers with minimal training	INH + RIF	30·3	≤1 step	3 (<2 min‡)	As above	Once a year by qualified personnel
GenoFlow DR-MTB	DiagCor Bioscience (Hong Kong)	69·5–97·4%	100·0%	Health-care workers with moderate training	INH + RIF	NA	≤5 steps	3‡	As above	Once a year by qualified personnel
STANDARD M10 MDR-TB	SD Biosensor (South Korea)	92·3–100·0%	100·0%	Health-care workers with minimal training	INH + RIF	NA	≤1 step	1·5‡	As above	Once a year by qualified personnel
Smart Sure MDR-TB Kit	Genetix Biotech Asia (India)	96·2–100·0%	99·0–100·0%	Health-care workers with moderate training	INH + RIF	NA	≤5 steps	NA	As above	Once a year by qualified personnel
MALDI-TOF-MS	Digena (China)	92·8–98·7%	92·9–99·0%	Health-care workers with moderate training	INH + RIF + EMB + MFX + STR + PZA	NA	≤5 steps	A few hours	As above	Once a year by qualified personnel

(Table continues on next page)

	Manufacturer	Diagnostic performance for INH resistance		Target user	Drug resistance tested	Cost per test* (US$)	Specimen preparation steps	Time-to-result (hours)	Power source requirements	Maintenance
		Sensitivity	Specificity							
(Continued from previous page)										
Conlight TB&DR	Shanghai Conlight Medical Laboratory (China)	90·9%	98·6%	Health-care workers with moderate training	INH + RIF + EMB + STR + FQs + SLIDs	NA	>5 steps	A few hours	As above	Once a year by qualified personnel
DNA microarray (2 tests)										
GeneChip	CapitalBio Technology (China)	60·4–97·3%	81·0–99·6%	Health-care workers with moderate or extensive training	INH + RIF	24·3	>5 steps	5·8–6	As above	At least once a year by qualified personnel
XDR-TB TruArray	Akonni Biosystems (USA)	100·0%	100·0%	Health-care workers with moderate training	INH + RIF + FQs + SLIDs	NA	≥5 steps	A few hours‡	Yes	At least once a year by qualified personnel
Whole-genome sequencing (1 platform)										
Illumina platform	Illumina (USA)	40·0–100·0%	50·0–94·7%	Health-care workers with moderate or extensive training	INH + RIF + EMB + PZA + STR + FQs + SLIDs + ETH + BDQ + DLM + LZD	211·2–307·6 (40–70)§	≥5 steps	<48‡	UPS available for some instruments‡	More than once a year Alert available Remote software updates available
Targeted next-generation sequencing (2 tests)										
GenoScreen Deeplex Myc-TB	GenoScreen (France)	94·1–100·0%	83·3–100·0%	Health-care workers with moderate or extensive training	INH + RIF + EMB + PZA + STR + FQs + SLIDs + ETH + BDQ + LZD	150–240 (40–70)§	≥5 steps	<48‡	UPS available for some instruments‡	Once a year by qualified personnel
AmPORE-TB	Oxford Nanopore Technologies (UK)	NA	NA	Health-care workers with moderate or extensive training	INH + RIF + EMB + PZA + STR + FQs + SLIDs + ETH + BDQ + LZD	NA	≥5 steps	5–6	Can be powered via a laptop‡	Once a year by qualified personnel

AMK=amikacin. BDQ=bedaquiline. CFZ=clofazimine. DCS=D-cycloserine. DLM=delamanid. ETH=ethionamide. EMB=ethambutol. FQs=fluoroquinolones. INH=isoniazid. LFX=levofloxacin. LZD=linezolid. MFX=moxifloxacin. NA=not applicable. Pa=pretomanid. PZA=pyrazinamide. SLIDs=second-line injectable drugs. STR=streptomycin. RIF=rifampicin. UPS=uninterruptible power supply. WHO TPP=WHO's target product profiles for tuberculosis diagnosis and detection of drug resistance. *The price for reagents and consumables only. The price was converted to US dollars on Jan 20, 2025, using inflation rates published by the US Department of Labor. †Price for reagents and consumables only as per the Global Drug Facility Diagnostics, Medical Devices, and other health products catalogue, version January, 2025. ‡Information publicly provided by the manufacturers. The price for cobas MTB-RIF/INH was collected from Roche's Global Access Program with applicable conditions. §Price for a test in China, based on expert input. ¶These tests include nine WHO-approved tests and 13 additional tests that are not yet approved by WHO, each with at least one entry that met both WHO TPP diagnostic performance targets.

Table: **Key characteristics of some molecular diagnostic tests for isoniazid-resistant tuberculosis¶**

The strengths of this study include a comprehensive search strategy, clearly defined selection criteria, and a transparent, standardised process for evaluation entry screening, data extraction, and analysis. Although multiple databases were searched without language restriction, and the search was updated to ensure currency, we acknowledge the possibility of missing relevant studies. The tests were evaluated across four characteristic domains (ie, performance or accuracy, scope of use, cost per test, and ease of operation) to provide a holistic overview of mDST for detection of isoniazid-resistant tuberculosis. Although TPP outlined many characteristics, we prioritised those identified as key by the TPP authors to maintain focus. We recommend this stepwise approach to policy makers: starting with key characteristics to guide initial decisions and considering additional factors, such as sample capacity and throughput, biosafety requirements, operating environment, and reagent storage conditions, whenever further evaluation is needed. This approach helps to avoid unnecessary complexity in the early stages of decision making. Several of the operational characteristics could not be evaluated due to unclear definitions in the TPP. For example, the library preparation for GenoScreen Deeplex Myc-TB includes DNA fragmentation, library amplification, and library pooling and quantification. Whether these are counted as three separate steps or collectively as a single step under library preparation when evaluating the minimal requirement of five manual steps for sample preparation remains unclear.

There are several important study limitations. First, this Review was restricted to diagnostic tests for which evaluations had been published in the databases we searched. This approach might have excluded several assays, particularly copycat real-time PCR tests that had not been formally evaluated or published. Second, owing to the high volume of relevant publications identified, only 20% of data were extracted in duplicate by a second reviewer (EL-HM). Nevertheless, high agreement was achieved between reviewers, providing confidence in the reliability of the extracted data.[28] Furthermore, we did not perform pooled sensitivity and specificity meta-analyses, since relevant systematic reviews have been published for all the WHO-approved tests of late.[20–26] Most newer tests had a small number of evaluation entries, making pooled estimates unreliable, particularly given the methodological limitations noted in the next paragraph.

Although a formal quality assessment of the included studies was not conducted in this scoping review, methodological concerns were identified in several studies. First, the diagnostic performance of moderate-to-high complexity tests varied across evaluation entries on the same sample types. This variation was likely due to the variation in sample-handling procedures between studies. Better standardisation or automation of some steps (eg, DNA extraction and data analysis) and integration of multiple steps into a single platform could reduce the workload, simplify the testing process, and increase consistency. Second, some studies involved direct participation of the manufacturer in the design and conduct of test evaluation, which could have introduced bias due to potential conflicts of interest. Third, some studies reported limited performance data, presenting only sensitivity and specificity without providing the underlying test performance numbers. Consequently, the indeterminate rates might be underestimated, as some of the outcomes were based on repeated testing. Fourth, details regarding pricing and operational characteristics were frequently under-reported.

Several important research questions remain. One of the most pressing questions is the optimal treatment for people with isoniazid-resistant tuberculosis. WHO recommends a 6-month four-drug regimen of rifampicin, ethambutol, pyrazinamide, and levofloxacin. However, this recommendation is conditional and not supported by sufficient data from clinical trials.[64] Optimal treatment strategies for isoniazid-resistant tuberculosis require evidence from well designed randomised trials. Although many tests showed broadly similar performance in a range of high-burden and low-burden settings, mDST might perform differently due to lineage-specific influences on drug-resistance profiles and the variable distribution of these lineages by region.[65] Thus, data from multiple geographical regions are required to confirm the generalisability of study findings. Additionally, only few evaluations of mDST for isoniazid-resistant tuberculosis have been conducted in children.[66] Addressing this gap is crucial to improve the detection and management of paediatric isoniazid-resistant tuberculosis.

The molecular diagnostics options for isoniazid-resistant tuberculosis have increased rapidly since 2020. Nine WHO-approved tests showed good diagnostic performance and met the TPP target price for consumables and reagents distributed through the GDF. However, most of these tests were better suited for intermediate and central laboratories owing to their infrastructure, sample-processing requirements, and complexity. Manufacturers should be encouraged to simplify diagnostic workflows and further reduce pricing barriers to enhance accessibility in high-burden, low-resource settings. Only one assay was appropriate for decentralised use. This reliance on a single platform underscores the risk of monopolisation in the diagnostics market. To ensure long-term sustainability and equitable access, diversifying decentralisable diagnostic options becomes crucial. Several new NAATs, although not yet approved by WHO, could potentially provide accurate point-of-care diagnosis of isoniazid-resistant tuberculosis, but robust supporting data and more refinement are required to facilitate their adoption. To support this aim, field validation of these NAATs in decentralised settings should be prioritised.

Contributors

TMN, EL-HM, and GJF conceptualised the study. TMN, EL-HM, and XZ collected the data. TMN and EL-HM analysed the data and interpreted the results. TMN produced the tables and figures. TMN and EL-HM prepared

the first draft of the manuscript. SBG, HX, JB, MS, T-AN, BJM, and GJF reviewed the manuscript and provided critical feedback. All authors had full access to all the data in the study, provided essential review and revision of the text, approved the final version, and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Acknowledgments

TMN is supported by the University of Sydney International Stipend and International Tuition Fee Scholarships. EL-HM is supported by a Canadian Institutes for Health Research Fellowship (472823). XZ is funded by the National Health and Medical Research Council (NHMRC) 2024 e-ASIA Joint Research Program. GJF was supported by an NHMRC Investigator Grant (Leadership Level 1). The authors thank the University of Sydney Library for the valuable consultation regarding the development of the search strategy for this scoping review. We thank Thu Ha Doan and Thi Huong Dinh for their valuable input regarding the evaluated characteristics of diagnostic tests for isoniazid-resistant tuberculosis in Viet Nam. During the preparation of this work, the authors used Microsoft Copilot, with access provided by the University of Sydney to improve the readability and grammar of the work. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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