

Original Article

Cost-Effectiveness of Targeted Next-Generation Sequencing for Diagnosing Pre-XDR and XDR Tuberculosis in Rifampicin-Resistant Patients Across High-Burden Settings

1 Ginenus Fekadu^{a,b,*}, Tadesse Tolossa^{c,d}, Busha Gamachu Labata^b, Meseret Belete Fite^d,
2 Tesfaye Regassa Feyissa^e, Xinyao Yi^a, Sze Chai Chan^a, Yanya Chen^{a,f}, Cemre Arpa^g, Firomsa Bekele^b,
3 Lan Gao^c, Nathorn Chaiyakunapruk^{h,i}, Lianping Yang^{j,k,l}, Meseret Jeldu^m, Shanquan Chenⁿ,
4 **QI** Martin Siegel^o, Wai Kit Ming^{a,p,*}

^a Department of Infectious Diseases and Public Health, Jockey Club College of Veterinary Medicine and Life Sciences, City University of Hong Kong, Hong Kong

^b School of Pharmacy, Institute of Health Sciences, Wollega University, Nekemte, Ethiopia

^c Deakin Health Economics, School of Health and Social Development, Institute for Health Transformation, Deakin University, Victoria, Australia

^d School of Public Health, Institute of Health Sciences, Wollega University, Nekemte, Ethiopia

^e Deakin Rural Health, School of Medicine, Faculty of Health, Deakin University, Victoria, Australia

^f College of Nursing, Jinan University, Guangzhou, China

^g Department of Empirical Health Economics, Technische Universität Berlin, Berlin, Germany

^h Department of Pharmacotherapy, University of Utah College of Pharmacy, Salt Lake City, UT, USA

ⁱ IDEAS Center, Veterans Affairs Salt Lake City Healthcare System, Salt Lake City, UT, USA

^j School of Public Health, Sun Yat-sen University, Guangzhou, China

^k Institute for Global Health and Development, Peking University, Beijing, China

^l Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

^m Department of Obstetrics and Gynecology, Saint Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia

ⁿ International Centre for Evidence in Disability, Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, UK

^o Chair of General Economics, Health Economics and Econometrics, University of Greifswald, Greifswald, Germany

^p Institute of Global Governance and Innovation for a Shared Future, City University of Hong Kong, Hong Kong

ARTICLE INFO

Article history:

Received 4 October 2025

Accepted 6 April 2026

Available online xxx

Keywords:

Targeted next-generation sequencing

Pre-XDR/XDR-TB

Cost-effectiveness analysis

Early treatment initiation

Drug-resistant tuberculosis

High-burden settings

ABSTRACT

Objectives: To evaluate whether targeted next-generation sequencing (tNGS)—alone or in combination with phenotypic drug susceptibility testing (pDST)—is cost-effective for diagnosing pre-extensively drug-resistant and extensively drug-resistant tuberculosis (pre-XDR/XDR-TB) in rifampicin-resistant tuberculosis (RR-TB) patients across South Africa, India, and Georgia, and to quantify mortality reduction from earlier treatment initiation enabled by rapid molecular diagnostics.

Methods: We developed a decision-analytic model combining a short-term decision tree with a 10-year Markov model to simulate outcomes in a hypothetical RR-TB cohort. Three diagnostic strategies were compared: pDST, tNGS, and tNGS + pDST. Outcomes included costs, quality-adjusted life years (QALYs), early treatment initiation, TB-related mortality, and incremental cost-effectiveness ratios (ICERs). Cost-effectiveness was assessed against country-specific willingness-to-pay (WTP) thresholds. Sensitivity analyses were conducted to characterize uncertainty.

Results: Tngs-based strategies improved early treatment initiation (South Africa: +9.8%; India: +19.1%; Georgia: +29.6%) and reduced mortality across all settings. In South Africa, tNGS was cost-effective (ICER, \$2805/QALY). In Georgia, the combination strategy was cost-effective (ICER, \$6361/QALY). In India, neither tNGS (ICER, \$4453/QALY) nor the combination strategy (ICER, \$6198/QALY) met the WTP threshold; tNGS would require cost reduction to \leq \$116/test. The HR, for delayed treatment and tNGS cost were primary ICER drivers. Probabilistic analysis confirmed robustness, with tNGS cost-effective in 58% of simulations in South Africa and the combination strategy in 42% in Georgia.

* Corresponding authors.

E-mail addresses: take828pharm@gmail.com, gmekonen@cityu.edu.hk (G. Fekadu), wkming2@cityu.edu.hk (W.K. Ming).

Conclusions: Tngs is cost-effective in South Africa and Georgia when the survival benefit of earlier treatment initiation is accounted for. In India, tNGS pricing exceeds affordability thresholds, necessitating cost reductions and targeted deployment. These findings provide context-specific guidance for national TB programs.

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Introduction

Tuberculosis (TB) remains a major global public health challenge, particularly in high-burden, resource-constrained settings [1,2]. In 2023, TB re-emerged as the leading cause of death among infectious diseases, surpassing COVID-19, with approximately 1.25 million deaths—a substantial proportion linked to drug-resistant TB (DR-TB) [1,3]. The emergence of pre-extensively drug-resistant TB (pre-XDR-TB) and extensively drug-resistant TB (XDR-TB) has further complicated treatment strategies and increased the risk of poor health outcomes [1,4,5].

An estimated 400,000 DR-TB cases were reported globally in 2023, yet a significant diagnostic gap persists, with only 42% of cases diagnosed and treated [1]. The burden of DR-TB-related mortality and disability is especially pronounced in low- and middle-income countries (LMICs), where socioeconomic challenges, limited healthcare infrastructure, and HIV co-infection exacerbate the situation [1,2,6].

Early and accurate detection of DR-TB is essential for effective management and reducing transmission [7,8]. Phenotypic drug susceptibility testing (pDST)—the current gold standard for determining TB drug resistance—is hindered by long turnaround times, technical complexity, and limited accessibility [4,8,9]. Targeted next-generation sequencing (tNGS) has emerged as a promising alternative for rapid drug resistance detection and timely treatment guidance [4,10,11].

By amplifying selected genes, tNGS can simultaneously identify mycobacterial species, genotype strains, and predict resistance to multiple anti-TB drugs from a single sample [4,12]. Clinical studies show tNGS results concordant with pDST, offering advantages in speed and elimination of bacterial culture [4,11].

Integrating tNGS into routine practice in high-burden settings raises important health and economic questions [13]. A recent WHO-commissioned analysis by Shrestha et al. [14] provided foundational evidence on tNGS cost-effectiveness in South Africa, India, and Georgia but did not explicitly model the mortality impact of diagnostic delay—a critical mechanism by which rapid diagnostics may improve outcomes [15].

Our study advances the evidence by directly quantifying the survival benefit of earlier treatment initiation—a key pathway missing from prior analyses—while incorporating updated 2022 WHO guidelines and regimen-specific treatment pathways [4,16]. We therefore evaluated whether tNGS—alone or in combination with pDST—is cost-effective for diagnosing pre-XDR/XDR-TB in RR-TB patients across South Africa, India, and Georgia and quantified the mortality reduction attributable to earlier treatment initiation enabled by rapid molecular diagnostics.

By focusing on these high-burden settings, we provide actionable insights into the economic viability and health benefits of integrating tNGS into national TB programs, filling a critical evidence gap for policy decisions.

Methods

Model design

This economic evaluation followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines (Checklist S1) [17]. We developed a decision-analytic model combining a short-term decision tree with a 10-year Markov model to simulate long-term TB-related outcomes in a hypothetical cohort of RR-TB patients undergoing resistance testing for pre-XDR/XDR-TB (Fig. 1). A 10-year horizon was selected to capture the majority of DR-TB relapses and deaths [18,19], to balance long-term outcomes against uncertainty beyond clinical trial follow-up (24–36 months) [20–22], and to align with standard TB economic evaluations for comparability with published studies [13,23].

The analysis adopted a healthcare provider perspective in South Africa, India, and Georgia—selected based on empirical tNGS cost data from the WHO Guideline Development Group [4]. Three diagnostic strategies were compared: (a) pDST (standard practice), (b) tNGS alone, and (c) tNGS + pDST in parallel. Outcomes included direct medical costs, quality-adjusted life-years (QALYs), early treatment initiation, TB-related mortality, and incremental cost-effectiveness ratios (ICERs).

The decision tree captured the initial diagnostic and treatment pathways based on resistance detection (Fig. 1a). Patients entered the model as either fluoroquinolone-resistant (FqR) or fluoroquinolone-susceptible (FqS). FqR patients could also harbor bedaquiline (Bdq) or linezolid (Lzd) resistance. Patients with positive test results received early treatment, defined as initiation of guideline-recommended pharmacotherapy during the initial evaluation. False-negative results delayed treatment until confirmatory pDST results became available—termed late treatment [16]. Inappropriate treatment occurred when resistance was undetected and confirmatory pDST was unavailable, leading to ineffective regimens [1,16]. Patients receiving early, late, or inappropriate treatment could either survive or experience TB-related mortality.

Patients resistant to fluoroquinolones (Fqs) plus Bdq or Lzd were classified as XDR-TB and received 18–20-month WHO-recommended longer oral regimens [16,24]. Pre-XDR-TB patients (FqR only) received a 6-month Bdq–pretomanid–Lzd (BPAL) regimen, while MDR/RR-TB patients without additional resistance received a 6-month Bdq–pretomanid–Lzd plus moxifloxacin (BPALM) regimen [16]. WHO definitions for DR-TB classifications [16,24] are provided in Table S1.

In the pDST strategy, sputum samples underwent culture-based testing [4]. Patients initially received a shorter oral MDR-TB regimen, which was adjusted based on pDST results. XDR-TB cases transitioned to late treatment, and Fq resistance determined whether moxifloxacin was continued or discontinued. In the tNGS strategy (Deeplex Myc-TB assay), resistance was detected from a single sputum sample, enabling early initiation of guideline-aligned treatment [16]. False-negative tNGS results led to inappropriate treatment.

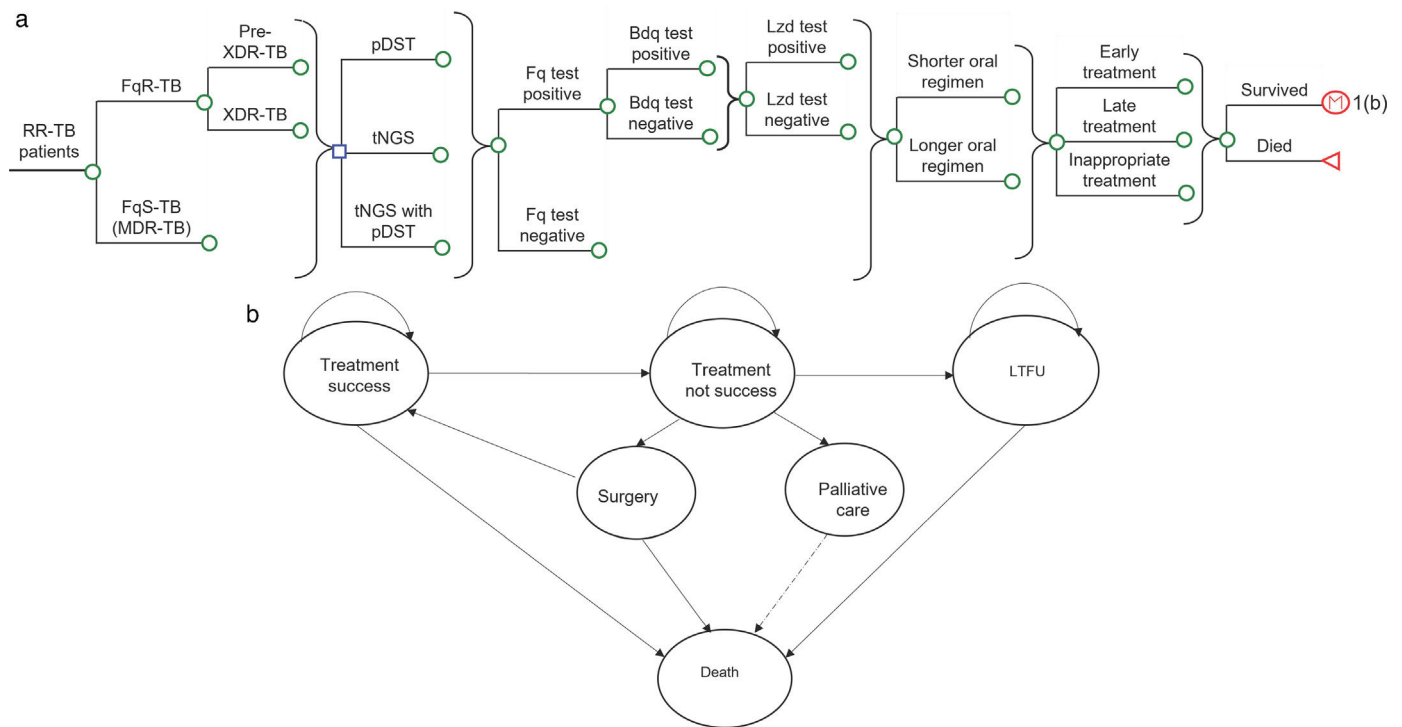


Fig. 1. Simplified decision-analytic model for detecting pre-XDR and XDR-TB in RR-TB patients. (A) Decision tree structure capturing initial diagnostic and treatment pathways based on resistance detection. Squares represent decision nodes, circles represent chance nodes, and triangles represent terminal states. (B) Markov model structure with six states simulating long-term TB outcomes over a 10-year horizon. Ellipses represent health states; arrows represent possible annual transitions between states (all transition probabilities defined in Table S3). Death is an absorbing state with no exits. Bdq indicates bedaquiline; Fq, fluoroquinolone; FqR-TB, fluoroquinolone-resistant tuberculosis; FqS-TB, fluoroquinolone-susceptible tuberculosis; LTFU, loss to follow-up; Lzd, linezolid; MDR-TB, multidrug-resistant tuberculosis; pDST, phenotypic drug susceptibility testing; RR-TB, rifampicin-resistant tuberculosis; tNGS, targeted next-generation sequencing; TB, tuberculosis; and XDR-TB, extensively drug-resistant tuberculosis.

In the combination strategy, sputum samples were tested in parallel using both tNGS and pDST. Early treatment was guided by tNGS results and adjusted based on pDST confirmation. False-negative tNGS results were corrected by pDST, while false-positive tNGS results (e.g., misclassified XDR-TB) were revised to shorter regimens if pDST excluded resistance.

Following the decision tree, surviving patients transitioned into a 10-year Markov model with six health states: “treatment success,” “no treatment success,” “loss to follow-up (LTFU),” “surgery,” “palliative care,” and “death” (Fig. 1b). Patients progressed through these states in annual cycles. Those with treatment success faced risks of TB relapse or age-specific mortality; those without relapse remained in long-term health. Patients with no treatment success either experienced treatment failure or were LTFU. Treatment failure could lead to surgical intervention or palliative care. Successful surgery allowed re-entry into treatment, while patients ineligible for surgery remained in palliative care until death. LTFU patients faced elevated mortality risks due to untreated TB. WHO definitions for DR-TB treatment outcomes [25] are detailed in Table S2.

Model inputs

A detailed description of model inputs is presented in Appendix S1. All model inputs (clinical, health utility, and costs) are summarized in Table S3, with explicit categorization of parameters as country-specific, setting-adjusted, or global to ensure transparency in cross-country comparisons (detailed justification for parameter categorization is provided in Appendix S2). Model inputs were derived from published literature and public data, including country-specific health department reports and WHO sources, with priority given to local sources for country-specific parameters. For global parameters (e.g., diagnostic accuracy, HR), we drew from multicenter studies and meta-analyses to maximize generalizability.

Cost-effectiveness and sensitivity analyses

All analyses were conducted using TreeAge Pro Healthcare 2025 and Excel 365. Cost-effectiveness was assessed incrementally by calculating ICERs as the cost difference divided by QALY difference. A strategy was considered cost-effective if it yielded higher QALYs at lower cost or higher QALYs at higher cost with an ICER below the country-specific willingness-to-pay (WTP) threshold [26]. Following WHO guidelines, interventions with an ICER below the national GDP per capita were considered highly cost-effective [27]. WTP thresholds were defined using 2024 GDP per capita estimates: \$6253 for South Africa, \$2485 for India, and \$8120 for Georgia [28].

One-way sensitivity analyses varied all parameters within predefined ranges (Table S3) to quantify their impact on ICERs and identify key drivers of uncertainty. Threshold analyses determined the maximum per-test price for tNGS to remain cost-effective when replacing pDST. Scenario analyses evaluated the impact of alternative discount rates (5% and 10%) and time horizons (1, 5, 20 years, and lifetime) on ICER estimates, assessing the minimum horizon for tNGS to demonstrate economic value and the robustness of the 10-year base case.

Probabilistic sensitivity analyses used 10,000 Monte Carlo simulations, sampling inputs from their probability distributions and calculating mean incremental costs and QALYs. For visualization, we superimposed 95%CI, confidence ellipses—derived from the empirical covariance matrix of simulated incremental cost–QALY pairs—onto each country strategy scatter plot to summarize joint uncertainty. Cost-effectiveness acceptability curves were then generated to estimate the probability that each strategy is cost-effective across WTP thresholds from zero to three times GDP per capita [27,29].

Table 1
Base-case cost-effectiveness results for South Africa, India, and Georgia.

Testing strategy	TB patients receiving early treatment per 1000	Early treatment initiation (% change vs less costly strategy)	TB-related mortality per 1000	TB-related mortality (% change vs less costly strategy)	Direct medical cost, \$	Incremental cost, \$	QALYs	QALYs gained	ICER, \$/QALY
<i>South Africa</i>									
pDST	901.40	–	154.65	–	8217	–	5.2683	–	–
tNGS	999.10	9.78%	147.18	–4.83%	8340	123	5.3120	0.0437	2805
tNGS + pDST	999.10	0%	147.02	–0.11%	8392	52	5.3137	0.0017	30,984
<i>India</i>									
pDST	805.20	–	30.13	–	3449	–	6.0806	–	–
tNGS	995.55	19.12%	27.02	–10.32%	3534	85	6.0998	0.0191	4453
tNGS + pDST	995.55	0%	25.67	–5.01%	3585	51	6.1080	0.0082	6198
<i>Georgia</i>									
pDST	701.40	–	45.92	–	5737	–	5.8749	–	–
tNGS	996.76	29.63%	40.84	–11.07%	5827	90	5.9042	0.0294	3073
tNGS + pDST	996.76	0%	39.83	–2.49%	5871	44	5.9112	0.0069	6361

Note: Comparison of three diagnostic strategies (pDST, tNGS, and tNGS + pDST) for detecting pre-XDR and XDR-TB in RR-TB patients. Outcomes include early treatment initiation rates (per 1000 individuals tested), TB-related mortality (per 1000 individuals tested), direct medical costs (US\$), quality-adjusted life-years (QALYs), incremental costs, QALYs gained, and incremental cost-effectiveness ratios (ICERs). ICERs are calculated as incremental cost per QALY gained compared with the next less costly strategy. pDST indicates phenotypic drug susceptibility testing; QALY, quality-adjusted life-year; RR-TB, rifampicin-resistant tuberculosis; tNGS, targeted next-generation sequencing; TB, tuberculosis; and XDR-TB, extensively drug-resistant tuberculosis.

Results

Base-case analysis

The base-case results are presented in Table 1. In South Africa, tNGS was cost-effective (ICER, \$2805/QALY) below the WTP threshold of \$6253/QALY. Compared with pDST, tNGS increased early treatment initiation by 9.78% (999.10 vs. 901.40 per 1000 individuals tested) and reduced TB-related mortality by 4.8% (147.18 vs. 154.65 deaths per 1000 individuals tested).

In India, neither tNGS (ICER, \$4453/QALY) nor the combination strategy (ICER, \$6198/QALY) met the WTP threshold of \$2485/QALY, rendering both strategies not cost-effective under current economic conditions. Nevertheless, both approaches improved clinical outcomes compared with pDST, increasing early treatment rates by 19.12% (995.55 vs. 805.20 per 1000) and reducing mortality (25.67–27.02 vs. 30.13 deaths per 1000).

In Georgia, the combination strategy (tNGS + pDST) was the most cost-effective, with an ICER of \$6361/QALY—below the WTP threshold of \$8120/QALY. This strategy achieved the lowest mortality rate (39.83 deaths per 1000) and the highest QALYs (5.9112) among all evaluated approaches.

One-way sensitivity analyses

The tornado diagram (Fig. 2) highlights the top 10 parameters influencing ICERs across settings. The HR, for mortality associated with delayed TB treatment initiation (base case: 1.5; range: 1.07–2.96) was the most influential factor. In South Africa and India, tNGS became cost-effective compared with pDST when the HR, exceeded 1.27 and 1.78, respectively, at their corresponding WTP thresholds (Fig. S1).

Threshold and scenario analyses

Threshold analyses identified tNGS cost as a key determinant of cost-effectiveness. In South Africa and Georgia, tNGS remained cost-effective at per-test prices up to \$356 and \$311, respectively. However, in India, the cost threshold was substantially lower, at \$116, to achieve cost neutrality when replacing pDST.

Scenario analyses showed that base-case results were robust to discount rate variations. However, varying the time horizon substantially affected cost-effectiveness estimates. At a 1-year horizon,

no tNGS-based strategy was cost-effective in any country because short-term benefits in mortality reduction and relapse prevention had not yet accrued. At 5 years, results approached the base case, although the combination strategy in Georgia remained above the WTP threshold. Extending the horizon to 20 years or lifetime produced findings similar to or more favorable than the base case, reflecting accumulation of long-term QALY gains and reductions in TB-related mortality (Table S4).

Probabilistic sensitivity analyses

The probabilistic sensitivity analysis (10,000 Monte Carlo simulations) assessed joint parameter uncertainty. Scatter plots (Fig. 3) illustrate incremental costs versus QALYs gained.

In South Africa (Fig. 3-Ia), tNGS (compared with pDST) incurred an incremental cost of \$122 (95%CI, \$118–\$127; $P < .01$) with a QALY gain of 0.0468 (95%CI, 0.0461–0.0475; $P < .01$). In 72.14% of simulations, tNGS was cost-effective at the country-specific WTP threshold, with cost savings in 29.08% and higher costs in 43.06% of iterations.

In India, tNGS (Fig. 3-IIa) and the combination strategy (Fig. 3-IIb) produced ICERs of \$4239/QALY (95%CI, \$4175–\$4299) and \$6369/QALY (95%CI, \$5914–\$6633), with 44.35% and 29.29% probability of cost-effectiveness, respectively.

In Georgia (Fig. 3-IIIb), the combination strategy (compared with tNGS) gained 0.0086 QALYs (95%CI, 0.0082–0.0092; $P < .01$) at an incremental cost of \$47 (95%CI, \$46–\$48; $P < .01$), with a 66.63% probability of cost-effectiveness.

Cost-effectiveness acceptability curves

Cost-effectiveness acceptability curves (Fig. 4) show the probability of each strategy being cost-effective across WTP thresholds. In South Africa, tNGS demonstrated the highest probability of cost-effectiveness when WTP exceeded \$2075/QALY, reaching 57.91% at the \$6253 threshold.

In India, pDST remained the preferred strategy below \$6240/QALY, with 50.36% acceptability at the \$2485 threshold.

In Georgia, the combination strategy was most cost-effective when the WTP exceeded \$5238/QALY, with 42.47% acceptability at the \$8120 threshold.

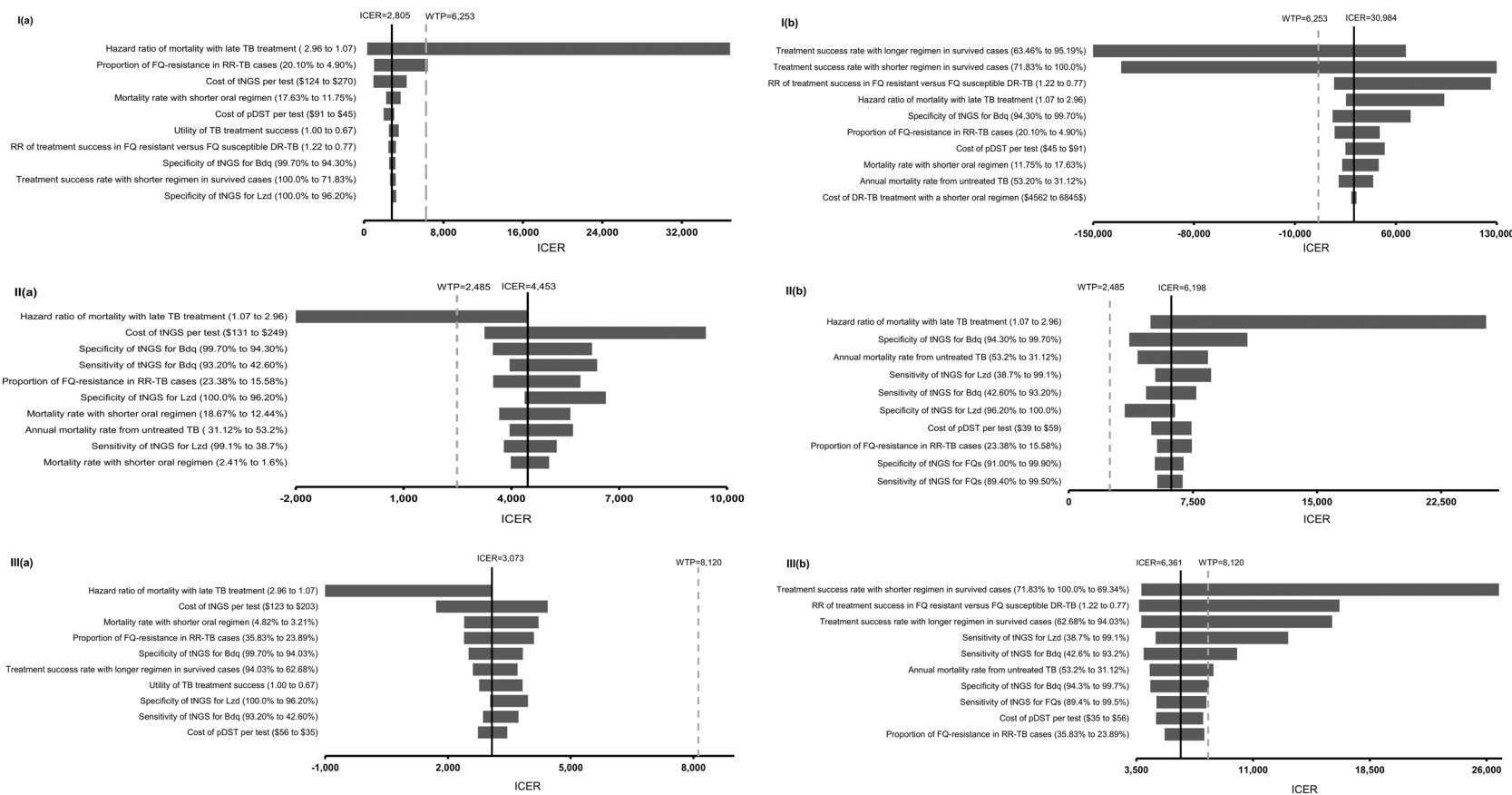


Fig. 2. Tornado diagrams from one-way sensitivity analyses showing the most influential parameters on ICERs for (A) tNGS versus pDST and (B) tNGS + pDST versus tNGS in (I) South Africa, (II) India, and (III) Georgia for detecting pre-XDR and XDR-TB in RR-TB patients. The horizontal bars represent the range of ICER values when each parameter is varied across its plausible range (as defined in Table S3). Longer bars indicate greater impact on the ICER. Parameters are listed in descending order of influence, from top to bottom. The vertical line indicates the base-case ICER when all parameters are set to their base-case values. The dashed vertical line represents the country-specific WTP threshold. Bdq indicates bedaquiline; DR-TB, drug-resistant tuberculosis; Fq, fluoroquinolone; ICER, incremental cost-effectiveness ratio; Lzd, linezolid; pDST, phenotypic drug susceptibility testing; QALY, quality-adjusted life-year; RR, risk ratio; RR-TB, rifampicin-resistant tuberculosis; tNGS, targeted next-generation sequencing; and WTP, willingness-to-pay.

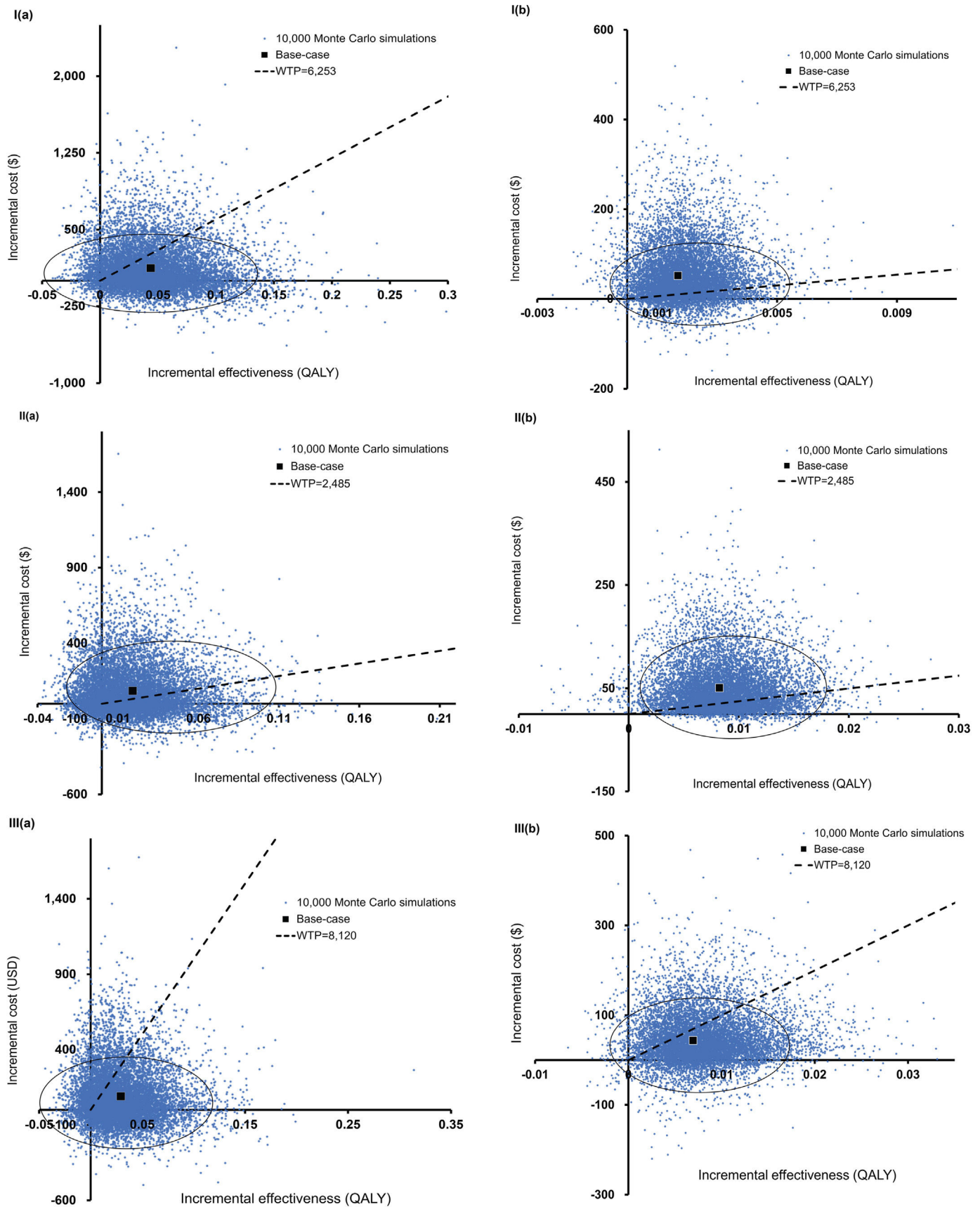


Fig. 3. Scatter plots of incremental cost versus QALYs gained from 10,000 Monte Carlo simulations for (A) tNGS versus pDST and (B) tNGS + pDST versus tNGS in (I) South Africa, (II) India, and (III) Georgia. Each blue point represents the result of one simulation iteration. Ellipses denote the 95% confidence region of the bivariate distribution of incremental cost and incremental QALYs, calculated from the empirical covariance matrix of the simulated pairs; approximately 95% of points are expected to fall within the ellipse under a bivariate normal approximation. The dashed diagonal line indicates the country-specific WTP threshold (South Africa, \$6253/QALY; India, \$2485/QALY; Georgia, \$8120/QALY). Points below this line represent simulations in which the intervention is cost-effective, whereas points in the lower-left quadrant represent cost-saving simulations. QALY indicates quality-adjusted life-year; pDST, phenotypic drug susceptibility testing; tNGS, targeted next-generation sequencing; and WTP, willingness-to-pay.

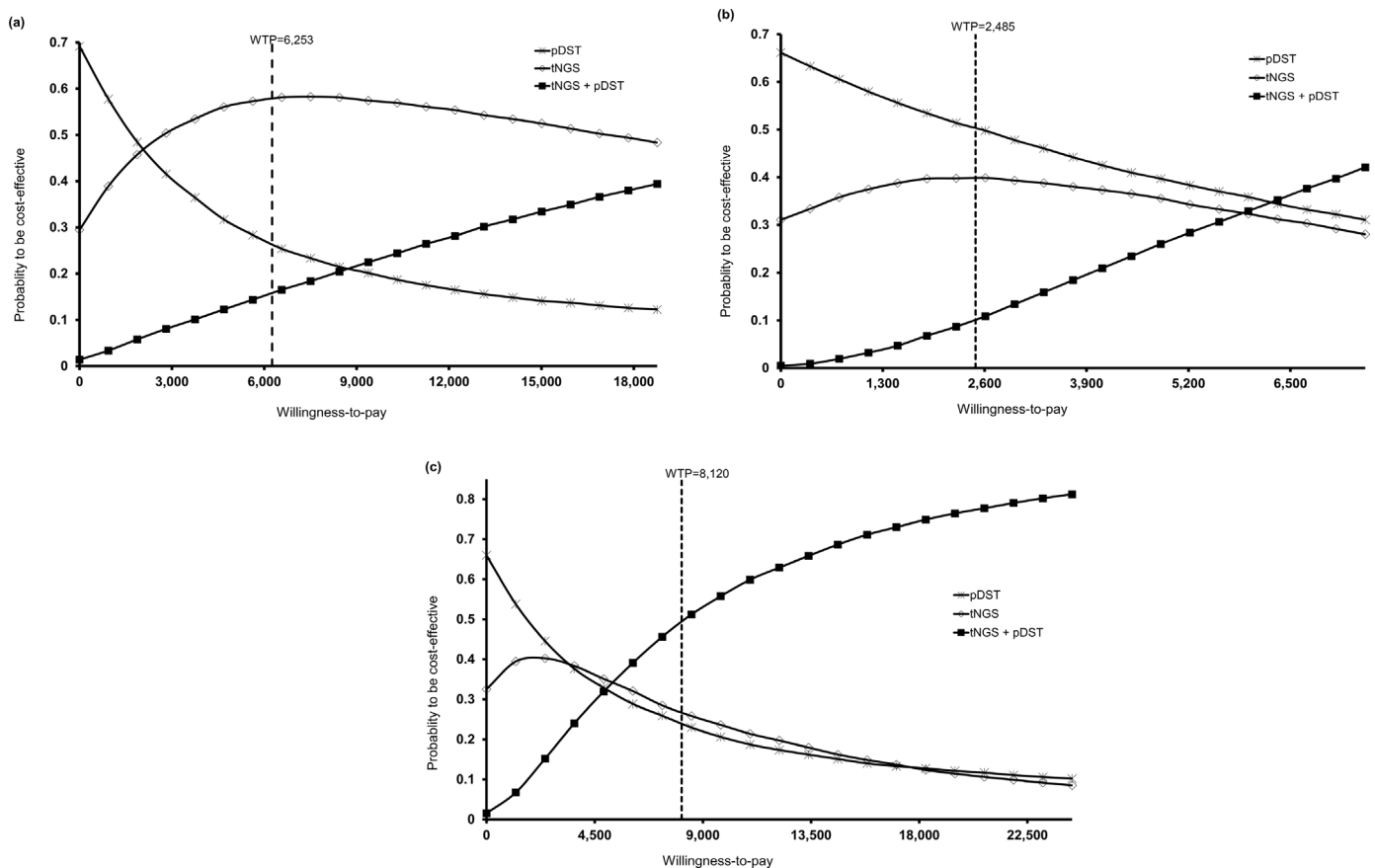


Fig. 4. Cost-effectiveness acceptability curves for pDST, tNGS, and tNGS + pDST strategies for diagnosing pre-XDR and XDR-TB in (A) South Africa, (B) India, and (C) Georgia. The vertical axis shows the probability that each strategy is cost-effective given joint parameter uncertainty. The horizontal axis shows the WTP threshold in US dollars per QALY (2024 USD). The vertical dashed line indicates each country's GDP per capita-based WTP threshold: South Africa, \$6253; India, \$2485; and Georgia, \$8120. The curves demonstrate the probability of cost-effectiveness across a range of WTP values from \$0 to 3 times GDP per capita. GDP indicates gross domestic product; pDST, phenotypic drug susceptibility testing; tNGS, targeted next-generation sequencing; XDR-TB, extensively drug-resistant tuberculosis; and WTP, willingness-to-pay.

Discussion

This study evaluated the cost-effectiveness of tNGS for diagnosing pre-XDR and XDR-TB in RR-TB patients across South Africa, India, and Georgia. tNGS-based strategies improved early treatment initiation and reduced TB-related mortality in all settings, but cost-effectiveness varied substantially by context. In South Africa, tNGS alone was cost-effective (ICER, \$2805/QALY) below the national WTP threshold (\$6253). In Georgia, the combination strategy (tNGS + pDST) was cost-effective (ICER, \$6361/QALY) below the national WTP threshold (\$8120). In India, neither strategy met the WTP threshold (\$2485) at current prices; tNGS would require cost reduction to \leq \$116/test to achieve cost-effectiveness. Probabilistic sensitivity analysis confirmed robustness, with tNGS cost-effective in 58% of simulations in South Africa and the combination strategy cost-effective in 42% of simulations in Georgia.

Our findings complement and extend the WHO-commissioned analysis by Shrestha et al. [14], which evaluated tNGS cost-effectiveness in the same three countries but reached different conclusions—notably, that tNGS was more costly and less effective than universal pDST in the base case, with cost-effectiveness observed only under specific conditions (e.g., at three times GDP per capita in South Africa) [4,14]. The primary distinction lies in model structure: whereas Shrestha et al. [14] focused on diagnostic accuracy, our model explicitly incorporates time-to-treatment effects by linking diagnostic delay to mortality risk, aligns regimen assignment with 2022 WHO guidance (BPAL, BPALM, and longer oral regimens) [16], and includes a broader health-state structure

(surgery, palliative care, and LTFU). These additions demonstrate that tNGS improves outcomes not merely through resistance detection but fundamentally by enabling earlier initiation of effective therapy [13,15]. Consequently, tNGS becomes cost-effective in South Africa and Georgia when this mechanism is accounted for, whereas India remains not cost-effective at current prices. We also provide implementation thresholds (e.g., $tNGS \leq$ \$116/test in India) and alternative WTP perspectives to support policy decisions. A structured comparison is provided in Appendix S3 and Table S5.

The HR, for delayed treatment (HR, 1.53) and tNGS cost were the primary drivers of cost-effectiveness across all settings. Threshold analyses identified tNGS price as a modifiable leverage point: cost-effectiveness in South Africa and Georgia was maintained at up to \$356 and \$311 per test, respectively, whereas India required a price of \leq \$116 to achieve cost neutrality. These findings highlight the importance of volume-based pricing negotiations, technology transfer, and pooled procurement to reduce costs in resource-constrained settings. The predominance of the HR, underscores that interventions to reduce diagnostic delays—such as optimized sample transport systems and rapid result communication—are essential to realize the full survival benefits of tNGS.

The choice of cost-effectiveness threshold also influences interpretation. Although we used GDP per capita-based thresholds following WHO guidelines [28], more recent literature advocates more conservative, empirically derived thresholds that reflect true health opportunity costs [30–32]. Applying the Pichon-Rivière framework [30]—which derives thresholds from health expenditure growth and life expectancy gains—yields alterna-

tive benchmarks of \$4512 for South Africa ($0.72 \times \text{GDP}$), \$487 for India ($0.20 \times \text{GDP}$), and \$4710 for Georgia ($0.58 \times \text{GDP}$). Against these conservative thresholds, tNGS remains cost-effective in South Africa and Georgia (tNGS alone), whereas the combination strategy in Georgia becomes borderline, and India remains unaffordable. This sensitivity analysis (Appendix S4, Table S6) strengthens confidence in our conclusions for South Africa and India while underscoring the need for context-specific threshold deliberation in Georgia. We therefore interpret our results as upper-bound estimates and recommend that country programs consider local opportunity cost-based thresholds when making adoption decisions.

Our findings were also sensitive to the analytic time horizon, reflecting the lag between diagnostic investment and downstream health gains [33]. Short horizons (e.g., 1 year) systematically undervalue tNGS because the survival benefits of earlier treatment accrue over several years through reduced mortality and relapse. Conversely, very long horizons introduce additional uncertainty without materially altering conclusions. Scenario analyses showed that 5–10 years were sufficient to capture the major health and economic impacts of tNGS, supporting the base-case 10-year horizon as an appropriate balance between clinical realism and model stability.

The superior cost-effectiveness of tNGS in South Africa reflects higher baseline mortality rates and greater capacity to absorb diagnostic costs. In Georgia, favorable outcomes for the combination strategy reflect moderate XDR-TB prevalence and a relatively high WTP threshold. In India, the lack of cost-effectiveness is driven by tNGS pricing exceeding affordability thresholds and by the use of shorter oral regimens that limit incremental QALY gains from mortality reduction. These disparities underscore that a one-size-fits-all approach is impractical. In South Africa, scaling up tNGS should be accompanied by investments in laboratory capacity and supply chains. In India, a phased rollout contingent on cost reductions and pilot studies in high-prevalence regions is advisable. Georgia may benefit from selectively deploying combination strategies in areas with high DR-TB prevalence.

These country-specific findings align with recent policy analyses emphasizing the urgency of strengthening RR-TB diagnostic capacity in LMICs. Yates et al. [34] highlight that progress in RR-TB treatment is threatened by emerging drug resistance and poor political choices, making efficient resource allocation paramount. Cavalcanti et al. [35] demonstrate that reductions in health sector funding can substantially worsen mortality, heightening the importance of investing in cost-effective diagnostics. In this context, the selective adoption of tNGS, guided by local cost-effectiveness evidence, provides a pragmatic strategy for maximizing health gains under constrained budgets.

Several limitations must be acknowledged. First, our findings are limited to three countries and may not be generalizable to other high-burden settings with different epidemiological or economic profiles; although the modeling framework is adaptable, local data would be required for context-specific guidance. Second, the model relies on published literature and secondary data, with assumptions—such as perfect pDST accuracy and immediate tNGS results—that may not reflect real-world constraints, including logistical delays, operational barriers, and systemic challenges such as infrastructure deficits and fragmented healthcare delivery. Third, we focused on direct medical costs, excluding indirect costs (e.g., patient transportation and lost productivity) and transmission dynamics, which may underestimate the full societal benefits of tNGS. Future research should incorporate these elements and extend the analysis to other LMICs scaling up molecular diagnostics, enabling cross-country comparisons and evidence-based adoption globally.

Conclusions

This study provides robust evidence supporting the selective adoption of tNGS for diagnosing pre-XDR/XDR-TB in high-burden settings while advancing mechanistic understanding of how rapid diagnostics generate clinical and economic value. By explicitly accounting for the survival benefit of earlier treatment initiation, we demonstrate that tNGS is cost-effective in South Africa and that the combination strategy is cost-effective in Georgia, with context-specific price thresholds guiding implementation. In India, where current tNGS pricing exceeds affordability thresholds, cost reductions and targeted deployment in high-prevalence regions are essential. These findings move beyond whether tNGS is cost-effective to provide actionable guidance on why, how, and under what conditions it delivers value—information critical for national TB programs designing context-specific strategies to reduce diagnostic delays and improve survival.

Author contributions

GF conceived and designed the study. GF, TT, BGL, and TRF developed the model structure and defined the input parameters. GF, TT, FB, MBF, CA, and MJ retrieved and verified the underlying data estimates. GF, FB, XY, SCC, CA, MS, and WKM conducted the cost-effectiveness analysis and interpreted the results. WKM supervised the statistical analyses and overall project coordination. GF, TT, BGL, MBF, and TRF drafted the initial manuscript. XY, CA, LG, NC, LP, MJ, SC, MS, and WKM reviewed and revised subsequent drafts. All authors had full access to the data, contributed to the final edits, and approved the final version of the manuscript for submission.

Ethical approval

Not applicable. This study is a decision-analytic cost-effectiveness modeling study based exclusively on published, publicly available, aggregated, and de-identified data from scientific literature and public health reports. It did not involve direct interaction with human participants, access to individual-level patient data, or identifiable records. Therefore, institutional ethics approval and informed consent were not required.

Artificial intelligence involvement

The initial draft of the graphical abstract was generated using the DALL-E 3 image generation model (accessed via the DeeVid.ai platform) based on text prompts provided by the authors. The final version was substantially modified, edited, and formatted by the authors using Adobe software to ensure scientific accuracy and visual clarity. No AI tools were used for data analysis, interpretation, or manuscript text generation.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data sharing

All data used in this study were obtained from publicly available sources, which are fully referenced in the manuscript. No restrictions apply to data access. All data supporting the findings are included within the article and its supplementary materials.

Conflicts of interest

The authors declare that they have no conflicts of interest that may be considered to influence directly or indirectly the content of the manuscript.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.arbres.2026.04.007.

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