



Rapid, Point-of-Care Diagnosis of Tuberculosis With Novel Truenat Assay: Cost-Effectiveness and Budgetary Impact Analysis for India's Public Sector

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RAPID, POINT-OF-CARE DIAGNOSIS OF TUBERCULOSIS
WITH NOVEL TRUENAT ASSAY:
COST-EFFECTIVENESS AND BUDGETARY IMPACT ANALYSIS
FOR INDIA'S PUBLIC SECTOR

DAVID J. LEE

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Rapid, Point-of-care Diagnosis of Tuberculosis with Novel Truenat Assay:
Cost-effectiveness and Budgetary Impact Analysis for India's Public Sector

Abstract

Background: Truenat is a novel, battery-powered molecular assay that rapidly detects tuberculosis (TB) and rifampicin-resistance. Due to its portability, it may be valuable in peripheral healthcare settings in India, the country with the largest TB burden in the world.

Methods: Using a microsimulation model, we compared four TB diagnostic strategies for HIV-negative adults with suspected TB: (1) sputum smear microscopy in designated microscopy centers (DMCs) (*SSM*); (2) Xpert MTB/RIF in DMCs (*Xpert*); (3) Truenat in DMCs (*Truenat DMC*); and (4) Truenat for point-of-care testing in primary healthcare facilities (*Truenat POC*). We projected life expectancy, costs, incremental cost-effectiveness ratios (ICERs), and 5-year budget impact of deploying *Truenat POC* in India's public sector. We defined a strategy "cost-effective" if its ICER was <US\$990/year-of-life saved (YLS). Model inputs included: TB prevalence, 17%; sensitivity for TB detection, 89% (*Xpert*) and 86% (*Truenat*); per test cost, \$12.63 (*Xpert*) and \$13.20 (*Truenat*); and linkage-to-care after diagnosis, 84% (*DMC*) and 95% (*POC*). We varied these parameters in sensitivity analyses.

Results: Compared to *SSM*, *Truenat POC* increased life expectancy by 0.39 years and was cost-effective (ICER \$210/YLS). Compared to *Xpert*, *Truenat POC* increased life expectancy by 0.08

years due to improved linkage-to-care, and was cost-effective (ICER \$120/YLS). In sensitivity analysis, the cost-effectiveness of *Truenat POC*, relative to *Xpert*, depended on the diagnostic sensitivity of Truenat and linkage-to-care with Truenat. Deploying *Truenat POC* instead of *Xpert* increased 5-year expenditures by \$270 million, due mostly to treatment costs. Limitations of our study include uncertainty in Truenat’s sensitivity for TB detection and not accounting for the “start-up” costs of implementing Truenat in the field. Findings may not be generalizable to settings of high HIV prevalence.

Conclusions: Used at the point-of-care in India, Truenat for TB diagnosis should improve linkage-to-care, increase life expectancy, and be cost-effective compared with smear microscopy or *Xpert*.

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Introduction

With approximately 2.8 million cases annually, India has the world's highest incidence of tuberculosis (TB).¹ However, due to the widespread use of insensitive diagnostics (e.g., sputum smear microscopy) and low linkage-to-care rates, over 25% of Indian patients seeking care in the public sector are neither diagnosed nor started on treatment.²

New rapid molecular diagnostics could dramatically increase TB detection and linkage-to-care, which are key components of both the World Health Organization's (WHO) End TB Strategy and India's National Strategic Plan for Tuberculosis Elimination 2017—2025.^{1,3} The Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) is currently the only WHO-endorsed molecular test able to rapidly detect both TB and rifampicin (RIF)-resistance.¹ While there has been interest in deploying Xpert in peripheral laboratories,³⁻⁶ its decentralization may be limited by infrastructure requirements, including continuous power supply and air-conditioning.^{7,8}

Truenat (Molbio Diagnostics/Bigtec Labs, Goa/Bengaluru, India), is a new battery-powered, micro real-time polymerase chain reaction (RT-PCR) test.^{1,9,10} Truenat uses chips to detect tubercle bacilli in sputum samples in approximately one hour and “add-on” chips to detect RIF-resistance (additional one hour test time). The Truenat platform is available in 1, 2, or 4-module configurations, with the lattermost capable of testing four sputum samples simultaneously. Truenat's portability makes it appealing for use in peripheral healthcare settings, such as designated microscopy centers (DMCs) and primary healthcare facilities in India.

If used as a point-of-care (POC) test within primary healthcare facilities, Truenat could increase treatment initiation by reducing turnaround time for test results and decreasing the need for laboratory referrals.^{2,11} However, uncertainties in parameter values, such as test

characteristics and linkage-to-care, must be investigated. Furthermore, in resource-constrained settings, the potential benefits of Truenat must be weighed against its costs. Using a mathematical model, therefore, we projected the clinical impact, costs, and cost-effectiveness of Truenat, as a replacement for smear microscopy or Xpert. We also evaluated the budget impact of deploying Truenat widely in India's public sector.

Methods

Analytic Overview

We expanded the Cost-Effectiveness of Preventing AIDS Complications-International (CEPAC-I) model, a validated and widely published, individual-based Monte Carlo state-transition model,^{12–14} to account for TB natural history, diagnosis, and treatment. We simulated a cohort of adult, HIV-negative patients with suspected pulmonary TB, defined as individuals aged ≥ 15 years with cough of ≥ 2 weeks duration,^{4,15} undergoing TB testing at DMCs and their attached primary healthcare facilities (e.g., primary health centers, hospital outpatient clinics, etc.) under India's Revised National Tuberculosis Control Programme (RNTCP). Although HIV is an important risk factor for TB, we focus on the HIV-negative population, among whom 97% of new TB cases in India occur.¹

We compared the clinical and economic outcomes of four TB diagnostic strategies: (1) sputum smear microscopy in DMCs (SSM); (2) Xpert in DMCs (Xpert); (3) Truenat in DMCs (Truenat DMC); and (4) Truenat for point-of-care testing in primary healthcare facilities (Truenat POC). In each strategy, patients for whom clinical suspicion of TB remains high despite a negative test result may undergo additional testing. Patients previously treated for TB, and therefore at higher risk of drug-resistance, may receive additional tests to confirm multidrug-resistant TB (MDR-TB) (S1 Appendix; Figs A—C in S1 Appendix).

Model-generated outcomes included the correct detection and linkage-to-care of TB cases; life expectancy; lifetime TB-related healthcare costs; and incremental cost-effectiveness ratio (ICER), the difference between two strategies in costs (2017 US dollars) divided by the difference in life-years. We considered a strategy cost-effective if its ICER was less than

US\$990/year-of-life saved (YLS), an opportunity-based cost-effectiveness threshold that is 50% of India's 2017 gross domestic product (GDP) per capita (S1 Appendix). We also projected outcomes at different time horizons. We report outcomes discounted 3%/year for cost-effectiveness analysis and undiscounted outcomes for clinical and budget evaluations.¹⁶

Model Overview

A simulated cohort of patients enters the model upon seeking care in India's public sector for symptoms suggestive of TB. They undergo a TB diagnostic protocol per national guidelines.^{4,15} The model draws randomly from user-defined characteristics (e.g., age, sex, TB status), informed by a recent implementation study of Xpert for Indian patients with suspected TB.⁴ As individuals transition monthly through "states" of TB progression and treatment, the model tracks clinical outcomes (e.g., cure, relapse, life-years accrued) and monthly TB-related healthcare costs (e.g., diagnostic tests, drugs, clinic visits). Throughout the simulation, all individuals are subject to age- and sex-stratified background mortality risks specific for India, while those with active, untreated TB have an excess mortality risk. Model details are in the S1 Appendix and at <http://www.massgeneral.org/mpec/cepac/>.

To initiate TB treatment, a simulated individual must: (1) complete the diagnostic pathway, including retrieving test results; (2) receive a diagnosis of TB and/or drug-resistance, as determined by test characteristics; and (3) link to a primary healthcare facility that will initiate and monitor TB treatment ("linkage-to-care"). Those who receive a TB diagnosis via Truenat POC initiate treatment immediately, whereas those diagnosed in DMCs require referral to a primary healthcare facility and, therefore, have a lower probability of linkage-to-care (S1 Appendix).²

Base Case Input Parameters

Cohort Characteristics and TB Prevalence

Cohort characteristics were derived from an Indian implementation study of Xpert for individuals with suspected TB in DMCs of 18 sub-district level TB program units, chosen for being geographically and demographically representative of the national population (Table 1).⁴ Mean age was 41 years, 36% were women, and 17% had been previously treated for TB. Among patients with suspected TB, we assumed TB prevalence was 15% for patients with no prior TB treatment and 27% for previously treated patients (S1 Appendix).⁴

Table 1. Input parameters for model-based analysis of TB diagnostic strategies for patients with suspected TB in India.

Parameter	Base case	Range^a	References
Baseline cohort characteristics			
Age, years, mean (SD)	41.4 (16.1)	---	4
Men/Women	64/36%	---	4
Proportion previously treated for TB	17%	7 – 27%	4
Prevalence of TB			
among those not previously treated for TB	15%	8 – 23%	S1 Appendix
among those previously treated for TB	27%	18 – 40%	S1 Appendix
Prevalence of MDR-TB			
among those not previously treated for TB	6%	4 – 7%	17
among those previously treated for TB	36%	29 – 42%	17
Diagnostic tests			
Sputum smear microscopy			
Sensitivity (2 samples)	64%	60 – 69%	18
Specificity (2 samples)	98%	97 – 99%	18
Proportion of patients who provide a second sputum sample	89%	85 – 93%	2
Cost per test (USD 2017)	\$0.86	\$0.24 – 1.58	19

Table 1. Input parameters for model-based analysis of TB diagnostic strategies for patients with suspected TB in India (continued).

Parameter	Base case	Range ^a	References
Diagnostic tests (continued)			
Clinical diagnosis for smear-negative patients ^b			
Sensitivity	16%	6 – 26%	20
Specificity	94%	84 – 100%	20
Proportion of smear-negative patients who undergo a clinical diagnostic work-up	39%	20 – 39%	2
Cost per patient (USD 2017)	\$8.24	\$7.17 – 9.28	21
Xpert			
Sensitivity, TB detection	89%	85 – 92%	22
Specificity, TB detection	99%	98 – 99%	22
Sensitivity, RIF-resistance detection	95%	90 – 97%	22
Specificity, RIF-resistance detection	98%	97 – 99%	22
Probability of test failure (for power or temperature issue)	1%	0 – 5%	6
Cost per test (USD 2017)	\$12.63	\$11.47 – \$14.84	19
Truenat			
Sensitivity, TB detection	86%	66 – 100%	Methods; 9
Specificity, TB detection	99%	80 – 100%	Methods
Sensitivity, RIF-resistance detection ^c	94%	74 – 100%	S1 Appendix
Specificity, RIF-resistance detection ^c	98%	88 – 100%	S1 Appendix
Cost per test (USD 2017)	\$13.20	\$12.75 – \$13.79	Communication with manufacturer; 19
Liquid culture & DST			
Culture sensitivity, TB detection	100%	---	Gold standard assumption
Culture specificity, TB detection	100%	---	Gold standard assumption
DST sensitivity, MDR-TB detection	100%	---	Gold standard assumption
DST specificity, MDR-TB detection	100%	---	Gold standard assumption
Cost per test, liquid culture (USD 2017) ^d	\$13.30	\$10.32 – \$16.29	19
Cost per test, DST (USD 2017) ^d	\$30.93	\$27.23 – \$34.63	19
Treatment of TB			
Linkage-to-care			
after DMC-based test	84%	80 – 88%	S1 Appendix
after POC test (i.e., <i>Truenat</i> POC)	95%	88 – 100%	S1 Appendix
Monthly probability of loss to follow-up during treatment ^e	1%	0.008 – 2% ^f	5
Monthly cost of treatment ^g			
First-line regimen, 6 months (USD 2017)	\$28.13	\$24.13 – \$32.49	19,23,24
Retreatment regimen, 8 months (USD 2017)	\$32.25	\$28.30 – \$36.23	19,23,24
Second-line regimen, 24 months (USD 2017)	\$104.23	\$96.15 – \$112.13	19,23,24

TB: tuberculosis. MDR-TB: multidrug-resistant tuberculosis. RIF: rifampicin. SD: standard deviation. USD: 2017 United States dollars. C&DST: culture and drug-susceptibility testing. DST: drug-susceptibility testing. DMC: designated microscopy center. POC: point-of-care.

^aRange used for univariate sensitivity analysis.

^bClinical diagnosis includes chest radiography and antibiotic trial.

^cSensitivity and specificity of Truenat for RIF-resistance detection is based on the line probe assay as the gold standard (S1 Appendix).

^dCosts for liquid culture and DST are based on the BACTEC MGIT (BD, Sparks, MD, USA) system.¹⁹

^eMonthly probability of loss to follow-up is the weighted probability of loss to follow-up during all treatment regimens.⁵

^fRange based on variation across sites.

^gTreatment costs include drugs, monitoring tests, clinic visits, and hospitalizations (S1 Appendix).

Diagnostic Tests

Sensitivity and specificity of smear microscopy for two sputum samples were 64% and 98% (Table 1).¹⁸ One validation study reports Truenat's sensitivity for TB detection as 96% compared to Xpert.⁹ We used this value as a multiplier to scale Truenat's sensitivity against Xpert's sensitivity reported in a meta-analysis.²² Therefore, the sensitivities of Truenat and Xpert for TB detection were 86% and 89%. We assumed 99% specificity for Truenat, similar to Xpert (Table 1).²² We varied Truenat sensitivity and specificity in sensitivity analyses.

Linkage-to-Care and Treatment

Linkage-to-care was 84% for patients diagnosed in DMCs and 95% for those diagnosed by a POC test (*Truenat POC* only).² The latter was an evidence-supported assumption (S1 Appendix) that we varied in sensitivity analyses. For patients who received a negative result after POC testing with Truenat but were subsequently diagnosed via culture, linkage-to-care remained 84%. Other treatment-related parameters, including loss to follow-up, were derived from Indian TB surveillance data (Table 1).⁵

Costs

Using a microcosting approach, we derived unit costs of TB care from a health system perspective.^{19,21,23,24} We multiplied unit costs by their expected quantities, either as indicated by published guidelines (e.g., number of clinic visits) or as reported in epidemiological studies (e.g., hospitalization rates) (S1 Appendix). The costs per test for Xpert and Truenat were \$12.63 and \$13.20 (Table 1), which included costs of overhead and building space, labor, reagents (cartridges for Xpert and chips for Truenat), and capital (test machine). The monthly costs of TB treatment were \$28.13 (first-line), \$32.25 (retreatment), and \$104.23 (second-line), which included the costs of drugs, monitoring tests, clinic visits, and hospitalizations during treatment (S1 Appendix).^{19,21,23,24}

We obtained price estimates for Truenat from the manufacturer (Sriram Natarajan, Director and CEO of Molbio, personal communication). The price of the Truenat machine capable of testing four specimens simultaneously is \$14,150. We used this cost in the base case for comparison with a 4-module Xpert machine (assumed to be the standard in India). This cost was annualized over the expected lifespan of the machine, discounted 3%/year, and divided by the expected number of tests it would perform annually. The price of the Truenat chip for TB

detection is \$12.40, and the chip for RIF-resistance detection will be provided free of cost based on an average estimated TB-positive proportion of 20%. These initial price estimates for the public sector may change based on volume commitment by the government. We assumed that overhead, building space, and staff-related costs for Truenat strategies would be similar to those of Xpert.¹⁹

Additional input parameters regarding TB prevalence, natural history, diagnostics, and treatment are in S1 Appendix.

Sensitivity and Scenario Analyses

To account for uncertainty, we varied key parameters (e.g., test sensitivity, linkage-to-care, costs) across a wide range of possible values, informed by literature whenever possible (Table 1). We also evaluated the effect of empirical treatment on cost-effectiveness. Specifically, we considered the scenario in which 16% of those with a negative smear, Xpert, or Truenat result receive empirical treatment (S1 Appendix).

We conducted a two-way sensitivity analysis, simultaneously varying Truenat's sensitivity for TB detection and linkage-to-care at a 5-year horizon, to define the combination of parameter values by which *Truenat POC* would be more economically efficient than *Xpert*. Furthermore, because the public sector cost of Truenat may decrease based on volume commitment by the Indian government, we conducted this same analysis for a scenario in which the Truenat chip cost is negotiated to 60% of the current estimate (S1 Appendix).

Budget Impact Analysis

We projected costs associated with widespread deployment of diagnostic strategies in India's public sector over a 2-year and 5-year period. We assumed 7.9 million adults with suspected TB would be tested annually (S1 Appendix).

Results

Base Case Clinical Outcomes

Truenat DMC, compared to *SSM*, increased life expectancy by 0.30 years (undiscounted) but, compared to *Xpert*, decreased life expectancy by 0.01 years (Table 2). *Truenat POC* was the most effective strategy, increasing life expectancy by 0.39 years compared to *SSM* and by 0.08 years compared to *Xpert*. Compared to *SSM* and *Xpert*, *Truenat POC* also increased the number of TB cases correctly detected and linked to care by 590 and 140, respectively, per 10,000 individuals with suspected TB.

Table 2. Model-generated clinical and economic outcomes of TB diagnostic strategies.

Strategy	Cases detected ^a	Cases detected and linked ^b	Lifetime outcomes (per person)				
	per 10,000 individuals with suspected TB		Life-years		Costs (2017 USD)		ICER (\$/YLS) ^e
			Undisc.	Disc. (3%/y)	Undisc.	Disc. (3%/y)	
<i>SSM</i>	1,000	840	31.17	18.58	80	80	–
<i>Truenat DMC</i>	1,510	1,270	31.47	18.76	130	120	dominated ^f
<i>Xpert</i>	1,530	1,290	31.48	18.76	130 ^c	120 ^c	dominated ^f
<i>Truenat POC</i>	1,510	1,430	31.56	18.80	140	120 ^d	210

TB: tuberculosis. SSM: sputum smear microscopy. DMC: designated microscopy center. POC: point-of-care. Undisc: undiscounted. Disc. (3%/y): discounted 3%/year. USD: United States dollars.

ICER: incremental cost-effectiveness ratio. YLS: year-of-life saved.

^aNumber of individuals with suspected TB seeking care at model entry who were correctly identified as having TB by each strategy.

^bNumber of individuals with suspected TB seeking care at model entry who were correctly identified as having TB and linked to treatment by each strategy.

^cLifetime cost of *Xpert* is higher than that of *Truenat DMC*, but appears the same due to rounding.

^dLifetime cost of *Truenat POC* is higher than that of *Xpert*, but appears the same due to rounding.

^eICERs were calculated using exact numbers, then rounded to the nearest \$10.

^f“dominated”: weakly dominated (higher ICER than that of a strategy offering more life-years)

Base Case Lifetime Costs and Cost-effectiveness

Compared to *SSM*, *Truenat DMC* and *Truenat POC* strategies both increased discounted per-patient lifetime costs by ~\$40 (Table 2). Compared to *Xpert*, *Truenat DMC* decreased discounted per-patient lifetime costs by \$1 and *Truenat POC* increased costs by \$5.

While *Truenat DMC* was cost-effective compared to *SSM* (ICER \$240/YLS), it resulted in lower life expectancy and higher ICER than *Xpert* and was, therefore, “weakly dominated” (i.e., economically inefficient). *Truenat POC* was cost-effective compared to both *SSM* (ICER \$210/YLS) and *Xpert* (ICER \$120/YLS). When viewed over different time horizons, *Truenat POC* became cost-effective compared to *Xpert* and *SSM* after 4 and 6 years, respectively. *Xpert* also became cost-effective compared to *SSM* after 6 years (Fig E in S1 Appendix).

One-Way Sensitivity and Scenario Analyses

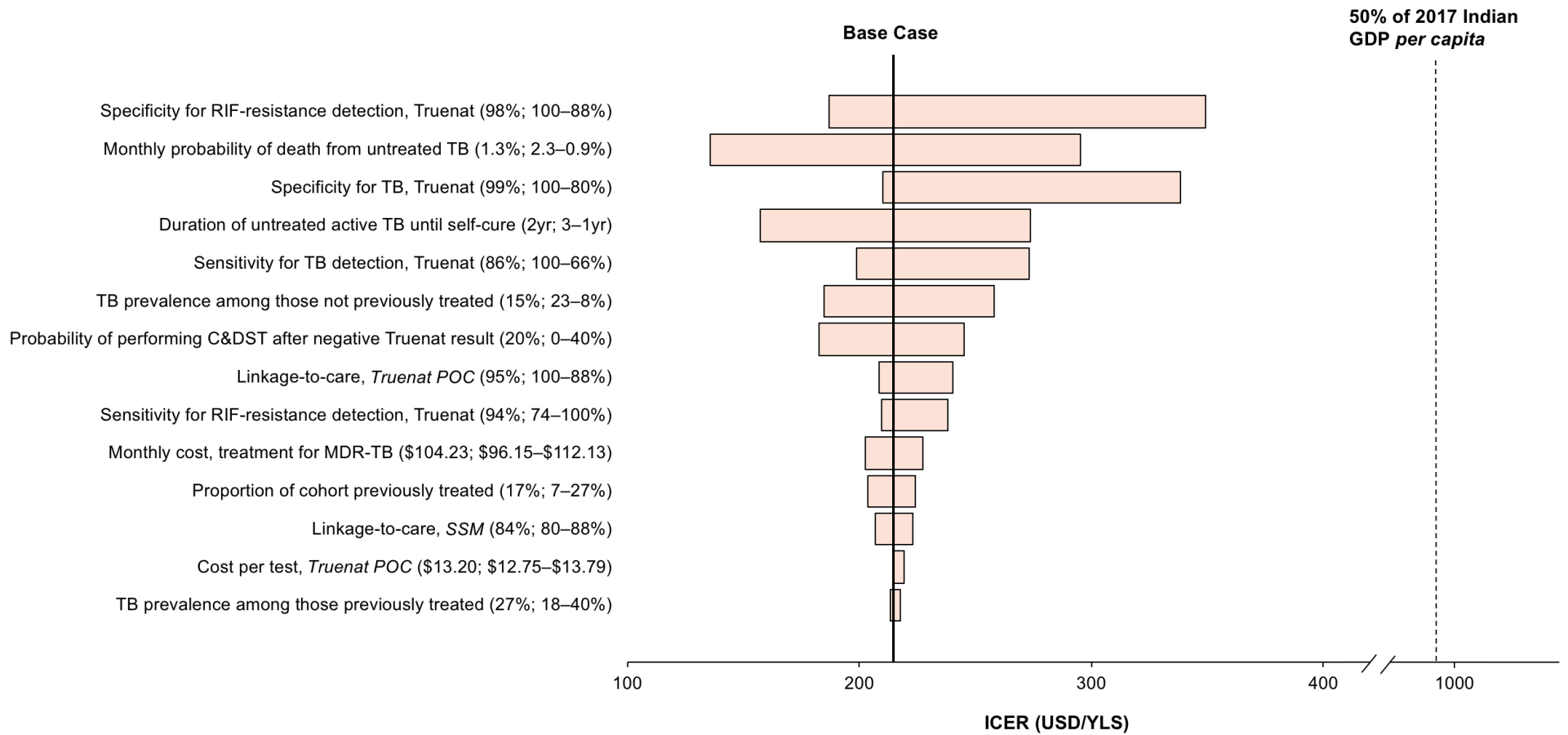
In one-way sensitivity analyses comparing *Truenat POC* to *SSM* at a lifetime horizon, *Truenat POC* remained cost-effective compared to *SSM* across parameter values analyzed (Fig 1;

Fig F in S1 Appendix). Decreasing Truenat’s sensitivity for TB detection by an absolute 20% (from 86% to 66%) resulted in ~27% change in the base case ICER of *Truenat POC* versus *SSM*, at a lifetime horizon. Varying TB and MDR-TB prevalence had little influence on the ICER of *Truenat POC*. While Truenat’s specificity for RIF-resistance detection was the most influential among the parameters considered, the ICER (\$350/YLS) that resulted from decreasing the specificity by 10% remained well below the cost-effectiveness threshold of \$990/YLS. When accounting for empirical treatment in 16% of those with a negative smear, Xpert, or Truenat result, *Truenat POC* remained cost-effective compared to *SSM* (ICER \$290/YLS) and compared to *Xpert* (ICER \$200/YLS).

Fig 1. One-way sensitivity analyses of key model parameters, comparing *Truenat POC* to *SSM*, at lifetime horizon.

TB: tuberculosis. MDR-TB: multidrug-resistant tuberculosis. RIF: rifampicin. C&DST: culture and drug-susceptibility test. yr: year. POC: point-of-care. “previously treated”: previously treated for TB. GDP: gross domestic product. ICER: incremental cost-effectiveness ratio. USD: United States dollars. YLS: year-of-life saved.

Horizontal bars represent ranges of ICERs when varying each model parameter across its plausible range. The vertical dashed line represents 50% of the GDP *per capita* of India in 2017 (\$990), which we consider the cost-effectiveness threshold (see Methods). ICERs less than \$990/YLS (left of dashed line) are considered cost-effective.

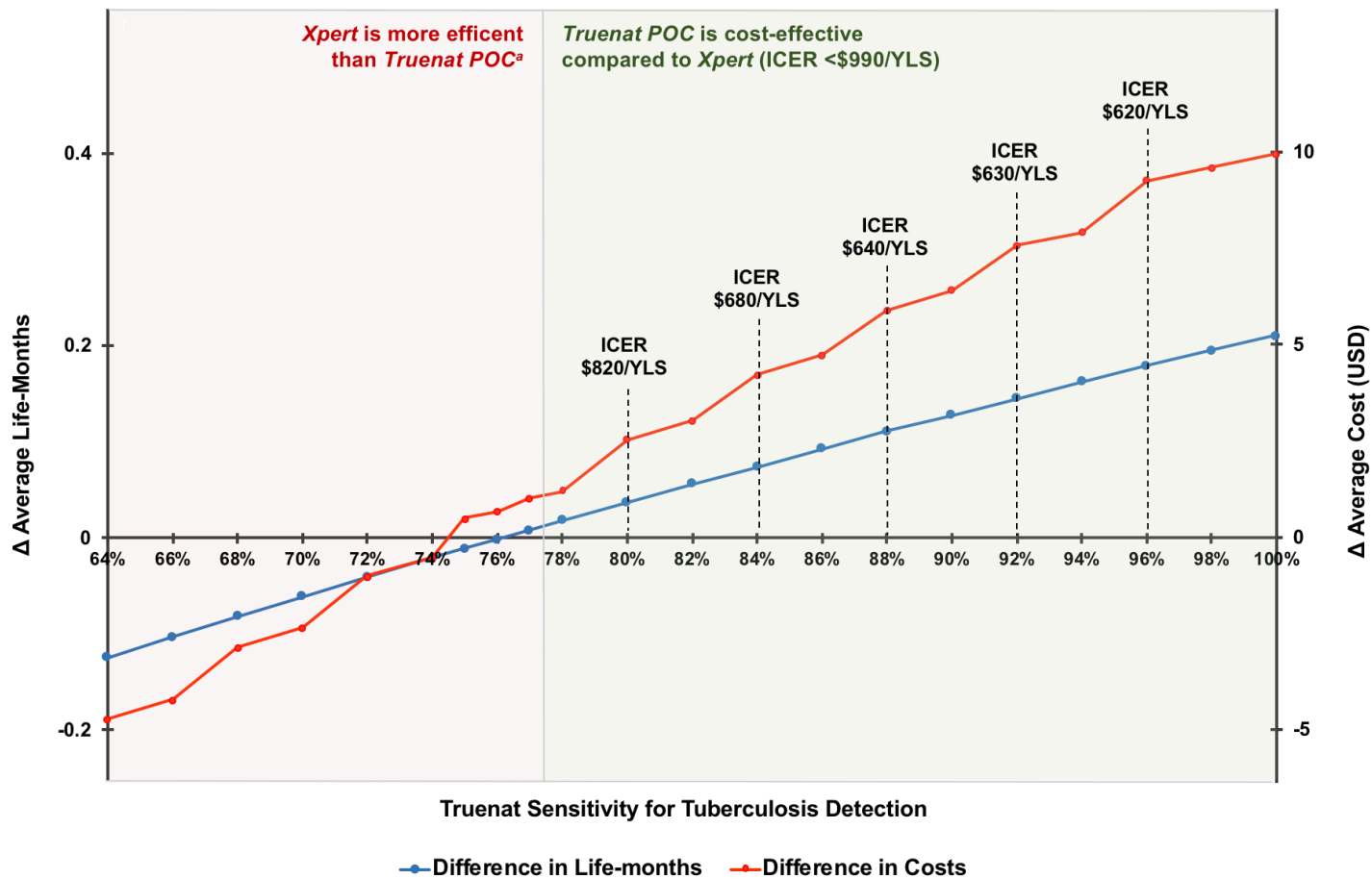


We compared *Truenat POC* to *Xpert* over a shorter 5-year horizon, varying Truenat's sensitivity for TB detection (Fig 2). When Truenat's sensitivity was $\geq 78\%$, *Truenat POC* increased life-years, increased costs, and was cost-effective compared to *Xpert*. The higher cost was driven mostly by the increased number of patients initiating treatment; however, these costs were offset by improvements in clinical outcomes, resulting in overall decreasing ICERs as sensitivity increased. When Truenat's sensitivity was $< 75\%$, *Truenat POC*, compared to *Xpert*, resulted in fewer life-years and lower cost. In this scenario, the ICER of *Xpert* compared to *Truenat POC* was below the cost-effectiveness threshold, indicating that *Xpert* was cost-effective.

Fig 2. Sensitivity analysis of Truenat sensitivity for TB, comparing *Truenat POC* to *Xpert* at 5-year horizon.

TB: tuberculosis. POC: point-of-care. ICER: incremental cost-effectiveness ratio. YLS: year-of-life saved. USD: United States dollars.

This plot shows the differences in life expectancy and costs between *Truenat POC* and *Xpert* at a 5-year horizon when varying the sensitivity of Truenat for TB detection. The horizontal axis is the sensitivity of Truenat for TB detection. The blue line corresponds to the left vertical axis, which is the difference in life expectancy between *Truenat POC* and *Xpert*. The red line corresponds to the right vertical axis, which is the difference in per-person lifetime costs between *Truenat POC* and *Xpert*. The ICER (i.e., the difference in costs divided by the difference in life expectancy) is provided at regular intervals of test sensitivity values. For integer values of test sensitivity $\geq 78\%$ (green panel), *Truenat POC* is cost-effective compared to *Xpert* (ICER $< \$990/\text{YLS}$). For integer values $< 78\%$ (red panel), *Xpert* is more efficient than *Truenat POC*.



^a“*Xpert* is more efficient than *Truenat POC*”: For *Truenat* sensitivity values <75%, *Xpert* was cost-effective compared to *Truenat POC* (ICER <\$990/YLS). At *Truenat* sensitivity of 75—76%, *Xpert* was cost-saving (lower cost, higher clinical benefit [more life-years accrued]) compared to *Truenat POC*. At *Truenat* sensitivity of 77%, *Xpert* was decrementally cost-effective (lower cost and lower clinical benefit but with ICER >\$990/year-of-life lost [YLL]—that is, at least \$990 saved per year-of-life-lost) compared to *Truenat POC*.

Two-Way Sensitivity and Scenario Analyses

We simultaneously varied Truenat’s sensitivity for TB detection (68–100%) and linkage-to-care (84–100%), comparing *Truenat POC* to *Xpert* over a 5-year horizon (Fig 3A). We kept *Xpert*’s sensitivity and linkage-to-care at base case values. *Truenat POC*, at 86% sensitivity, was cost-effective when linkage-to-care was $\geq 88\%$. This linkage threshold for cost-effectiveness increased as Truenat sensitivity decreased. For sensitivity values $\leq 74\%$, *Truenat POC* was not cost-effective at any linkage value. Above 90% sensitivity, *Truenat POC* was cost-effective at linkage values as low as 84% (same linkage as *Xpert*). In the scenario that Truenat’s chip cost is reduced to 60% of its current estimate, the range of parameter values for which *Truenat POC* was cost-effective (or cost-saving) compared to *Xpert* broadened (Fig 3B).

Fig 3. Two-way sensitivity and scenario analysis heat maps, comparing *Truenat POC* to *Xpert* at 5-year horizon.

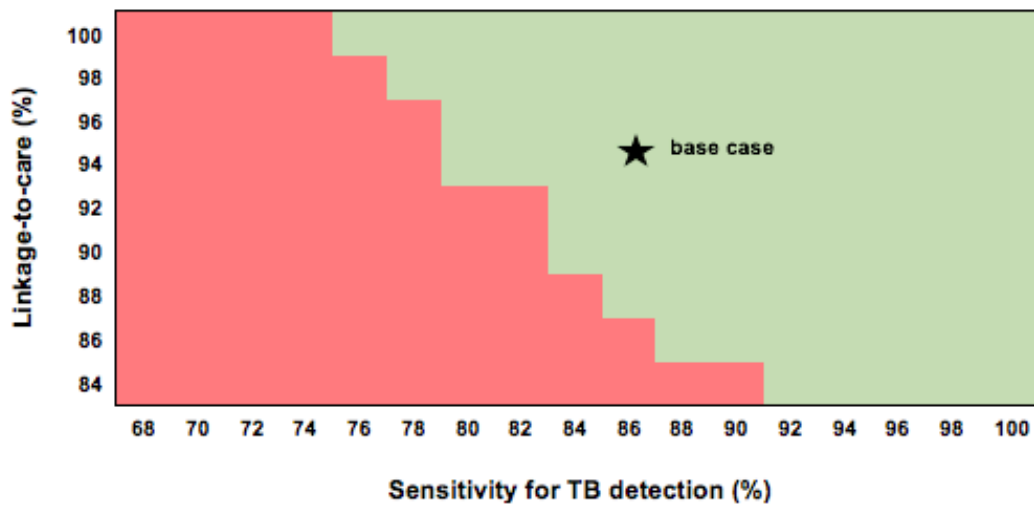
TB: tuberculosis. POC: point-of-care. YLS: year-of-life saved. YLL: year-of-life lost.

These heat maps evaluate the incremental cost-effectiveness ratio of *Truenat POC* strategy relative to *Xpert* at a 5-year time horizon for different values of Truenat sensitivity for TB detection and linkage-to-care. Each panel displays different costs of Truenat, including the scenario (B), in which the price of the Truenat chip is negotiated to 60% of its current estimate for the public sector (S1 Appendix). Sensitivity of Truenat for TB detection increases from left to right on the horizontal axes. The probability of patients linking to care upon receiving a positive TB test result with Truenat increases up the vertical axes.

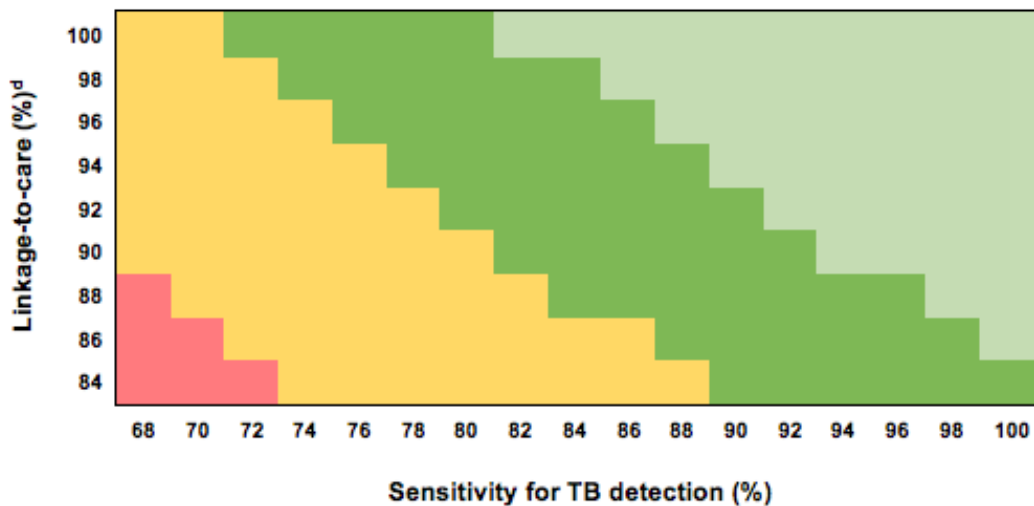
Legend

- Truenat POC* is cost-effective compared to *Xpert* (ICER <\$990/YLS)
- Truenat POC* is cost-saving compared to *Xpert* (higher clinical benefit [i.e., life-years accrued], lower cost)
- Truenat POC* is decrementally cost-effective compared to *Xpert* (ICER >\$990/YLL)^a
- Xpert* is more efficient than *Truenat POC*^c

A) \$13.20 per test (base case)



B) \$8.30 per test (price of Truenat chip reduced to 60% of its current price)^c



^a“Decrementally cost-effective”: *Truenat POC* results in lower cost and lower clinical benefit compared to *Xpert*, but with ICER >\$990/year-of-life lost (YLL)—that is, at least \$990 is saved per year-of-life lost.

^b“*Xpert* is more efficient than *Truenat POC*”: *Xpert* is either cost-effective (ICER <\$990/YLS), cost-saving (lower cost, higher clinical benefit [more life-years accrued]), or decrementally cost-effective (ICER >\$990/YLL), compared to *Truenat POC*.

^cAt 95% linkage (as assumed for POC test), *Truenat POC* was cost-effective when sensitivity was $\geq 88\%$, cost-saving when sensitivity was 77–87%, and decrementally cost-effective (“much less costly and almost as good”) when sensitivity was $\leq 76\%$. When linkage was 84% (typical of DMC), *Truenat POC* was cost-saving when sensitivity was >88%, and decrementally cost-effective when sensitivity was 74–88%.

Budget Impact Analysis

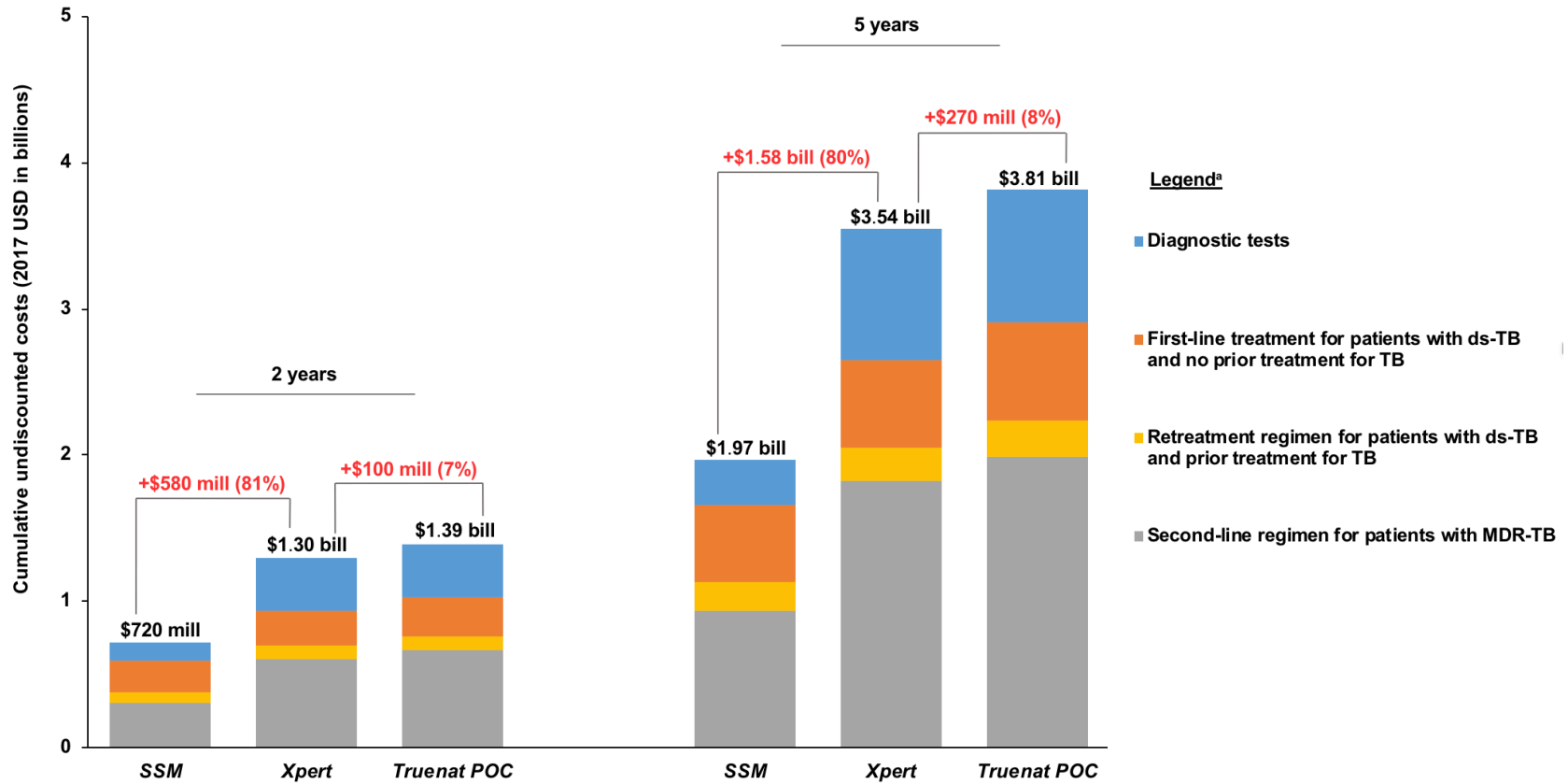
Compared to country-wide use of *SSM* in India’s public sector, scaling up *Xpert* increased cumulative TB-related healthcare expenditures by \$580 million (81% increase) over 2 years and by \$1.58 billion (80% increase) over 5 years (Fig 4). Most of the difference in costs over 5 years was due to increased spending on MDR-TB treatment (56% of the increase), followed by diagnostic tests (37% of the increase). Deploying *Truenat POC* instead of *Xpert* increased cumulative healthcare expenditures by \$100 million (7% increase) over 2 years and by \$270 million (8% increase) over 5 years. Most of the difference in costs over 5 years was due to increased spending on MDR-TB treatment (63% of the increase), followed by drug-susceptible TB treatment (22% of the increase).

Fig 4. Budget impact analysis over 2 and 5 years.

TB: tuberculosis. ds-TB: drug-susceptible tuberculosis. MDR-TB: multidrug-resistant tuberculosis.

SSM: sputum smear microscopy. POC: point-of-care. mill: million. bill: billion.

Budget impact analysis of full public sector implementation of sputum smear microscopy (*SSM*), *Xpert*, and *Truenat POC* strategies over 2- and 5-year time horizons. Cumulative TB-related costs (2017 USD, billions) are on the vertical axis. This analysis assumes that 7.9 million adults in India are tested each year for symptoms suggestive of TB (S1 Appendix).⁴ All calculations were made using exact numbers before rounding to the nearest \$10 million (for costs) and 1% (for percentages).



^aEach treatment regimen is associated with a frequency of clinic visits and rate of hospitalization during the course of TB treatment, as reported by published guidelines and/or epidemiological data (S1 Appendix). These clinical costs are incorporated into the budget impact projection for each category.

Discussion

A major WHO priority for TB diagnostics is to implement a rapid, sputum-based molecular test to replace smear microscopy at the peripheral level (i.e., microscopy centers and attached primary healthcare facilities).^{7,8} Our model-based analysis shows that in India, Truenat, when replacing smear microscopy and used at point-of-care, increases the number of TB cases correctly detected and linked to care by 590 per 10,000 individuals with suspected TB. It also increases life expectancy by nearly 0.4 years and is cost-effective. While *Truenat DMC* was economically inefficient among the four strategies (including compared to Xpert), it was cost-effective when compared directly to *SSM*. The cost-effectiveness of *Truenat POC*, compared to *SSM*, was consistent across a wide range of clinical and cost parameter values.

The WHO's target product profile (TPP) of the "smear replacement test" includes a set of minimal and optimal requirements.^{7,8} Truenat fits many minimal TPP standards, including battery-powered operation and <2 hours to result. However, it currently falls short of optimal TPP standards for test characteristics (i.e., sensitivity for TB detection ideally better than Xpert) and minimal standards for price (i.e., <\$6 per reagent and <\$1,400 per instrument).^{7,8} Our analysis shows that despite these limitations, *Truenat POC* increases life expectancy and is cost-effective compared to *SSM* or *Xpert*.

Our analysis, however, reveals an important relationship between TB detection sensitivity and linkage-to-care. As Truenat's TB detection sensitivity decreases, the linkage-to-care level necessary for *Truenat POC* to be cost-effective compared to *Xpert* increases. This interplay is consistent with other modeling work showing that a theoretical, peripheral-level TB test with inferior performance characteristics but improved treatment initiation rates, compared to district-

level Xpert testing, would reduce TB transmission and incidence.²⁵ Our results show that such a test can also be cost-effective. These findings together imply that increasing case detection (via improved test performance characteristics) and increasing the number of patients on life-prolonging treatment (via improved linkage-to-care) may yield synergistic results from a cost-effectiveness standpoint.

Truenat POC will be even more economically efficient if the price of the Truenat chip is reduced to 60% of its current estimate (with Truenat, therefore, becoming less expensive than Xpert). This reduced price would still be higher than the <\$6 TPP stipulation. The 4-module Truenat machine is also currently ten times more expensive than the TPP price stipulation for a test instrument. Even so, our scenario analysis shows *Truenat POC* is cost-effective, cost-saving, or decrementally cost-effective (“much less costly and almost as good”), relative to *Xpert*, across the wide range of parameter values considered.

Results from our scenario analysis are notable in that improvements in Truenat’s TB detection sensitivity and linkage-to-care yield favorable but higher ICERs. For example, *Truenat POC*, at 86% sensitivity and 90% linkage-to-care, is cost-saving (more life-years, lower cost) compared to *Xpert*, but becomes cost-effective (more life-years, higher cost) if linkage-to-care improves to 100%. This occurs because TB treatment costs, not diagnostic test costs, are the main driver of lifetime costs. Factors leading to higher treatment initiation increase the cumulative costs per patient. Our analysis, nonetheless, shows that this increase in cumulative costs is justified, from a cost-effectiveness perspective, by the clinical benefit of more patients receiving life-prolonging treatment (i.e., more life-years are saved at an acceptable additional cost). Such findings have also been observed in HIV screening programs, where a major driver

of cost is the treatment pathway triggered when a previously undetected case is identified and the patient is linked to life-prolonging care.^{26,27}

The RNTCP can consider these findings as it pursues its ambitious National Strategic Plan (NSP) to eliminate TB in India by 2025.³ The NSP's projected budget of \$2.49 billion for the 2017—2020 period assumes approximately half of patients with TB receive molecular testing. Additional diagnostics are being planned for another 4.5 million patients during this period.³ Our analysis shows that scaling up molecular diagnostics will increase the required budget but the majority of the cost will be from MDR-TB treatment. A recent economic analysis for India similarly found that full replacement of smear microscopy with Xpert would substantially increase budget requirements but would result in lower cost per MDR-TB case initiated on treatment.²¹ As the RNTCP plans its NSP budget for 2020—2025, it should consider MDR-TB treatment costs as much as, if not more than, the prices of diagnostic tests.

A “real-world” economic evaluation by Vassall et al. showed that Xpert did not improve the cost-effectiveness of drug-susceptible TB diagnosis and treatment over a 6-month horizon, contrary to previous projections.²⁸ This finding underscores the need for cost-effectiveness analyses to account for uncertainties in implementation constraints.²⁹ In modeling our diagnostic and treatment pathway, we adjusted for many demand-side constraints, including care-seeking, test uptake, and adherence. We also adjusted for some supply-side constraints, including infrastructure limitations. While these parameters vary with geographical region (e.g., rural, urban, etc.), we drew on aggregated sources, including national surveillance data and studies using demographically and geographically representative population samples from India,^{2,4,6} to adjust for the “average” peripheral healthcare setting in India. We found that neither *Xpert* nor

Truenat POC was cost-effective compared to *SSM* until 6 years after initial testing, well beyond the 6-month time horizon considered by Vassall et al.²⁸

Our findings apply to an HIV-negative population. In populations with high prevalence of undertreated HIV,²⁸ the potential clinical benefits of *Xpert* and *Truenat POC* could be offset by high HIV-related mortality. HIV is also associated with lower sensitivity of TB diagnostics and substantial costs of screening and treatment.^{1,22,26,27} Thus, studies of *Truenat POC* testing in this vulnerable population would be valuable.

We did not consider a POC strategy for *Xpert*. Studies conducted primarily within well-resourced clinics in South Africa have demonstrated the feasibility of *Xpert POC* testing.³⁰⁻³⁴ We are aware of only one study in India evaluating *Xpert POC* testing, within an outpatient clinic of a well-resourced tertiary hospital.³⁵ It remains unclear whether this strategy can be replicated universally across diverse settings, including rural and tribal/hilly areas of India.³⁶⁻³⁸ While infrastructure concerns may have, to an extent, deterred interest in a POC strategy for *Xpert* in many high-burden countries,^{38,39} they have also spurred substantial research and development in a new generation of molecular diagnostics, such as *Truenat*, specifically intended for the primary healthcare setting.^{7,8} Our study is focused on this latter area of policy interest.

Limitations of our study include those related to parameter inputs and model structure. We did not account for reduced transmission from faster diagnosis and treatment initiation, which could improve the cost-effectiveness of POC testing at a broader scale. We did not consider some supply-side constraints that could disrupt successful POC testing and treatment, such as irregularities in test reagent and drug supply chains and variations in provider adherence to the diagnostic and treatment pathway.²⁹ Importantly, more data are needed regarding *Truenat* test characteristics. In our analysis, the estimated sensitivity of *Truenat* for TB detection was

based on a single study, and the RIF-resistance detection performance was based on a clinical validation study conducted by the manufacturer. We, therefore, varied these parameters widely in sensitivity analyses. Test characteristics may improve with newer versions of Truenat under evaluation.

Our healthcare expenditure projections should be interpreted only for diagnostic test costs, drug costs, and treatment-associated clinic, monitoring, and hospitalization costs. We did not include “start-up” costs of establishing Xpert or Truenat in the field, such as costs of training staff to utilize the machines and costs of maintaining steady supply chains and reporting systems. Implementation studies are needed and ongoing to demonstrate Truenat’s efficacy under real-world conditions. As results become available, dedicated studies will be needed to estimate the implementation costs of Truenat on a larger scale, as there have been for Xpert.^{36,40–42}

Truenat is, nonetheless, the first TB test with capacity comparable to 4-module Xpert but with operational features suited for the peripheral level. Our model-based analysis shows that, when used at point-of-care for TB diagnosis, Truenat improves linkage-to-care, increases life expectancy, and is cost-effective compared with smear microscopy or Xpert. Appropriate diagnostics are needed at every level of the healthcare system.⁸ Truenat deployed at the peripheral level may be complementary to other diagnostic technologies, such as Xpert and Xpert Ultra,⁴³ which are appropriate for the district- and sub-district levels, and the 1-module Xpert Omni, which may be valuable for community-based active case-finding (clinicaltrials.gov, NCT 03168945). In this way, Truenat should contribute to TB control and, thus, should be more widely utilized in India.

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Technical Appendix

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S1. Methods: Additional Information

S1.1 Analytic Overview

Diagnostic Strategies

The sputum smear microscopy (*SSM*) strategy (Fig A) was modeled according to published national guidelines for India.¹ Patients provide two sputum samples, one collected at the time of testing initiation and the second collected the following morning. We assume that all patients are able to provide the first sputum sample, but only a proportion of patients return the following morning to provide the second sputum sample. If smear-negative, a proportion of patients undergo a multi-step clinical diagnostic algorithm, which includes an antibiotic trial and chest radiography. Patients with a positive smear or clinical diagnosis are started on first-line treatment if they have no history of tuberculosis (TB) treatment. Patients who receive a positive smear or clinical diagnosis and were previously treated for TB are considered at higher risk for drug-resistance. They receive additional culture and drug-susceptibility testing (C&DST) to test for multidrug-resistant TB (MDR-TB). If C&DST is positive for MDR-TB, they initiate second-line treatment.

For *Xpert* and *Truenat* strategies (Figs B—C), patients provide only one sputum sample at the time of testing initiation. As in the *SSM* strategy, we assume that all patients are able to provide this sample. *Xpert* tests simultaneously for active TB and for rifampicin (RIF)-resistance, whereas *Truenat* tests for RIF-resistance only after a positive TB result. With *Xpert*, there is an additional probability of test failure due to power- and temperature-related issues, as informed by results from a recent feasibility study of *Xpert* for designated microscopy centers (DMCs) in India.² Upon test failure, we assume patients return for repeat testing in the following

month. Furthermore, patients who receive a negative test result with Xpert or Truenat but retain high clinical suspicion for TB may receive confirmatory C&DST.

Cost-effectiveness Threshold

It is increasingly recognized that cost-effectiveness thresholds should account for the “opportunity cost” of forgone health benefits of not providing some interventions to fund others.^{3–8} This is especially relevant for low-resource settings where there are substantial constraints against raising healthcare expenditures.³ Woods et al. recommend opportunity-cost based thresholds of 1—51% the national annual gross domestic product (GDP) *per capita* for low/middle countries and 18—71% for middle/high income countries.³ In considering these estimates for India, a lower middle-income country,⁹ we chose a cost-effectiveness threshold that is 50% of the GDP *per capita* of India in 2017. Therefore, a strategy was considered “cost-effective” if its ICER was less than US\$990/year-of-life saved (YLS).¹⁰

S1.2 Model Overview

TB Natural History

Our model simulates the natural history, diagnosis, and treatment of TB (Fig D). We simulated cohorts of five million individuals to achieve stable per-person estimates. Individuals are in one of several possible TB “states” (uninfected, latent TB infection, active TB disease, previously treated TB, or treatment default) and may transition between these states in monthly cycles. Transition probabilities depend on disease- and treatment-related factors, including incidence of infection, symptom occurrence, relapse, and loss to follow-up (LTFU) during diagnostic testing or treatment. These probabilities are informed by literature and surveillance

data. An individual also may transition to the “dead” state with a monthly probability that depends on the individual’s current TB state and treatment status.

For this analysis, we modeled a cohort of adult patients with suspected TB (i.e., ≥ 2 weeks of cough) who seek care and receive TB testing in India’s public sector. While all individuals are symptomatic at model entry, only some have true active TB disease. The prevalence of active TB disease in this cohort and the distribution of drug-susceptible tuberculosis (ds-TB) and MDR-TB are user-defined. All individuals, however, have a probability of developing active TB later in life, whether as a first infection and rapid progression (uninfected individuals), reactivation (latently infected individuals), or as reinfection and rapid progression or reactivation (previously infected individuals). Those without active TB also have a separate user-defined probability of developing symptoms suggestive of TB (but actually reflecting a disease other than TB) and may present to care for the initiation of TB testing.

TB Diagnostic Testing

When a patient with suspected TB presents to care either at model entry or later in life, s/he is offered a user-defined sequence of TB diagnostic tests. For example, a patient who receives a negative test result (e.g., smear-negative) may be offered a follow-up confirmatory test (e.g., clinical diagnosis with chest radiography and antibiotic trial). For each test in the sequence, the patient has a probability of completing the test and a probability of retrieving the test result. Furthermore, the observed TB strain may differ from the patient’s true TB strain, due to suboptimal test characteristics.

TB Treatment and Loss to Follow-up

Patients who receive a positive test result for TB have a probability of linking to care. If successfully linked to care, patients begin a treatment regimen based on their observed TB strain's resistance profile and history of TB treatment.¹¹ A first-line treatment regimen (rifampicin/isoniazid/pyrazinamide/ethambutol) is given to patients with observed ds-TB and no prior TB treatment. A retreatment regimen (rifampicin/isoniazid/pyrazinamide/ethambutol/streptomycin) is given to patients with observed ds-TB and prior TB treatment ("previously treated"). A second-line regimen (kanamycin/levofloxacin/ethionamide/cycloserine/pyrazinamide/ethambutol) is given to patients with observed MDR-TB, regardless of treatment history. Treatment regimens vary in duration (i.e., 6 months for first-line, 8 months for retreatment, and 24 months for second-line), during which there is a monthly probability of LTFU.

Because the observed TB strain may differ from the patient's true TB strain, patients may be placed on an inappropriate treatment regimen (e.g., first-line regimen for MDR-TB). Such patients "fail" their treatment and are subject to the same mortality as those with untreated, active TB. Patients are monitored while receiving treatment, and, therefore, have a monthly probability of observing treatment failure and switching to the appropriate treatment regimen.

All patients have a monthly probability of LTFU during treatment. Because this is a monthly probability, patients who are on a longer treatment regimen (e.g., 24 months for MDR-TB treatment) have a greater overall risk of not completing their treatment course. Patients lost to follow-up, however, have a probability of being "cured" of active TB disease after receiving partial treatment, and this probability increases with the proportion of treatment duration completed before LTFU.

Taking these variables together, there are four possible treatment outcomes. First, those who successfully complete treatment (i.e., no LTFU) and achieve cure transition to the “previously treated” state. Second, those who complete treatment (i.e., no LTFU) but do not achieve cure remain in the “active” state. Third, those who are lost to follow-up but, nonetheless, achieve cure transition to the “treatment default” state. These individuals are at risk of developing resistance to the treatment regimen received. Fourth, those who are lost to follow-up before achieving cure remain in the “active” state. These individuals are at risk of developing resistance to the treatment regimen received. Those in either the “previously treated” or “treatment default” state may have recurrence of active TB disease due to either exogenous reinfection or endogenous relapse.

S1.3 Base Case Input Parameters

TB Prevalence

Data regarding the true prevalence of TB in India are limited. National TB prevalence surveys are being planned for 2018—2019.¹² Therefore, we used prevalence estimates by Khaparde et al.,¹³ based on the same Indian cohort as that in the Xpert implementation study.¹⁴ The authors estimated the true prevalence of TB among the cohort using the test characteristics of sputum smear microscopy and Xpert and the proportion of bacteriologically confirmed cases in both phases of the implementation study. Their calculations can be found in the Supplement to their study.¹³ Based on this method, the prevalence of TB was 15% among those not previously treated for TB and 27% among those previously treated for TB.

Natural History

In our model, individuals have a monthly probability of becoming infected with a new TB strain and developing active pulmonary disease as a result. Data for this parameter are limited. While the World Health Organization (WHO) provides an estimate for the annual incidence of active TB cases (all forms) per year (i.e., 2.6 million for individuals age ≥ 15 years in 2016), it does not stratify this incidence by pulmonary versus extrapulmonary disease. It also does not stratify incidence by the source of infection—that is, infection from a new strain versus from relapse of an older strain that was in remission from previous treatment.

Therefore, to estimate our parameter of interest (i.e., monthly incidence of developing active pulmonary TB due to infection or reinfection with a new *Mycobacterium TB* strain), we subtracted from the WHO incidence the estimated burden of relapsed and extrapulmonary TB, as reported in literature. More specifically, among the 2.6 million new active TB cases for individuals ages ≥ 15 years, we assumed 16% were due to extrapulmonary disease,¹² 91% of which occurred among adults.¹⁵ Of the remaining pulmonary TB cases, we assumed that 14% were recurrent cases,¹⁶ 69% of which are due to relapse.^{17,18} Given the lack of age-stratified data, we assumed that the relapse rate was equal for pediatric and adult cases. After subtracting these rates, we estimated that the monthly probability of developing active pulmonary TB due to infection, or reinfection for previously treated individuals, with a new *Mycobacterium tuberculosis* strain was 0.02% (Table A).

Other parameters related to the natural history of TB, including the monthly mortality risk from untreated TB, are provided in Table A.

Suspected TB

In our model, individuals undergo TB testing if they (1) develop symptoms suggestive of TB (i.e., ≥ 2 or more weeks of cough) and (2) subsequently seek medical care for their symptoms. We assumed all individuals with active TB remained symptomatic while in the active TB state. The monthly probability of seeking medical care among these individuals was 8%. This probability was derived from results of a recent national-level analysis.²¹

Individuals who do not have active TB (i.e., uninfected or previously treated individuals) also have a monthly probability of developing symptoms suggestive of TB and seeking medical care. Their symptoms are due to causes other than TB, such as bacterial pneumonia. Data regarding this parameter are lacking. However, an estimate can be derived by, first, estimating the incidence of individuals (with and without active TB) in the population who develop symptoms suggestive of TB and seek medical care (variable 1) and, second, subtracting from this estimate the proportion of individuals who truly have active TB (variable 2). The Xpert implementation study provides an estimate for variable 1, based on the total number of individuals who were tested for TB at selected DMCs and the total person-years in the DMCs' catchment areas over the study period.¹⁴ Using data from the Xpert implementation study, we then estimated variable 2 by applying the method used by Khaparde et al., which was described in the prior section regarding TB prevalence.¹³ Subtracting variable 2 from variable 1, the monthly probability of developing symptoms suggestive of TB and seeking medical care, among individuals without active TB, was 0.04%.

Diagnostic Tests

In the *SSM* strategy, the proportion of patients who undergo clinical diagnostic testing (e.g., antibiotic trial and chest radiography) after a smear-negative result was 39%.²¹ In *Xpert* and *Truenat* strategies, patients who receive a negative test result with *Xpert* or *Truenat* may also undergo additional testing (i.e., confirmatory C&DST). However, given that *Xpert* and *Truenat* have higher sensitivity than sputum smear,^{26–28} we assumed that the proportion of individuals who receive additional testing after a negative *Xpert* or *Truenat* result was half of that among those with a negative smear result (Table A).

Also, in the *SSM* strategy, patients who are smear-positive and were previously treated for TB may provide an additional sputum sample to test for MDR-TB with C&DST (Fig A). We assumed that the proportion of smear-positive patients who submit this additional sputum sample was 75%. This was based on the *Xpert* implementation study in India, in which 75% of patients submitted an additional sputum sample for C&DST when requested.¹⁴

There are currently no published studies on *Truenat*'s performance characteristics for RIF-resistance detection. The manufacturer, however, reports a clinical validation study, based at a TB referral center in India, in which 115 TB positive sputum samples were tested by both a Line Probe Assay (LPA) and *Truenat* for RIF-resistance detection.²⁹ Using LPA as the gold standard, *Truenat*'s sensitivity and specificity for RIF-resistance detection was 94% and 98%. These values were used for the base case, and parameters were varied widely in sensitivity analyses.

Linkage-to-Care

A recent national-level analysis of the TB “cascade of care” estimated that the proportion of smear-positive patients diagnosed at DMCs who register for treatment at a healthcare facility is 84% (95% confidence interval, 80–88%).²¹ We assumed that this 16% gap between diagnosis and treatment initiation is the same for any sputum-based test conducted in DMCs, whether smear microscopy, Xpert, or Truenat.

Given the novelty of the Truenat assay, there are currently no published data on the linkage-to-care of individuals diagnosed via point-of-care (POC) testing with Truenat in India. However, as a proxy, we drew upon data from trials and implementation studies of POC testing with Xpert in the primary healthcare setting in high TB burden countries.^{30–33} Overall, these data suggest that POC testing with Xpert improves linkage-to-care. For example, the TB-NEAT study,³⁰ a randomized, controlled trial (RCT) of Xpert within peri-urban primary care clinics, showed that 97% of patients who received a positive TB result with POC Xpert testing started treatment within one week. In contrast, the XTEND study,³⁴ an RCT of Xpert in a laboratory setting, showed that only 83% of all patients who received a positive TB result from lab-based Xpert testing initiated treatment.

Two studies directly compared lab-based Xpert testing to POC Xpert testing in a primary healthcare setting. One prospective study showed that 95% of individuals who received a positive TB result on POC Xpert testing initiated treatment (median time to treatment, 0 days), compared to 87% of individuals who received a positive TB result via laboratory-based Xpert testing (median time to treatment, 5 days).³¹ Similarly, a recent RCT showed that 96% of patients who received a positive TB result via POC Xpert testing in rural primary care clinics in South

Africa initiated treatment within 30 days, compared to 90% of those who received a positive TB result via lab-based Xpert testing in the same time period.³²

We are aware of only one study that evaluated POC Xpert testing in India.³³ This study took place in an outpatient clinic of a tertiary care hospital. Among patients who received a positive TB result and whose follow-up data were available, all initiated TB treatment. However, same-day treatment initiation was limited to only those individuals who lived near the tertiary care hospital and did not need referral to a more local treatment center.

Taking these data together, we assumed linkage-to-care for individuals diagnosed with Truenat in the primary healthcare setting (*Truenat POC*) was 95% within one month of diagnosis. Other modeling work evaluating a theoretical “peripheral nucleic acid amplification test (NAAT) test” to replace sputum smear microscopy for the South East Asia Region have also used this value.³⁵ We did not assume that POC testing with Truenat would lead to same-day linkage-to-care, as this value would be substantially lower than 95%.

Costs

For TB treatment, we used published national guidelines and epidemiological data to determine the cost components for each treatment regimen.^{1,11,36,37} These components included drugs, clinic visits, monitoring tests, and expected hospitalizations during treatment. For example, first-line therapy for ds-TB includes 24 outpatient visits during the intensive phase of treatment, in which patients receive isoniazid/rifampicin/pyrazinamide/ethambutol, and 16 outpatient clinic visits during the continuation phase, in which patients receive isoniazid/rifampicin/ethambutol. We assumed a daily dose for an individual weighing 55—69 kg. To monitor response to first-line therapy, two sputum samples are collected for smear

microscopy at the end of the intensive phase, two months into the continuation phase, and upon treatment completion. We also assumed 7.5% of TB patients would be hospitalized during first-line therapy, for a mean duration of 30 days.³⁶

These components and their expected quantities were multiplied by their respective unit costs. Unit costs for drugs were based on prices offered by the Global Drug Facility (GDF),³⁸ while unit costs for outpatient visits and hospitalizations were based on WHO-CHOICE.³⁹ Unit costs for monitoring tests (i.e., sputum smear microscopy, culture, and drug-susceptibility testing) are provided in Table 1 of the main text.⁴⁰ Dividing the final sum of costs of each treatment regimen by the regimen's expected duration (i.e., 6 months for first-line, 8 months for retreatment, and 24 months for second-line), the monthly costs of TB treatment were \$28.13 (first-line), \$32.25 (retreatment), and \$104.23 (second-line).

Our study did not include costs associated with tax and distribution of drugs and diagnostics. We also did not incorporate “start-up” costs of establishing and maintaining Xpert or Truenat in the field. For example, we did not include the cost of training new staff to utilize the machines. The number of machines needed to be deployed may also differ for Xpert and Truenat as they may be intended for different settings (e.g., DMCs or primary healthcare facilities). These settings, furthermore may require different operational systems to maintain Truenat and Xpert in the field, such as a steady supply chain for cartridges (Xpert) and chips (Truenat), and to report test results to national surveillance programs. Together, these new machines and operational systems may require additional supervision and quality control. Dedicated studies will be needed to estimate such start-up costs for Truenat, as there have been for Xpert.^{41–44}

S1.4 Sensitivity and Scenario Analyses

Empirical Treatment

Under the *SSM* strategy, smear-negative individuals may be started on empirical TB treatment after undergoing a clinical diagnostic process, which includes an antibiotic trial and chest radiography. Molecular diagnostics like Xpert and Truenat may reduce the need for empirical treatment due to their higher sensitivity, which may increase clinicians' confidence in a negative test result.⁴⁵ However, the extent to which the utilization of empirical treatment will change with Xpert and Truenat is currently unknown. One study based in a South African hospital showed that after the implementation of Xpert, the proportion of patients who were started on empirical TB treatment decreased from 79% to 28%.⁴⁶ The TB-NEAT study, a randomized controlled trial of Xpert in the primary care setting, however, showed that the reduction in the proportion of patients started on empirical treatment was not as prominent (i.e., 26% in the sputum smear microscopy groups versus 17% in the Xpert group).³⁰

These studies were conducted in HIV-endemic settings, where providing empirical TB treatment is generally more common due to higher TB-related mortality.⁴⁵ Though our analysis focused on an HIV-negative population, we also evaluated a scenario in which empirical treatment is offered to a proportion of individuals who receive a negative Xpert or Truenat result and to at least as high a proportion for individuals who receive a negative sputum smear result. More specifically, for this scenario analysis, we assumed all individuals who receive a negative smear result undergo clinical diagnostic testing (i.e., antibiotic trial and chest radiography). Based on the test characteristics of clinical diagnostic testing, we estimated that 16% of these individuals would be offered empirical treatment. We assumed that the same proportion of individuals receiving a negative Xpert or Truenat result would be offered empirical treatment.

Linkage-to-care for empirical treatment remained 84% of DMC-based tests and 95% for POC testing (i.e., *Truenat POC*).

Truenat Chip Cost

Because the public sector cost of Truenat may decrease based on volume commitment by the Indian government, we conducted a scenario analysis in which the cost of the Truenat chip was negotiated to 60% of the current estimate. This number was chosen based on the historic precedent of price negotiations for the Xpert cartridge, in which a volume commitment of >3 million cartridges per year reduced Xpert's cartridge price to 60% of its base price for India and other approved countries.^{47,48}

S1.5 Budget Impact Analysis

We assumed 7.9 million patients with suspected TB would be tested every year, based on the incidence estimate reported in the Xpert implementation study in India and the population size of individuals aged ≥ 15 years in 2016.^{14,49} Because the implementation study did not stratify incidence by age group, we assumed that TB incidence in adults is the same as that in the general population.

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Table A. Additional model input parameters for model-based cost-effectiveness analysis of TB diagnostic strategies for patients with suspected TB in India.

Parameter	Base case	Range ^a	References
Natural history			
Monthly probability of new active TB	0.02%	0.008 – 0.03%	12,15,16,18–20
Monthly probability of seeking medical care among people with active TB	8%	6 – 10%	21
Monthly probability of seeking medical care for symptoms suggestive of TB among people who do not have active TB	0.04%	0.02 – 0.07% ^b	Assumption
Monthly probability of death from untreated TB	1.3%	0.9 – 2.3%	22
Duration of active TB until self-cure, years	2	1 – 3	23
Diagnostic tests (additional)			
Proportion of smear-positive patients previously treated for TB who provide additional sputum for C&DST	75%	38 – 100%	Assumption
Proportion of Xpert- and Truenat-negative patients with high clinical suspicion for TB who undergo confirmatory C&DST ^a	20%	0 – 40%	Assumption
Treatment for TB (additional)			
Monthly probability of observing treatment failure during first-line therapy and switching to second-line therapy	3%	0 – 21% ^b	24
Monthly probability of observing treatment failure during retreatment therapy and switching to second-line therapy	5%	2 – 21% ^b	24
Probability of developing resistance to first-line and retreatment regimen after loss to follow-up ^c	24%	14 – 49%	25
Probability of developing resistance to first-line and retreatment regimen after treatment failure	19%	14 – 49%	25

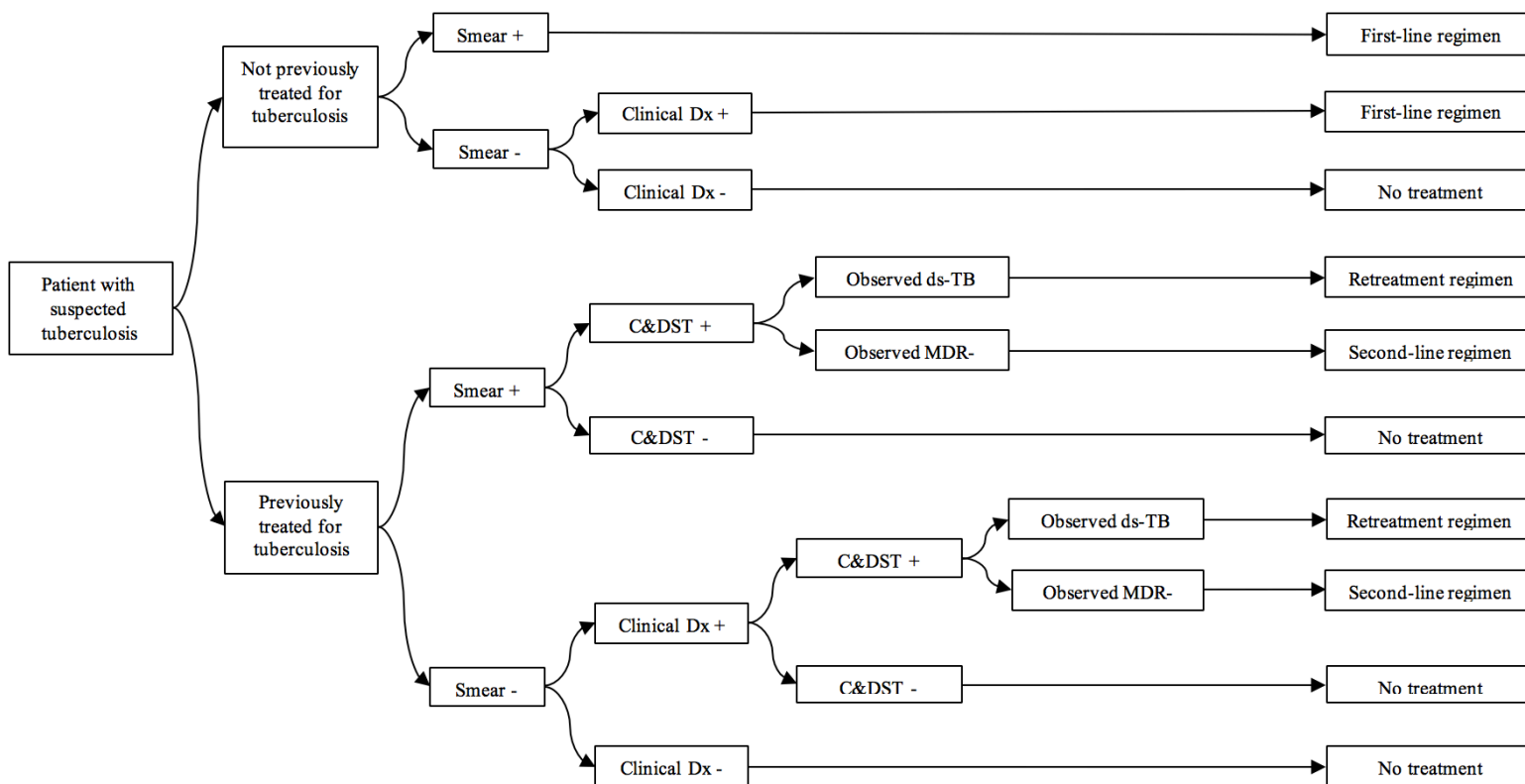
Abbreviations: TB: tuberculosis. C&DST: culture and drug-susceptibility

^aIn both *Xpert* and *Truenat* strategies (*DMC* and *POC*), patients who receive a negative test result but retain high clinical suspicion for TB may receive confirmatory C&DST.

^bRange based on variation across states.²⁴

^cProbability that patient’s drug-susceptible TB strain will become resistant to first-line regimen and progress to multidrug-resistant TB strain after a patient is lost to follow-up during treatment. The probability that multidrug-resistant TB will become resistant to the second-line regimen is assumed to be the same value.

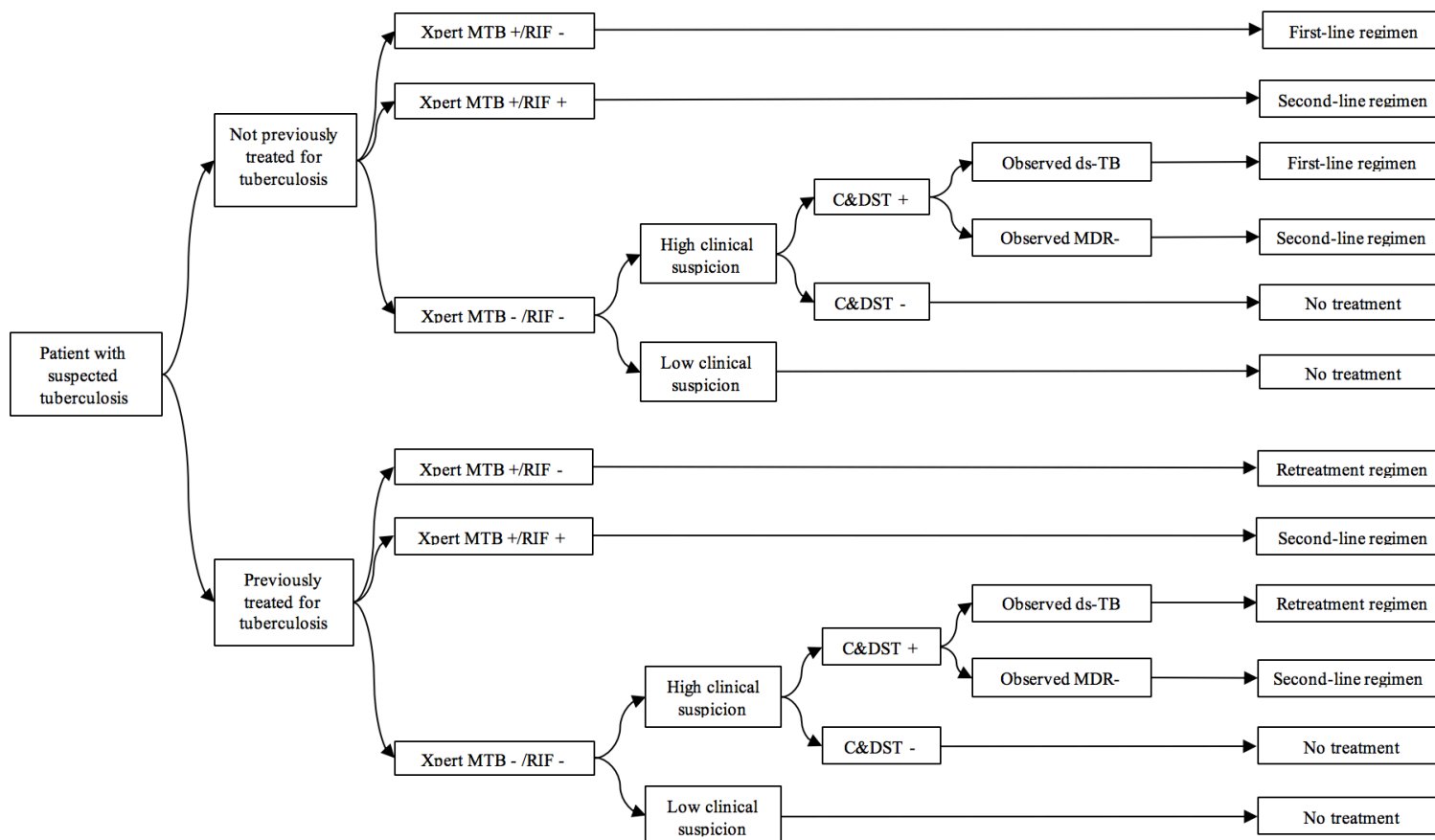
Fig A. Diagnostic and treatment algorithm for sputum smear microscopy strategy (SSM).



Abbreviations: Clinical Dx: clinical diagnosis. C&DST: culture and drug-susceptibility testing. TB: tuberculosis. ds-TB: drug-susceptible tuberculosis. MDR-TB: multidrug-resistant tuberculosis.

Schematic shows the possible combination of tests and the treatment line that patients with suspected TB may receive under the SSM strategy. Based on the observed TB strain (ds-TB or MDR-TB) and history of TB treatment, individuals may receive first-line regimen (rifampicin/isoniazid/pyrazinamide/ethambutol), retreatment regimen (rifampicin/isoniazid/pyrazinamide/ethambutol/streptomycin), or second-line regimen (kanamycin/levofloxacin/ethionamide/cycloserine/pyrazinamide/ethambutol).^{11,37}

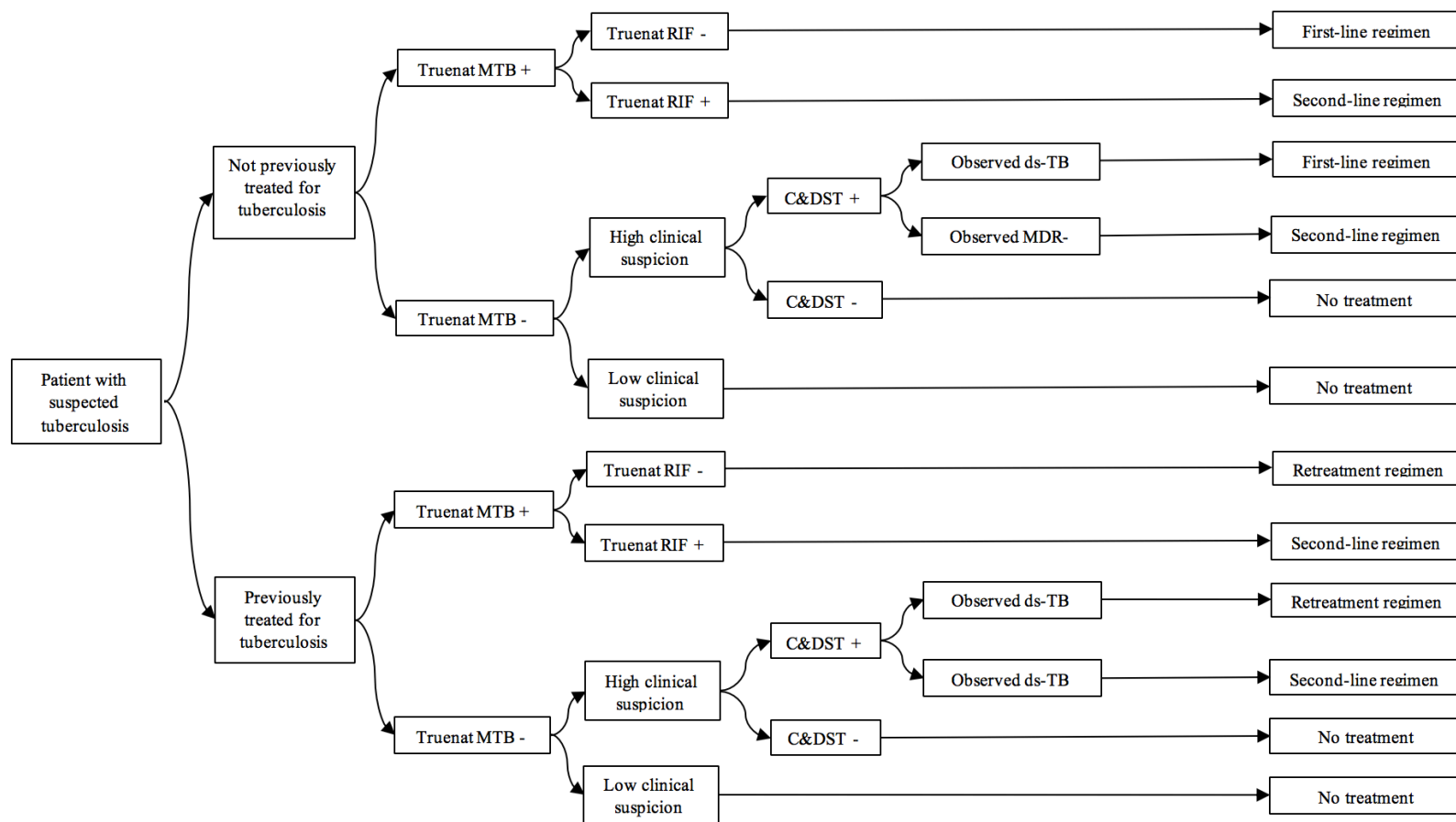
Fig B. Diagnostic and treatment algorithm for *Xpert* strategy.



Abbreviations: MTB: *Mycobacterium tuberculosis*. RIF: rifampicin. C&DST: culture and drug-susceptibility testing. TB: tuberculosis. ds-TB: drug-susceptible tuberculosis. MDR-TB: multidrug-resistant tuberculosis.

Schematic shows the possible combination of tests and the treatment line that patients with suspected TB may receive under the *Xpert* strategy. Individuals with “high clinical suspicion” for TB, despite a negative *Xpert* result, may receive confirmatory C&DST. Based on the observed TB strain (ds-TB or MDR-TB) and history of TB treatment, individuals may receive first-line regimen (rifampicin/isoniazid/pyrazinamide/ethambutol), retreatment regimen (rifampicin/isoniazid/pyrazinamide/ethambutol/streptomycin), or second-line regimen (kanamycin/levofloxacin/ethionamide/cycloserine/pyrazinamide/ethambutol).^{11,37}

Fig C. Diagnostic and treatment algorithm for *Truenat* strategies.

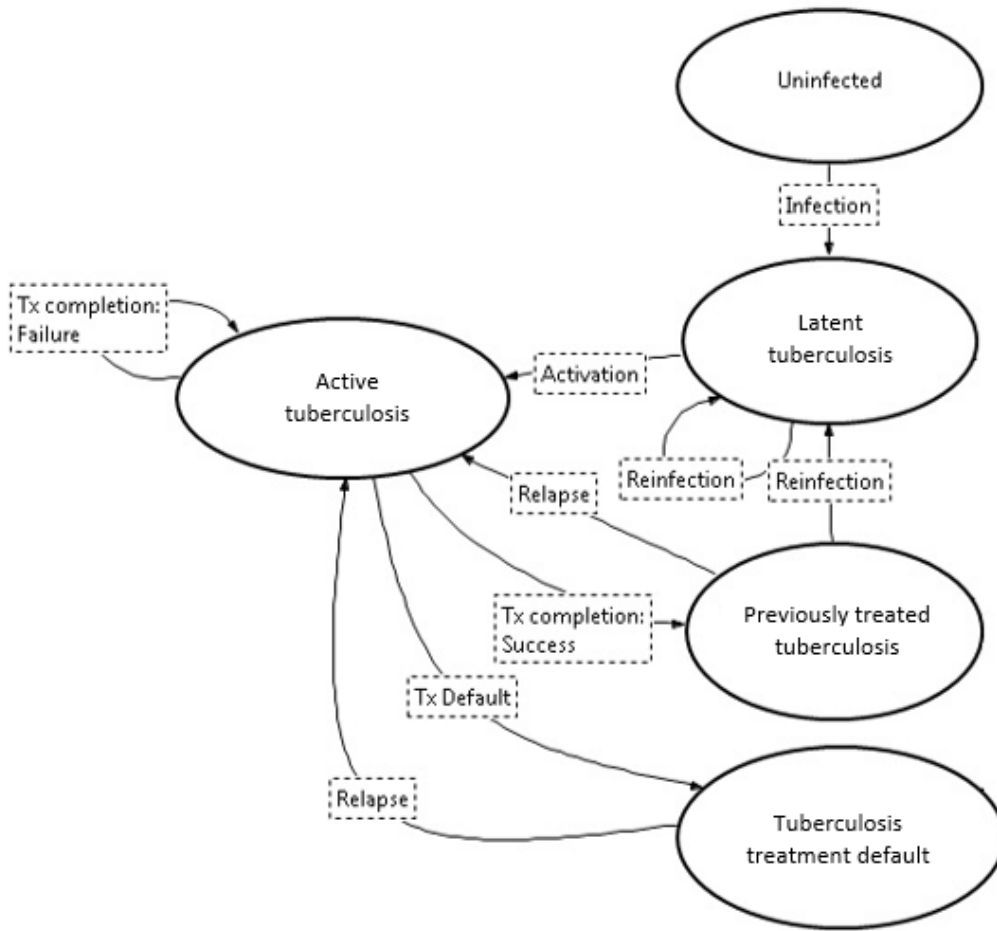


Abbreviations: MTB: *Mycobacterium tuberculosis*. RIF: rifampicin. C&DST: culture and drug-susceptibility testing. TB: tuberculosis.

ds-TB: drug-susceptible tuberculosis. MDR-TB: multidrug-resistant tuberculosis.

Schematic shows the possible combination of tests and the treatment line that patients with suspected TB may receive under the *Truenat* DMC or *Truenat* POC strategy. Individuals with “high clinical suspicion” for TB, despite a negative *Truenat* result, may receive confirmatory C&DST. Based on the observed TB strain (ds-TB or MDR-TB) and history of TB treatment, individuals may receive first-line regimen (rifampicin/isoniazid/pyrazinamide/ethambutol), retreatment regimen (rifampicin/isoniazid/pyrazinamide/ethambutol/streptomycin), or second-line regimen (kanamycin/levofloxacin/ethionamide/cycloserine/pyrazinamide/ethambutol).^{11,37}

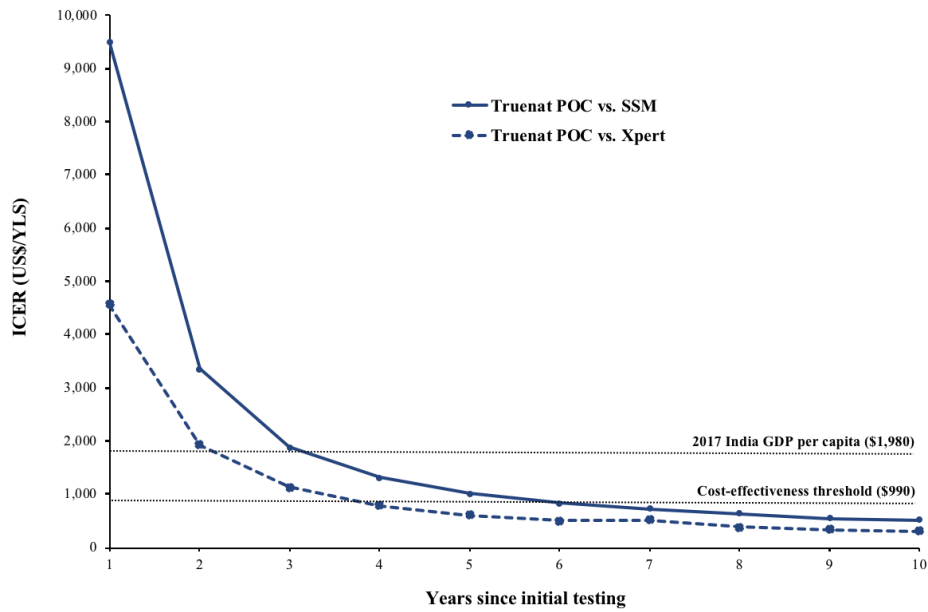
Fig D. Overview of TB states in the simulation model.



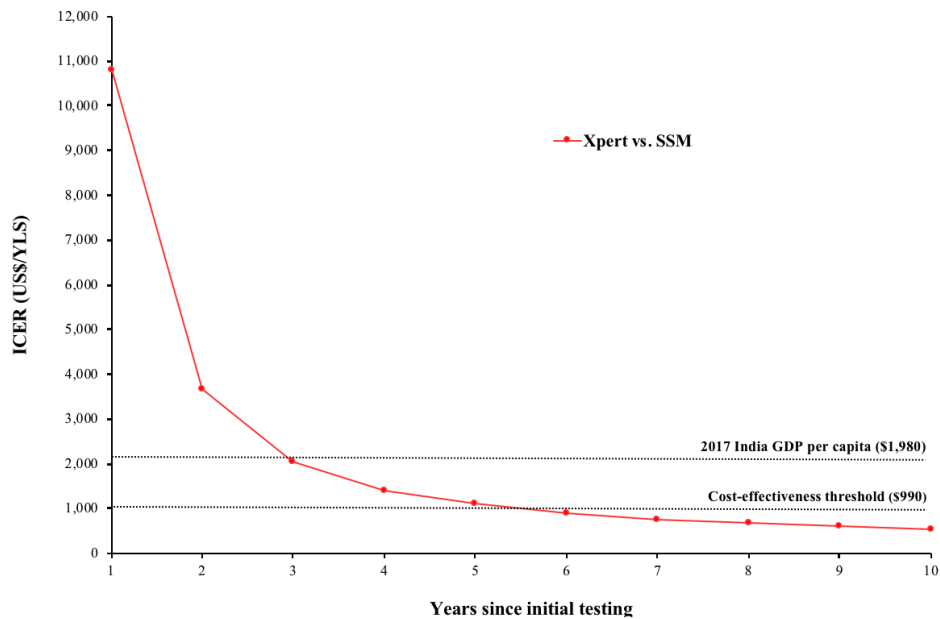
Abbreviation: Tx: treatment. Displayed is a simplified diagram of the TB model (CEPAC model technical specifications are available at <http://www.massgeneral.org/mpec/cepac/>). The circles represent “states” of TB natural history, and the arrows represent the possible monthly transitions that may occur between states. Simulated individuals also may remain in their current state (arrows not depicted). Individuals can transition from any of these states to the “Dead” state (also not depicted for simplicity).

Fig E. Incremental cost-effectiveness ratios of *Truenat POC* and *Xpert* over different time horizons.

a) Cost-effectiveness of *Truenat POC*, compared to *SSM* and *Xpert*, over different time horizons.



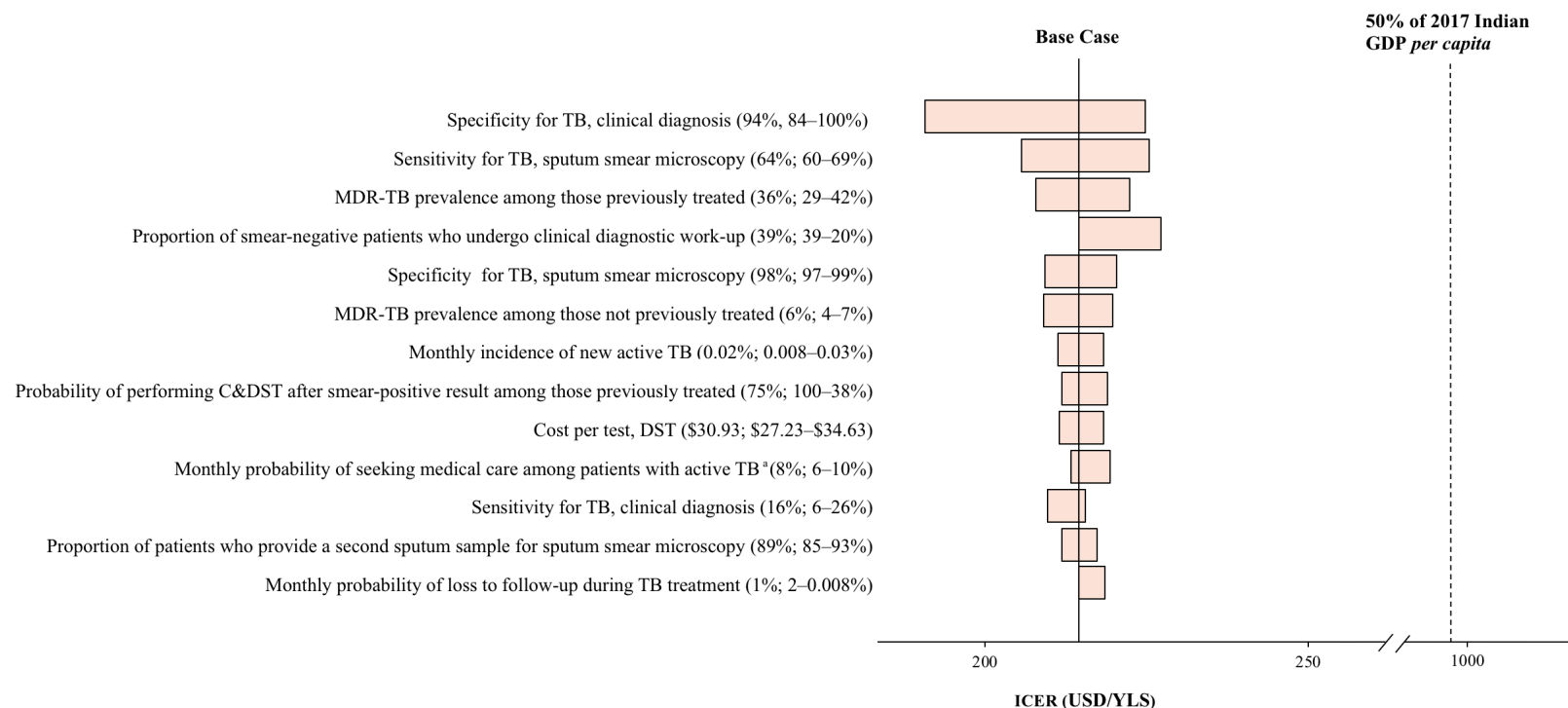
b) Cost-effectiveness of *Xpert*, compared to *SSM*, over different time horizons.



Abbreviations: POC: point of care. ICER: incremental cost-effectiveness ratio. YLS: year-of-life saved. GDP: gross domestic product. *SSM*: sputum smear microscopy strategy.

In the top graph (a), the blue solid line represents the ICERs of *Truenat POC*, compared to *SSM*, over different time horizons, and the blue dashed line represents the ICERs of *Truenat POC*, compared to *Xpert*, over different time horizons. In the bottom graph (b), the red solid line represents the ICERs of *Xpert*, compared to *SSM*, over different time horizons. In both graphs, the upper horizontal line represents the GDP *per capita* of India in 2017 (\$1,980).¹⁰ The lower horizontal line represents the cost-effectiveness threshold, defined as 50% the GDP *per capita* of India in 2017 (\$990). ICERs <\$990/YLS (below lower horizontal line) are considered cost-effective.

Fig F. Additional one-way sensitivity analyses of model parameters.



Abbreviations: TB: tuberculosis. MDR-TB: multidrug-resistant tuberculosis. “previously treated”: previously treated for TB. C&DST: culture and drug-susceptibility test. DST: drug-susceptibility test. GDP: gross domestic product. ICER: incremental cost-effectiveness ratio. USD: United States dollars. YLS: year-of-life saved.

One-way sensitivity analysis comparing the impact of model parameters on the ICER of Truenat used at point-of-care (*Truenat POC*) compared to sputum smear microscopy (*SSM*) strategy. Horizontal bars represent ranges of ICERs when varying each model parameter across different values. The vertical grey dashed line represents 50% of the gross domestic product (GDP) *per capita* of India in 2017 (\$990), which we consider the cost-effectiveness threshold.^{3,9,10} ICERs <\$990/YLS (left of dashed line) are considered cost-effective.

^aThis parameter applies to individuals with active TB after initial TB testing