Clinical Infectious Diseases

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Cost-effectiveness of a Pharmacogenomic Test for Stratified Isoniazid Dosing in Treatment of Active Tuberculosis

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Background. There is marked interindividual variability in metabolism and resulting toxicity and effectiveness of drugs used for tuberculosis treatment. For isoniazid, mutations in the *N*-acetyltransferase 2 (*NAT2*) gene explain >88% of pharmacokinetic variability. However, weight-based dosing remains the norm globally. The potential clinical impact and cost-effectiveness of pharmacogenomic-guided therapy (PGT) are unknown.

Methods. We constructed a decision tree model to project lifetime costs and benefits of isoniazid PGT for drug-susceptible tuberculosis in Brazil, South Africa, and India. PGT was modeled to reduce isoniazid toxicity among slow *NAT2* acetylators and reduce treatment failure among rapid acetylators. The genotyping test was assumed to cost the same as the GeneXpert test. The main outcomes were costs (2018 US dollars), quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios.

Results. In Brazil, PGT gained 19 discounted life-years (23 QALYs) and cost $11 064 per 1000 patients, a value of $476 per QALY gained. In South Africa, PGT gained 15 life-years (19 QALYs) and cost $33 182 per 1000 patients, a value of $1780 per QALY gained. In India, PGT gained 20 life-years (24 QALYs) and cost $13 195 per 1000 patients, a value of $546 per QALY gained. One-way sensitivity analyses showed the cost-effectiveness to be robust to all input parameters. Probabilistic sensitivity analyses were below per capita gross domestic product in all 3 countries in 99% of simulations.

Conclusions. Isoniazid PGT improves health outcomes and would be cost-effective in the treatment of drug-susceptible tuberculosis in Brazil, South Africa, and India.

Keywords. tuberculosis; pharmacogenomic; isoniazid; personalized medicine; cost-effectiveness.

In 2017, there were 10 million tuberculosis (TB) cases and 1.6 million deaths, making TB the leading cause of death by an infectious disease worldwide [1]. The World Health Organization (WHO) has initiated the End TB Strategy, which aims to cut cases by 90% and decrease deaths by 95% by 2035 [2]. Increasing treatment effectiveness and reducing adverse events are important components of achieving this goal.

The global treatment success for patients with TB was 82% in 2016 [1]. Standard treatment for people with drug-susceptible TB (DS-TB) consists of standardized, weight-based doses of isoniazid (INH), rifampicin, pyrazinamide, and ethambutol. Up to 33% of those undergoing treatment develop hepatotoxicity [3], which is associated with increased costs and, in some studies, substantial mortality up to 27% [4]. As many as 3% of new TB cases experience treatment failure [5], and between 2% and 14% relapse within 2 years (Supplementary Appendix).

There is substantial evidence that standardized, weight-based dosing leads to variable drug levels, which in turn have been associated with treatment response, toxicities, and acquisition of drug resistance during TB therapy [6, 7]. The most well-characterized variability in TB drug metabolism is with INH, which is primarily metabolized by *N*-acetyltransferase 2 (*NAT2*). Individuals with polymorphisms in *NAT2* have altered enzyme activity and can be classified into 3 phenotypic classes: slow, intermediate, or rapid acetylators. Acetylator class has been shown to explain 88% of the interindividual pharmacokinetic variability in INH levels [8]. *NAT2* genotype predicts clinically relevant endpoints as well. Multiple studies have revealed that slow acetylators are at increased risk of drug-induced liver injury from INH [9]. A meta-analysis found that rapid acetylators are at increased risk of treatment failure, relapse, and acquisition of resistance [7].

While pharmacokinetic data support INH dose adjustments by genotype to achieve target levels [10], there are limited

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prospective data on whether such adjustments improve outcomes. One randomized trial of pharmagogenomic-guided therapy (PGT) found a significant reduction in hepatotoxicity in slow metabolizers who were randomized to a lower dose of INH, as well as a reduction in 2-month culture positivity in *NAT2* rapid metabolizers who received a higher dose [11].

More than half of the global population are either slow acetylators or rapid acetylators [12], meaning that half of all patients are currently receiving nonoptimized doses. Acetylator phenotype can be accurately predicted by examining 2–7 single-nucleotide polymorphisms (SNPs) in *NAT2* [13]. Advances in molecular diagnostics have made point-of-care SNP-typing possible, but currently there are no rapid molecular diagnostics for *NAT2* genotype. A key question facing development of a *NAT2* rapid test is whether it would be clinically impactful and cost-effective. Here, we construct a decision-analytic model to project the clinical utility and cost-effectiveness of PGT for TB in Brazil, South Africa, and India.

METHODS

Overview and Analytic Framework

We constructed a decision tree model to project health outcomes and costs of PGT, compared with standardized treatment, for patients newly diagnosed with DS-TB. With standard therapy, individuals received a standard dose (5 mg/kg) irrespective of acetylator status. With PGT, slow metabolizers received lower INH doses (2.5 mg/kg), rapid metabolizers received increased doses (7.5 mg/kg), and intermediate metabolizers received standard doses (5 mg/kg) (Figure 1). We projected costs in 2018 USD and health outcomes in quality-adjusted life-years (QALYs) and compared strategies by incremental cost-effectiveness ratios (ICERs). We modeled health outcomes and costs based on overall population averages in each setting and did not separately model human immunodeficiency virus (HIV)–infected and HIV-uninfected patient groups.

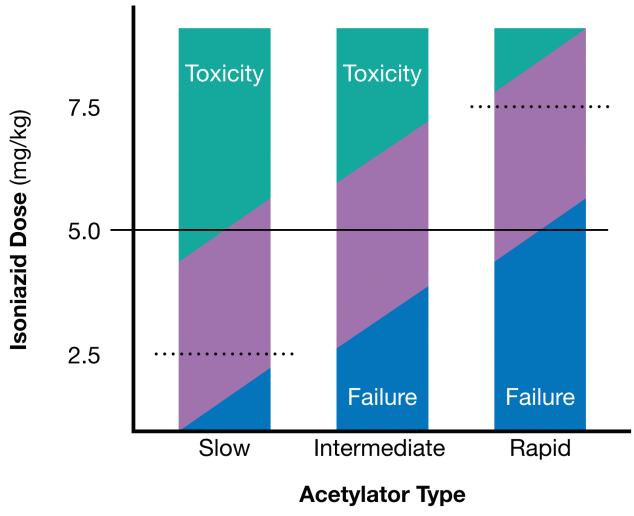

Figure 1. Conceptual schemata of risk of toxicity and treatment failure, according to *NAT2* acetylator type and isoniazid dose. Under standard therapy, all patients with drug-susceptible tuberculosis receive isoniazid dosed at 5 mg/kg. However, slow acetylator types have a higher risk of toxicity (green) and rapid acetylator types have a higher risk of treatment failure (blue) with this dosage. Using pharmacogenomic-guided dosing, slow acetylators receive 2.5 mg/kg and rapid acetylators receive 7.5 mg/kg, which optimizes their side effects and treatment efficacy (purple).

Model Structure and Assumptions

The decision tree includes branches for toxicity, treatment positivity, treatment failure, and death (Supplementary Figure 1). Treatment duration for each possible combination was modeled according to treatment guidelines [14, 15]. We assume that all patients had DS-TB at baseline and received 2 months of INH, rifampicin, pyrazinamide, and ethambutol followed by 4 months of INH and rifampicin. Patients who were culture positive at 2 months received 9 total months of treatment. A fraction of these patients was modeled as failing treatment and requiring 12 total months of treatment. We assumed a fraction of those who failed treatment developed multidrug-resistant TB, requiring costlier treatment with higher mortality (Supplementary Appendix). Patients who experienced toxicity and were unable to tolerate treatment upon rechallenge were moved to an alternative regimen, which was conservatively modeled as having the same monthly cost as normal TB treatment but lasting a total of 8 months.

Treatment Outcomes by Acetylator Status

Baseline risks of toxicity, 2-month culture positivity, and treatment failure (Table 1) were derived from random-effects models summarizing recent TB treatment trials (Supplementary Figures 2–4) and reflect the global acetylator distribution, so we adjusted them based on each country's acetylator distribution (Table 1 and Supplementary Table 3). We assume, based on data from meta-analyses, that individuals with rapid metabolizer phenotypes are more likely to fail treatments than slow and intermediate metabolizer phenotypes (risk ratio, 2.02) [27]. Conversely, we model INH hepatotoxicity to be more common among slow and intermediate metabolizer phenotypes than rapid metabolizer phenotypes (odds ratio, 3.68 and 1.12, respectively) [9].

Based on published data, we assume that 99% of slow or rapid acetylator patients receiving PGT dosing will achieve drug levels comparable to those of intermediate acetylators on standard dosing [10], and therefore experience the same risk of toxicity or failure. We modeled PGx testing as correctly identifying acetylators 95% of the time. Those who are misidentified and receive an incorrect dose are at higher risk of toxicity or treatment failure, according to their presumed drug level (Supplementary Appendix). We assumed that all other TB medications were given at standard doses.

In our model, patients who receive 6 months of treatment have a 5% risk of death [20]. This 6-month probability was converted to a monthly rate to confer additional risk of death to patients who receive >6 months of treatment. We calculated years

Table 1. Model Parameters

Parameter	Brazil			India			South Africa		
	Base Case Value	Range	Reference	Base Case Value	Range	Reference	Base Case Value	Range	Reference
Distribution of acetylators, %									
Slow	45		Supplementary Appendix	55		Supplementary Appendix	40		Supplementary Appendix
Intermediate	42		Supplementary Appendix	32		Supplementary Appendix	48		Supplementary Appendix
Rapid	14		Supplementary Appendix	13		Supplementary Appendix	13		Supplementary Appendix
Costs: intensive phase, 4 drugs, $									
Healthcare	359	(126–516)	[1]	10	(8–59)	[16]	216	(164–248)	[1]
Drug	8	(6–10)	[5, 17]	…	…	…	17	…	[5, 18]
Costs: continuation phase, 2 drugs, $									
Healthcare	359	(126–516)	[5, 17]	10	(8–59)	[16]	58	(44–67)	[5, 18]
Drug	4	(3–6)	[5, 17]	…	…	…	20	…	[5, 18]
MDR	5630	(5174–5765)	[5, 17]	3078	(2464–19 713)	[16]	11 011	(9291–26 495)	[5, 18]
Hospitalization from toxicity	388	(194–777)	[19]	52	(18–153)	[16]	80	…	[20]
Clinic visits from toxicity	26	(13–51)	[19]	…	…	…	…	…	…
Cost: *NAT2* genotype test, $	19	(18–21)	[21]	19	(16–19)	[22]	26	(25.8–26.0)	[23]
Mean age of TB onset, y	39.62	…	[24]	37.16	…	[24]	35.00	…	[25]
Mean life expectancy, y	73.52	…	[26]	68.11	…	[26]	61.94	…	[26]
Toxicity odds ratio									
Intermediate vs fast acetylators	1.12	(0.87–1.45)	[9]	…	…	…	…	…	…
Slow vs fast acetylators	3.68	(2.23–6.09)	[9]	…	…	…	…	…	…
Positivity and failure risk ratio									
Fast vs intermediate acetylators	2.02	(1.52–2.69)	[27]	…	…	…	…	…	…
Fast vs slow acetylators	2.02	(1.52–2.69)	[27]	…	…	…	…	…	…
Probabilities									
Toxicity	0.069	…	[28]	…	…	…	…	…	…
Proportion toxicity severe	0.304	…	[29]	…	…	…	…	…	…
Probability of toxicity following rechallenge	0.157	(0.106–0.289)	Supplementary Appendix	…	…	…	…	…	…
Culture positive, 2 mo	0.156	(0.114–0.209)	Supplementary Appendix	…	…	…	…	…	…
Treatment failure	0.017	(0.009–0.030)	Supplementary Appendix	…	…	…	…	…	…
Probability of acquired MDR	0.008	…	[30]	…	…	…	…	…	…
MDR survival	0.550	…	[1]	…	…	…	…	…	…
Probability of "normalizing" INH level by dose modification	0.99	…	[10]	…	…	…	…	…	…
Utilities									
No infection	1.00	…	[31]	…	…	…	…	…	…
Active TB	0.67	(0.776–0.546)	[31]	…	…	…	…	…	…
Severe toxicity	0.67	(± 0.05)	[32]	…	…	…	…	…	…
Mild toxicity	0.91	(± 0.01)	[32]	…	…	…	…	…	…
Death	0.00	…	…	…	…	…	…	…	…

Abbreviations: INH, isoniazid; MDR, multidrug-resistant; TB, tuberculosis.

of life gained using the average age of TB onset and average life expectancy for each country (Table 1).

Costs and Utilities

We took a healthcare perspective for costs. Country-specific costs related to TB treatment were derived from primary costing surveys and were adjusted to 2018 US dollars using consumer price index deflators [5]. Toxicity increased model costs through higher treatment costs (Table 1) and by increasing months on treatment for patients who failed rechallenge. Drug costs for rapid acetylators were modeled to be higher than for intermediate acetylators because they required an extra dose of INH. Drug costs for slow acetylators were also higher because in order to receive a lower dose of INH, they were no longer able

Table 2. Mean Costs, Discounted Life-Years, Quality-Adjusted Life-Years, and Incremental Cost-Effectiveness Ratios for Patients With Tuberculosis in Brazil, South Africa, and India Under Standard Treatment and Pharmacogenomic-Guided Treatment

Country and Treatment	Cost, $	Discounted Life-years	QALYs	Incr. Costs per 1000 DS-TB ($)	Incr. QALYs per 1000 DS-TB	ICER ($/QALY)
Brazil						
Current	952	20.22	19.72	…	…	…
PGT	964	20.24	19.75	11 064	23	476
South Africa						
Current	352	17.41	16.91	…	…	…
PGT	385	17.42	16.93	33 182	19	1780
India						
Current	71	19.08	18.59	…	…	…
PGT	84	19.10	18.61	13 195	24	546

Abbreviations: DS-TB, drug-susceptible tuberculosis; ICER, incremental cost-effectiveness ratio; Incr., incremental; PGT, pharmacogenomic-guided therapy; QALY, quality-adjusted life-year.

to use a fixed-dose combination (Supplementary Tables 1 and 2). Since no commercially available pharmacogenomic test for *NAT2* currently exists, we assumed that such a test would cost the same as the Xpert MTB/RIF test, which costs $19 in Brazil and India and $26 in South Africa, including capital, labor, and other consumable costs [21–23].

We measured utility by assignment of QALYs to individuals within a simulated cohort according to published utility weights [31, 32] by multiplying utilities by life-years. Future costs and benefits were discounted at 3% per year [33].

Sensitivity and Scenario Analyses

One-way sensitivity analysis assessed the impact of each input variable on the ICER by varying key parameters according across the confidence intervals of their empirical estimates (Supplementary Table 4). For parameters without empirical estimates, parameters were varied by 50% in each direction. Two-way sensitivity analysis assessed the cost-effectiveness of all reported acetylator distributions. We conducted a probabilistic sensitivity analysis using a 10 000 draw Monte Carlo simulation to assess the impact of all the input variables on the ICER (Supplementary Table 5).

Cost-effectiveness

We defined ICERs <1 times per capita gross domestic product (GDP) to be very cost-effective and <3 times per capita GDP to be cost-effective [34]. In 2018, per capita GDP for Brazil, South Africa, and India was $8921, $6340, and $2016, respectively [35].

Population Attributable Fraction

Using population of acetylator distributions and odds ratios for outcomes comparing acetylator types, we calculated the population attributable fraction (PAF) of INH for treatment failure and toxicity for Brazil, South Africa, and India, as well as for regional acetylator distributions representative of Africa, Central/South America, Europe, Asia (not including East Asia), and East Asia [36].

All analyses were conducted using R [37].

RESULTS

Clinical Impact and Cost-effectiveness

In Brazil, PGT cost an additional $11 064 per 1000 individuals with DS-TB while gaining an additional 19 discounted life-years (23 QALYs) (Table 2). The cost per QALY gained ($476) was less than Brazil's per capita GDP ($8921). In South Africa, PGT cost an additional $33 182 and gained 15 discounted life-years (19 QALYs) per 1000 DS-TB patients. The ICER of $1780 per QALY gained was less than South Africa's per capita GDP ($6340). In India, PGx-guided therapy cost an additional $13 195 and gained 20 discounted life-years (24 QALYs) per 1000 DS-TB patients. The ICER of $546 per QALY gained was less than India's per capita GDP ($2016).

The results were primarily driven by averting cases of prolonged culture positivity and treatment failure among rapid acetylators. In Brazil, among rapid acetylators, PGT was cost saving, decreasing costs by $37 439 and gaining 104 QALYs per 1000 people with DS-TB. Rapid acetylators accounted for 57% of QALYs gained through PGT while slow acetylators accounted for 43%. Among rapid acetylators in South Africa, PGT gained 93 QALYs and increased costs by $6235 per 1000 rapid acetylators with DS-TB. Rapid acetylators accounted for 60% of QALYs gained through PGT while slow acetylators accounted for 40%. Among rapid acetylators in India, PGT gained 100 QALYs and increased costs by $8172 per 1000 rapid acetylators with DS-TB. Rapid acetylators accounted for 51% of QALYs gained through PGT while slow acetylators accounted for 49%.

One-way Sensitivity Analysis

One-way sensitivity analyses showed that the cost-effectiveness of PGT was robust to changes in all parameters (Figure 2). Results were influenced by the risk ratio comparing treatment failure in rapid vs intermediate acetylators, but PGT was still cost-effective across the risk ratio values considered (Supplementary Table 4). For the base case, we assumed that 99% of rapid and slow acetylators' therapeutic drug levels were "normalized" (ie,

Figure 2. One-way sensitivity analyses of key model parameters on incremental cost-effectiveness ratios (ICERs) in Brazil (*A*), South Africa (*B*), and India (*C*). Only parameters found to be most influential on the ICER are presented. The cost-effectiveness of pharmacogenomic-guided treatment was robust to all inputs in Brazil, South Africa, and India. Abbreviations: ICER, incremental cost-effectiveness ratio; PGx, pharmacogenomic; QALY, quality-adjusted life-year; TB, tuberculosis.

to those of intermediate acetylators). However, even if only 16% were normalized, the ICER would still be below per capita GDP in Brazil. In South Africa and India, 37% and 34% of individuals, respectively, had to have their dose normalized for the ICER to be below per capita GDP (Supplementary Figure 5). While our base case assumed PGT would correctly identify acetylators 95% of the time, if the test was only 85% accurate, ICERs would be $646/QALY in Brazil, $2241/QALY in South Africa, and $618/QALY in India (Supplementary Figure 6). In Brazil, South Africa, and India, the pharmacogenomic test could cost 11, 4, and 3 times as much as similar tests, respectively, and PGT would still cost less than per capita GDP (Supplementary Figure 7).

Two-way Sensitivity Analysis

The benefits of PGT were primarily driven by rapid acetylators and their risk of prolonged culture positivity and treatment failure. Regions with many rapid acetylators, like East Asia, benefited the

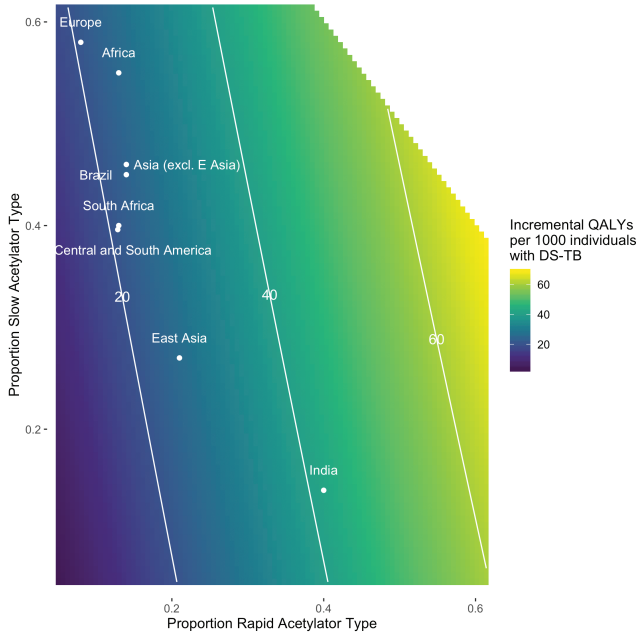

Figure 3. The impact of acetylation distribution in population on incremental quality-adjusted life-years of pharmacogenomic-guided therapy. Points indicate the estimated frequency of slow and fast acetylators in each population. Abbreviations: DS-TB, drug-susceptible tuberculosis; QALY, quality-adjusted life-year.

most from PGT (Figure 3). However, even in Africa, Asia, and Europe where there are more slow than rapid acetylators, PGT would cost <$1000/QALY assuming similar costs as in Brazil (Supplementary Figures 8–11).

Probabilistic Sensitivity Analysis

In our probabilistic sensitivity analysis, we found PGT to cost less than per capita GDP in 99% of simulations (Figure 4 and Supplementary Figure 12). PGT was cost-saving in some simulations for Brazil and India.

Acetylator Distribution Variability and PAF

Acetylator distributions vary widely by geographic location, which drives differences in the PAF of adverse events from INH (Figure 5). While Europe, Africa, Asia, Brazil, and India have many slow acetylators, East Asia has many rapid acetylators. In Brazil, 12% of treatment failures and 33% of hepatotoxicity events were attributable to INH dosing that was not optimized for *NAT2* status. In South Africa, these PAFs were 12% and 29% while in India they were 12% and 40% (Figure 5).

DISCUSSION

Although treatment for DS-TB is generally effective, toxicity and failure occur in a substantial minority of patients, causing additional healthcare costs, morbidity, and mortality [38, 39]. Observational studies and 1 randomized trial indicate that pharmacogenomic-guided dosing could minimize risks of drug-induced hepatitis and treatment failure. However, if

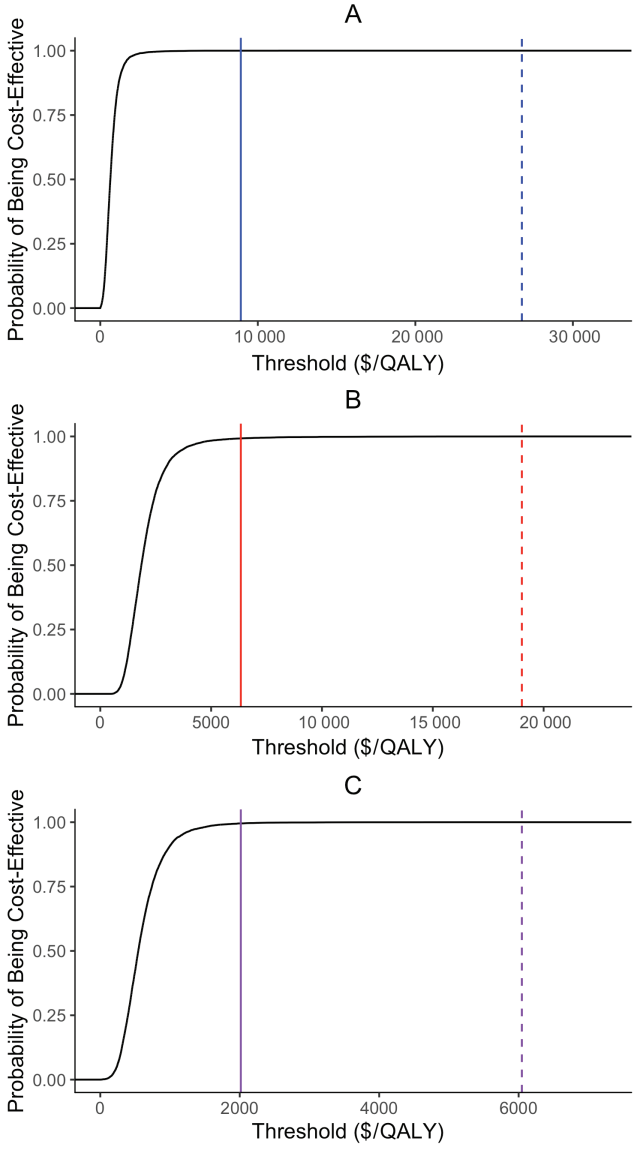

Figure 4. Cost-effectiveness acceptability curves from the probabilistic uncertainty analysis for Brazil (*A*), South Africa (*B*), and India (*C*). The curves show what percentage of the simulations would be cost-effective at a given threshold incremental cost-effectiveness ratio. The solid line indicates an incremental cost-effectiveness ratio of 1 times gross domestic product (GDP) per capita and the dashed line indicates 3 times GDP per capita. Abbreviation: QALY, quality-adjusted life-year.

effective, it was previously unclear whether such testing could be cost-effective in countries with high TB burdens where resources are often constrained. Using a model of TB treatment and costs, we find PGT to be highly cost-effective even with conservative estimates about its impact on drug-induced hepatitis and response to therapy.

The results supporting the use of PGT were robust to all input variables. The primary driver of cost-effectiveness was the failure risk ratio, which determined how effectivePGT was at averting treatment failure for rapid acetylators. Notably, the pharmacogenomic test could cost 11 times as much as similar tests on the market and the cost per QALY gained would remain less than per capita GDP in Brazil, which is considered a "very cost-effective" intervention [34]. In South Africa and India, it could cost 4 and 3 times as much, respectively, and still be less than per capita GDP. Our model only accounted for variable costs of PGT, not the fixed cost of implementation, which is likely to vary by country. However, similar to GeneXpert, over a 10-year horizon these upfront costs will be far outweighed by the cost of the consumables and personnel time.

Our main analysis found PGT to be cost-effective in Brazil, South Africa, and India. Patients on PGT were less likely to require additional months of treatment and were less likely to experience a toxic event. This resulted in reduced morbidity and mortality as well as fewer additional costs associated with clinic visits, laboratory testing, and therapy modifications. Although we modeled INH hepatotoxicity to occur in 7% of patients, other studies have found the incidence of INH-induced hepatotoxicity to be as high as 33% [3, 4], so our model likely underestimates the harms of INH-induced hepatotoxicity and the benefits of PGT dosing. Likewise, we used a conservative value (2.02 [27]) for the odds ratio comparing culture positivity between rapid and slow acetylators whereas some studies have found an odds ratio as high as 3.47 [11], which would have increased the benefits of PGT dosing.

In the absence of an available diagnostic for *NAT2* genotype, we assumed that PGT correctly identifies acetylator phenotypes 95% of the time. Under this assumption, intermediate acetylators experienced increased costs and decreased QALYs on PGT because they had a 5% risk of receiving nonoptimized dosing. However, the benefits of PGT to both slow and rapid acetylators far outweighed the deleterious effect on intermediate acetylators. We believe this assumption of accuracy may be conservative; the one US Food and Drug Administration–approved pharmacogenetic test has been found to have near 100% sensitivity and specificity [40], though it only measures a single-nucleotide variant, whereas the *NAT2* phenotype is determined by 7 variants. Even when the test was only modeled to be 85% accurate, the test was still very cost-effective (Brazil: $646/QALY; South Africa: $2241/QALY; India: $618/QALY).

We did not incorporate transmission effects in this model, as we presumed that individuals who are in treatment programs for DS-TB are unlikely to contribute substantially to transmission. Likewise, we did not account for the possibility that lower toxicity rates could improve medication adherence and thereby improve outcomes.

These results should be interpreted with consideration of the limitations of the model. Regarding clinical effectiveness, we assumed that PGT would reduce toxicity and improve treatment response to that of intermediate acetylators in 99% of patients. This assumption was based on empiric

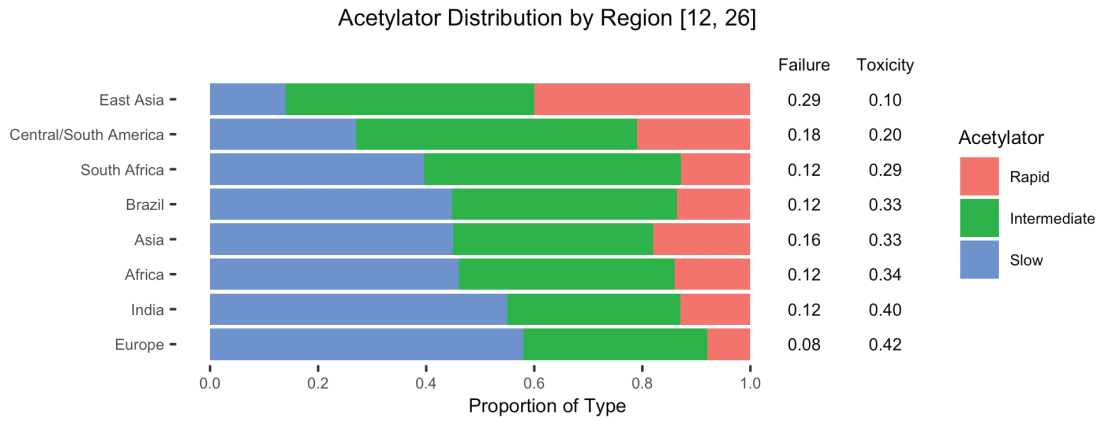

Figure 5. Distribution of acetylator types by region and population attributable fraction (PAF) of treatment failure and toxicity. Most regions of the world have <50% intermediate acetylators. Regions with high prevalence of rapid acetylators have a higher PAF of treatment failure due to nonoptimized isoniazid (INH) dosing. Regions with high prevalence of slow acetylators have a higher PAF of toxicity due to nonoptimized INH dosing.

data from pharmacokinetic studies showing that all slow and fast acetylators receiving the modified doses used in our model achieve drug levels comparable to those of intermediate acetylators under standard dosing [10]. We examined this assumption using broad sensitivity analyses; even when the reduction in risk was just 16% in Brazil, 37% in South Africa, and 34% in India, the ICER was still less than per capita GDP.

Additionally, our model does not account for INH monoresistance. Resistance to both INH and rifampicin occurs in 3.5% of new TB cases whereas 7.9% of new cases have INH monoresistance [1]. However, GeneXpert, the widely used test for drug susceptibility, only tests for rifampicin resistance. Therefore, some patients who test "drug-susceptible" will actually have INH-resistant TB and may not observe any of the benefits of PGT.

The generalizability of these results mainly depends on treatment costs and acetylator distributions. PGT is likely to be cost-effective in countries that have comparable or higher treatment costs and per capita GDP as the countries analyzed. Further analyses are needed to evaluate this in countries with fewer resources. The cost-effectiveness of PGT was robust to the proportion of the population that are fast or slow acetylators, across broad ranges representative of the global distribution (Figure 3). Additional trials testing the clinical effects of PGT would bolster the predictive accuracy of our model.

Despite being cost-effective, PGT has not been widely deployed and no company currently manufactures a test. Reasons for delayed adoption may include insufficient clinical evidence about the efficacy of modified doses, reluctance to implement "personalized" approaches to a disease traditionally treated by a public health approach, and the assumption that PGT would be too expensive.

Implementing PGT appears highly cost-effective even in resource-constrained settings under conservative assumptions about its impact. To be cost-effective, PGT only has to be moderately effective at reducing hepatitis and improving treatment response relative to standard dosing; observational data and one randomized trial indicate that the impact on both may be substantial. Future studies should be undertaken to replicate the randomized trial data and evaluate real-world clinical effectiveness of PGT for TB in other populations. If confirmed, this approach has the potential to reduce morbidity and improve treatment outcomes substantially for TB globally.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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