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The health and economic benefits of tests that predict future progression to tuberculosis disease.

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Abstract

Background: Effective targeting of latent tuberculosis infection (LTBI) treatment requires identifying those most likely to progress to tuberculosis (TB). We estimated the potential health and economic benefits of diagnostics with improved discrimination for LTBI that will progress to TB.

Methods: A base-case scenario represented current LTBI testing and treatment services in the United States in 2020, with diagnosis via interferon-gamma release assay (IGRA). Alternative scenarios represented tests with higher positive predictive value (PPV) for future TB but similar price to IGRA, and scenarios that additionally assumed higher treatment initiation and completion. We predicted outcomes using multiple transmission-dynamic models calibrated to different geographic areas, and estimated costs from a societal perspective.

Results: In 2020, 2.1% (range across model results: 1.1%-3.4%) of individuals with LTBI were predicted to develop TB in their remaining lifetime. For IGRA, we estimated the PPV for future TB as 1.3% (0.6%-1.8%). Relative to IGRA, we estimated a test with 10% PPV would reduce treatment volume by 87% (82%-94%), reduce incremental costs by 30% (15%-52%), and increase quality-adjusted life years by 3% (2%-6%). Cost reductions and health improvements

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were substantially larger for scenarios in which higher PPV for future TB was associated with greater initiation and completion of treatment.

Conclusions: We estimated that tests with better predictive performance would substantially reduce the number of individuals treated to prevent TB, but would have a modest impact on incremental costs and health impact of TB prevention services, unless accompanied by greater treatment acceptance and completion.

Keywords

latent TB infection; tuberculosis; mathematical modeling; United States

INTRODUCTION

Individuals latently infected with *Mycobacterium tuberculosis* may develop tuberculosis (TB) at some point in their lives, and clinical guidelines recommend treatment of latent TB infection (LTBI) to prevent future disease[1–5]. In the United States, 9 million individuals are estimated to have untreated LTBI[6], and most TB cases result from infections acquired >2 years previously[7,8]. For this reason, targeted LTBI testing and treatment of populations at high risk for TB is a key strategy for achieving US TB elimination[9]. In total, an estimated 13 million individuals receive LTBI testing annually, including administrative testing of low-risk individuals[10].

With the exception of infants and immunosuppressed individuals, newly-infected individuals are thought to face an estimated cumulative lifetime TB risk of 5-10%[11,12]. Approximately half of these TB cases will occur in the 2-3 years following infection, with subsequent risks declining progressively[13–17], such that a person infected many years ago may have a low future risk of developing TB[18,19]. The low TB risks faced by these individuals mean that many individuals with LTBI must be treated to prevent one TB case. While TB infection screening has additional benefits—identifying some individuals with TB disease, for whom treatment is urgent[5]—reducing the number of individuals treated for LTBI per TB case averted will improve the cost–benefit profile of these services.

The performance characteristics of current TB infection tests make it difficult to target LTBI treatment to those who will eventually develop TB[20,21]. Current TB infection diagnostics approved in the United States include the tuberculin skin test (TST), and interferon-gamma release assays (IGRAs), with IGRA increasingly replacing TST[22]. These tests cannot differentiate TB disease from infection, persistent infections from ones that have resolved, or LTBI that will progress to TB from LTBI that will not[23]. In addition, these tests may produce false-negative results. Specificity is lower for those with advanced immunosuppression[24–26], a population that is at higher risk of LTBI reactivation[27–29], and for whom TB confers high mortality risks. TST specificity is also lower with prior Bacille Calmette–Guerin (BCG) vaccination, which is common among individuals born abroad who make up the majority of the US LTBI population[30,31]. Recent research has identified several biomarkers predicting short-term (up to 24 months) progression to TB among IGRA-positive individuals[20], but longer-term predictive performance is poor.

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In the context of US LTBI testing and treatment services and the populations currently served by these services, we estimated the health and economic benefits of tests with better prognostic value for future TB, as compared to IGRA, and how the availability and adoption of these tests would affect the overall outcomes of LTBI screening and treatment in the United States.

METHODS

Mathematical models

We estimated results using three transmission-dynamic TB models[32–34], previously assessed in a published model comparison[35]. These models simulate LTBI testing and treatment services in the United States[32–34]. The Johns Hopkins model[33] was calibrated to four states (California, Florida, New York, Texas), the UCSF (University of California San Francisco) model[32] was calibrated to California, and the Harvard model[34] was calibrated to the United States nationally. Each model represents TB transmission, LTBI, and progression to TB, as well as immigration from settings with high TB prevalence, variation in TB exposure within the US, and individual risk factors such as HIV and diabetes that increase TB risks. Models were calibrated to reported TB data in the geographic area modeled. Models included diagnosis and treatment pathways for TB and LTBI, and estimated the long-term population-level implications of alternative intervention options. Further details are provided in the eAppendix; http://links.lww.com/EDE/B853.

Target population and setting

This study considered the populations that would be directly impacted by changes in the performance characteristics of LTBI diagnostic tests. This included individuals receiving LTBI testing and treatment as part of current TB prevention services in the United States. These services include targeted testing of populations at high risk of TB such as non-US-born individuals, contacts of persons with infectious TB disease, individuals who work in correctional facilities or other high-risk settings, and individuals with comorbidities that increase LTBI reactivation risks[1]. Testing also encompasses populations with lower risk (such as routine screening of healthcare personnel[4]) conducted in public and private settings[10]. The analysis did not distinguish the costs and impacts of testing for each group. Each model was used to simulate scenarios for TB prevention services in the setting to which they had been calibrated (Johns Hopkins model: California, Florida, New York, and Texas; UCSF model: California; Harvard model: national).

Modeling the LTBI testing and treatment cascade

We assumed a common approach to represent the LTBI testing and treatment cascade, to reflect factors reducing intervention effectiveness in routine settings (eFigure 1; http://links.lww.com/EDE/B853). We estimated the number and characteristics of individuals receiving LTBI treatment in each modeled population[1,36–38]. Sensitivity and specificity of IGRA for LTBI diagnosis were based on published values for QuantiFERON Gold In-Tube[25]. For adults without HIV, sensitivity and specificity for LTBI were 78.9% and 98.5% respectively for non-US-born individuals, and 78.0% and 97.9% for US-born individuals. Sensitivity and specificity estimates were lower for individuals with HIV.

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We assumed individuals testing positive would be offered LTBI treatment, with 72% accepting treatment[39]. For individuals initiating treatment, 78% were assumed to complete a 3-month weekly self-administered regimen of isoniazid and rifapentine (3HP)[40]. For scenarios describing tests with improved prognostic value for future TB, we performed sensitivity analyses with higher initiation and completion probabilities. We assumed the risk of TB progression would be reduced by 93% for individuals completing treatment (based on the efficacy estimated for a 9-month isoniazid regimen[41,42], and the noninferiority of 3HP compared to this regimen[43]), and by 0% for those not completing treatment[44]. Treatment of individuals with false positive test results was assumed to have no impact on TB epidemiology, but could result in costs and treatment side effects. We assumed that all individuals would be screened for TB disease before initiating LTBI treatment, and that the numbers diagnosed with TB disease would not be affected by changes in test specificity represented by the alternative scenarios below. We conducted sensitivity analyses to assess the robustness of results to changes in key cascade parameters (Supplement; http://links.lww.com/EDE/B853).

Modeling tests with improved discrimination for LTBI that will progress to TB in the future.

We divided the cohort receiving testing (eFigure 1; http://links.lww.com/EDE/B853) into individuals without LTBI (*'No LTBI'),* individuals with LTBI that will not progress to TB disease (*'LTBI, won't progress'*), and individuals with LTBI that will progress to TB disease in their remaining lifetime (*'LTBI, will progress'*). For this analysis we considered the ability of a new test to distinguish the third category (*'LTBI, will progress'*) from the first two. This differs from the conventional definition of LTBI test outcomes (ability to separate both LTBI categories from *'No LTBI'*), and so we used the superscript ^{LTBI} to refer to outcomes (e.g., sensitivity, specificity, positive predictive value [PPV]) calculated under the traditional definition, and ^{FTB} (for future TB) for outcomes describing the ability to distinguish the '*LTBI, will progress'* category. Sensitivity^{FTB} was defined as the fraction of those in the '*LTBI, will progress*' category that would test positive. Specificity^{FTB} was defined as the fraction of those who would not develop TB in their lifetime (*'No LTBI'* and *'LTBI, won't progress'*) that would test negative with the new test (eTable 1; http://links.lww.com/EDE/B853). We assumed that increases in specificity^{FTB} would be achieved by reducing the fraction of individuals in the '*LTBI, won't progress'* category testing positive. To do so we varied the false positive fraction (the complement of specificity^{FTB}) from a value equivalent to IGRA to 0.0, equivalent to perfect specificity. We assumed that sensitivity^{FTB} would be the same as reported sensitivity^{LTBI} of IGRA[25]. Additional details are provided in the Supplement; http://links.lww.com/EDE/B853.

Analytic scenarios

Base Case Scenario: the base case scenario estimated LTBI testing and treatment services in 2020 and 2035, assuming that current eligibility approaches would continue, with testing via IGRA. This base case represents the current standard of care in the United States.

Alternative Scenario 1 (higher specificity^{FTB}): this scenario modified the base case to assume that the test used for screening would have higher specificity^{FTB}, with the false

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positive fraction varied from the value estimated for IGRA, down to a value of 0.0 (perfect specificity^{FTB}). All other features of LTBI testing and treatment were fixed at their base case values.

Alternative Scenario 2 (higher test specificity^{FTB}, greater treatment initiation & completion): this scenario extended alternative scenario 1 to assume probabilities of treatment initiation and completion would increase to 90% respectively, as patients and providers might have greater motivation to complete treatment if the PPV^{FTB} rises.

Outcomes

Operational outcomes: for each model and geographic area, we estimated sensitivity^{FTB}, specificity^{FTB} and PPV^{FTB}, numbers needed to test and numbers needed to treat to avert one TB case, and potential reductions in LTBI treatment volume for testing and treatment conducted in 2020 and 2035.

Long-term costs and health outcomes: We calculated lifetime costs and health benefits for the modeled cohorts. Costs were estimated from a societal perspective, including changes in TB prevention and treatment costs, and changes in patient productivity from TB disease and TB interventions. We assumed individuals developing TB would experience a reduced quality of life, with a utility weight of 0.83[45] applied to a 12-month episode duration (assuming an average 3 months pre-treatment disease duration, and an average 9 months of treatment), and an assumed utility weight of 0.97 applied to the remaining life expectancy (representing post-TB sequelae). Individuals with TB also faced a 6.5% risk of TB death, based on 9.0% TB case fatality[46] and analyses suggesting 72% of these deaths are due to TB[47]. The average life years gained due to averted TB death (18.9 years) was based on US general population life tables[48] and the age distribution of US TB deaths 2013-2017 (mean 67 years), stratified by HIV status[49], assuming a 12.7% lower life expectancy for individuals with HIV[50]. Average productivity losses per TB death ($559,810) were based on Grosse et al[51], adjusted for the age distribution of TB deaths and inflated to 2018 dollars. TB treatment costs were estimated as $20,267 for health services and $2,257 for patient productivity costs, and applied to the fraction of individuals projected to survive to TB diagnosis. For every additional TB case we assumed 0.165 secondary TB cases, estimated using the Harvard model, and consistent with empirical estimates from contact investigations[17]. Three months of self-administered isoniazid and rifapentine treatment of LTBI was assumed to confer a 5.6% risk of treatment discontinuation due to adverse events[40]. We assumed adverse events (primarily hepatotoxicity) to temporarily reduce quality of life (utility weight 0.75 applied to a 2-week episode duration, incurred by 5.6% of all patients[52,53]). Costs were estimated for LTBI testing ($69 per individual tested[54], assumed the same for tests with higher specificity^{FTB}) and treatment ($405 health services cost, including costs of treating adverse events, and $99 productivity loss per patient[53,55]). Additional details are provided in the Supplement; http://links.lww.com/EDE/B853. We also conducted sensitivity analyses to assess the robustness of results to changes in key parameters (Supplement; http://links.lww.com/EDE/B853).

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We estimated incremental societal costs (LTBI testing and treatment costs minus averted costs of TB treatment), and incremental health benefits (quality adjusted life years, QALYs), of LTBI testing and treatment services under each alternative scenario compared to the base case. Results were estimated for a hypothetical cohort of 10,000 individuals receiving LTBI testing and treatment in the United States as part of current TB prevention services. Costs are reported in 2018 US dollars[56], and major outcomes are presented undiscounted.

We estimated results for each geographic area represented by the three models, producing six sets of results. We calculated summary estimates as the mean across these results, and the range across models shown in brackets.

RESULTS

Performance of testing and treatment services with diagnosis by IGRA

Table 1 reports estimates from each modeled location, describing LTBI prevalence and risk of future TB, for the tested population; sensitivity^{FTB}, specificity^{FTB}, and PPV^{FTB} of IGRA; and numbers needed to test and treat to avert one TB case. Results are shown for 2020 and for 2035, based on the base case scenario. eFigure 2; http://links.lww.com/EDE/B853 shows how PPV^{FTB} in 2020 is related to LTBI prevalence and the probability of future TB for those with LTBI. For all models, the number needed to test to avert one TB case increased by 40% [range across models: 11%, 65%] between 2020 and 2035, and the number needed to treat to avert one TB case increased by 15% [9%, 21%] over the same period. These changes were driven largely by declines in LTBI prevalence, which was predicted to drop by 26% [−2%, 49%] between 2020 and 2035. eTable 2 (http://links.lww.com/EDE/B853) shows how the testing cohort is divided into true-positive, true-negative, false-positive, and false-negative categories from testing with IGRA, when interpreted as a test for future TB.

Clinical outcomes of tests with improved discrimination for LTBI that will progress to TB in the future

The Figure shows how selected metrics of the LTBI testing and treatment cascade improve with increasing test specificity^{FTB}. Estimates of specificity^{FTB} for IGRA averaged 94.4% across models [91.3%, 96.9%] (Table 1). These specificity^{FTB} values are lower than the specificity^{LTBI} values for IGRA used as inputs for the analysis, as the results in Table 1 interpret a positive test among individuals with LTBI who will not progress to TB in the future as false positives (eTable 1; http://links.lww.com/EDE/B853). We estimated that a test with 98% specificity^{FTB} would increase PPV^{FTB} (the fraction of all those testing positive who would progress to TB in the future, without LTBI treatment) to 3.8% [0.9%, 6.7%] (Figure, Panel A). This would reduce the number needed to treat to avert one TB case to 54 [21, 149] (Panel B), and reduce overall treatment volume by 59% [36, 77] as compared to testing with IGRA (Panel C). A test with 99% specificity would increase PPV to 7.2% [1.8%, 11.6%], reduce the number needed to treat to avert one TB case to 28 [12, 75], and reduce overall treatment volume by 79% [68%, 87%], as compared to IGRA.

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Long-term health and economic outcomes of tests with improved discrimination for LTBI that will progress to TB in the future

Table 2 shows outcomes of LTBI testing and treatment with IGRA compared to tests with higher specificity^{FTB}. With IGRA, the QALYs lost from LTBI treatment are small compared to the gains from averted TB cases, reflecting analytic assumptions of much greater QALYs lost per case of TB disease (1.93 QALYs) than per LTBI treatment course (0.00058 QALYs). The incremental QALYs from LTBI testing and treatment are estimated to be 2.8% [1.6%, 6.0%] higher for a test with 10% PPV^{FTB}, compared to IGRA (PPV^{FTB} 1.3% [0.6%, 1.7%]). While treatment costs could be substantially reduced with a test with higher specificity^{FTB}, these costs are small compared to testing costs (assumed to be fixed), such that total costs of testing and treatment only decrease by 19% [13%, 27%] with a 10% PPV^{FTB} test, even though treatment costs decrease 87% [82%, 94%]. For a cohort of 10,000, this represents cost reductions of $176,000 [$107,000, $270,000] due to averted LTBI treatment, as well as 0.2 [0.1, 0.3] QALYs gained. The cost reductions associated with tests with higher specificity for future TB plateaued at higher PPV^{FTB} values (eFigure 3; http://links.lww.com/EDE/B853). Across models, cost reductions were higher where models estimated higher LTBI prevalence, and lower future TB risks among those with LTBI. As higher specificity tests were estimated to reduce costs and improve health outcomes, such tests should always be preferred to the base case and therefore no cost-effectiveness ratios were calculated. eFigure 4; http://links.lww.com/EDE/B853 shows the results of sensitivity analyses for model input parameters.

Impact of improved treatment initiation and completion

For tests with higher specificity^{FTB}, those receiving a positive result have much higher risks of future TB, and greater potential gains from LTBI treatment. We examined a scenario that assumed these greater treatment benefits would motivate better treatment initiation and completion. For a scenario in which 90% of individuals testing positive initiate treatment (versus 72% under the base case), and 90% of individuals initiating treatment complete the regimen (versus 78% under the base case), the percent reduction in future TB cases is estimated to be 58% [55%, 59%], as compared to 40% [38%, 41%] under other scenarios.

This greater prevention impact has consequences for the health and economic effects estimated for these scenarios. As compared to the base case, a test with 10% PPV for future TB combined with 90% treatment initiation and completion would result in societal cost reductions of $294,000 [$135,000, $476,000] and 4.3 [1.1, 7.4] additional QALYs in a cohort of 10,000 (eTable 3; http://links.lww.com/EDE/B853). As with other modeled scenarios, higher specificity tests were estimated to reduce costs and improve health outcomes, and such tests should always be preferred to the base case.

DISCUSSION

In this analysis we estimated the health and economic benefits of tests with better discrimination for LTBI that will progress to TB in the future, as compared to current diagnostics. For US LTBI testing and treatment services, we found current tests (represented by IGRA) to have poor ability to predict future TB for individuals with latent infection,

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with estimates of the positive predictive value for future TB ranging from 0.6% to 1.8% for cohorts tested in 2020. These low PPV estimates reflect low LTBI prevalence in modeled cohorts (ranging from 2.3-9.0%) and low risk of future TB among those with LTBI (ranging from 1.1-3.4%), combined with high but imperfect (91-97%) test specificity for individuals who will progress to TB in the future. As a consequence, an estimated 76-232 individuals need to be treated to avert one TB case.

Our estimates of future TB risk for IGRA-positive individuals (0.6-1.8%), were lower than reported in earlier systematic reviews[57,58]. Similarly, our estimates are lower than reported by the UK PREDICT study, in which 3.3% of IGRA-positives developed TB disease over an average 3-year follow-up[59]. These studies included cohorts with a high prevalence of LTBI and risk factors for disease progression, which differs from the overall US population receiving LTBI screening and treatment. While there is little population-based evidence on the characteristics of individuals receiving LTBI testing and treatment in the United States, 2011-2012 National Health and Nutrition Examination Survey data suggest 5.9% (5.0–6.9) of all previously tested individuals reported a positive test result[31], consistent with the mean value of 5.6% IGRA-positivity (eTable 2; http://links.lww.com/EDE/B853) from our analyses. However, LTBI prevalence and future TB risk varied widely across our modeled cohorts suggesting substantial uncertainty, even in models that have been demonstrated to perform similarly in other comparisons[35,60]. In general, PPV estimates will be higher for testing cohorts with elevated LTBI and risk factor prevalence (eFigure 1; http://links.lww.com/EDE/B853). For this reason, current clinical practice guidelines discourage testing of low-risk individuals[22].

Tests better able to identify individuals with LTBI who would progress to TB in the future were estimated to substantially reduce the number of individuals requiring treatment, with a test with 10% PPV for future TB estimated to reduce treatment volume by 82-94%. This would be achieved through reduced treatment of individuals who would receive no clinical benefit, and would have no negative impact on prevention of TB. On the other hand, the reduction would benefit those avoiding unnecessarily treatment, especially if they might have experienced side effects. Our analyses suggest the impact of a test with better predictive discrimination would reduce overall costs of LTBI testing and treatment only modestly if testing approaches continue to include low-risk persons, with incremental costs dropping by 14-39% for a test with 10% PPV for future TB, equivalent to $11-$27 per person tested. This is because treatment costs represent a small fraction (approximately 20%) of total intervention costs, with testing costs estimated to account for the remaining 80%. The impact on health was estimated to be small, with a test with 10% PPV for future TB predicted to result in one QALY gained for every 32,000-81,000 individuals tested, as compared to the base case.

While reducing costs and unnecessary treatment, improved test specificity for future TB would not directly improve the TB prevention impact of LTBI testing and treatment services. This changes if a more specific test were to catalyze greater treatment initiation and completion. This is not implausible, as the TB risks faced by those testing positive would be substantially higher. In a scenario in which a better test is accompanied by an increase in treatment initiation and completion to 90%, a test with 10% PPV for future TB would

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reduce societal costs by 16-58%, equivalent to $12-$40 per person tested, and result in one QALY gained for every 1,300-9,200 individuals tested, as compared to the base case. If the extent of behavior change is smaller than envisaged in this scenario, the change in costs and QALYs saved by averted TB cases would be commensurately smaller. Although we did not investigate this scenario, tests with improved sensitivity would have similar consequences to improvements in treatment initiation and completion. Future evaluation of candidate tests will need to take account of the combined effects of changes in sensitivity, specificity, and cost, relative to current tools.

To undertake this analysis, we used three transmission models calibrated to different areas of the United States. The use of multiple mathematical models to examine common research questions can lend robustness to modeling conclusions, through allowing variation in modeling assumptions[61], and revealing areas of uncertainty missed by single model analyses. In this analysis there was substantial variation between models—in particular, estimates of the fraction of tested populations who will develop TB in the future ranged from 3 to 18 per 10,000 (Table 1). This reflects uncertainty about LTBI burden (population-based LTBI prevalence data have only been collected periodically, and are only representative at the national-level), as well as the future TB risks associated with LTBI. While the use of multiple models provides some corroboration of results, each of these models requires natural history assumptions that are difficult to validate. Despite the variation between models, conclusions drawn about the relative impact of the various analytic scenarios were supported by all model results.

This analysis describes the impact of test performance for the pooled cohort receiving LTBI testing and treatment. However, it is likely that outcomes would differ between different populations—for example, individual-level factors that suggest higher LTBI prevalence (such as non-US birth) will increase the yield of testing. Similarly, factors associated with elevated TB risk for those with LTBI (such as recent TB exposure, or impaired immune function) will increase the prevention benefits of treatment.

Caution should be used in extrapolating these results to non-US settings. Our results reflect patterns of TB infection and risk factors in the US population, as well as the clinical recommendations and targeting approaches that determine the composition of the tested cohort. Findings may be similar in other settings with limited recent transmission and low LTBI prevalence, but we did not examine these possibilities. We also did not examine different test prices, and assumed the test price would be the same as for IGRA. As testing composes the majority of LTBI testing and treatment costs, changes in test cost would strongly influence the attractiveness of a new test.

A test with better prognostic value for future TB could greatly reduce the number of individuals treated for LTBI, without reducing the number of TB cases averted by prevention services. Avoiding unnecessary treatment would reduce the resources expended by prevention services, as well as the costs, inconvenience, and potential side-effects borne by treated patients. If able to motivate greater uptake and completion of treatment, this would lead to substantial health benefits and additional cost reductions.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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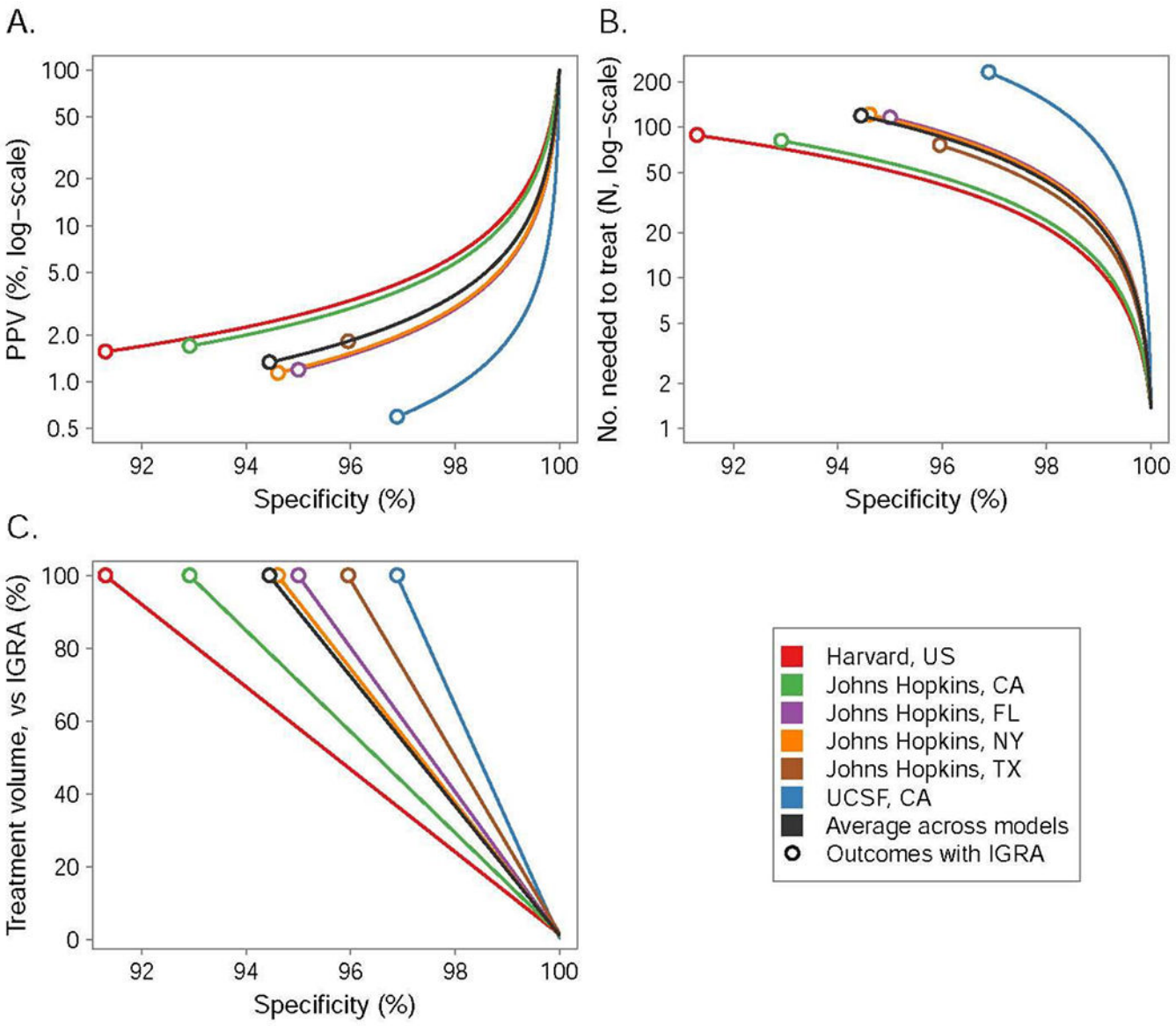

Figure: Changes in LTBI diagnosis and treatment for an assay with improved ability to identify LTBI that will progress to TB disease in the future, relative to IGRA, for 2020.

Panel A: Change in positive predictive value produced by improved specificity for LTBI that will progress to TB in the future (specificity^{FTB}), for each model. Panel B: Change in the number needed to treat to avert one TB cases produced by improved specificity^{FTB}, for each model. Panel C: Change in the volume of preventive treatment produced by improved specificity^{FTB}, for each model. These analyses assume that, apart from changes in specificity^{FTB}, all other features of LTBI testing and treatment are held fixed across scenarios. LTBI = latent TB infection. IGRA = interferon-gamma release assays. PPV = positive predictive value.

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Table 1:

Estimated performance of LTBI testing and treatment with IGRA in 2020 and 2035, for 6 models.

	LTBI and future TB risk in tested individuals			Estimated performance of IGRA to identify LTBI that will progress to TB in the future[a]			Numbers needed to test and treat to avert 1 future TB case	
	LTBI prevalence in tested individuals (%)	Risk of future TB in tested individuals with LTBI (%)	Risk of future TB in tested individuals (%)	Sensitivity for future TB (sensitivity^{FTB}) (%)	Specificity for future TB (specificity^{FTB}) (%)	Positive predictive value for future TB (PPV^{FTB}) (%)	Number needed to test (N)	Number needed to treat (N)
Outcomes in **2020** *Harvard, US*	9.0	2.0	0.18	77.9	91.3	1.6	1003	89
Hopkins, CA	6.8	2.3	0.16	78.0	92.9	1.7	1130	81
Hopkins, FL	4.0	1.9	0.08	78.0	95.0	1.2	2291	116
Hopkins, NY	4.5	1.7	0.08	78.0	94.6	1.1	2222	121
Hopkins, TX	2.8	3.4	0.10	78.0	95.9	1.8	1845	76
UCSF, CA	2.3	1.1	0.03	73.0	96.9	0.6	7394	232
Mean value	**4.9**	**2.1**	**0.10**	**77.2**	**94.4**	**1.3**	**2648**	**119**
Outcomes in **2035** *Harvard, US*	5.5	1.9	0.11	78.2	93.9	1.4	1652	101
Hopkins, CA	5.0	2.3	0.12	78.0	94.3	1.5	1534	89
Hopkins, FL	2.9	1.9	0.05	78.0	95.9	1.0	3222	135
Hopkins, NY	3.1	1.8	0.05	78.0	95.7	1.0	3231	141
Hopkins, TX	1.9	3.4	0.07	78.0	96.6	1.5	2643	92
UCSF, CA	2.4	1.0	0.02	68.9	96.9	0.5	8230	253
Mean value	**3.5**	**2.1**	**0.07**	**76.5**	**95.5**	**1.2**	**3419**	**135**

[a]Sensitivity, specificity, and PPV estimates relate to the outcome of LTBI that will progress to TB disease in the future. Individuals testing positive are assumed to be screened for TB disease before an LTBI diagnosis is made.

LTBI = latent TB infection. IGRA = interferon-gamma release assays. PPV = positive predictive value.

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Table 2:

Long-term outcomes of LTBI testing and treatment for tests with improved positive predictive value for LTBI that will progress to TB disease in the future, in 2020[a].

	Base case (IGRA)	Scenarios for improved test specificity for LTBI that will progress to TB disease in the future (PPV^{FTB})			
		PPV^{FTB} = 2%	PPV^{FTB} = 5%	PPV^{FTB} = 10%	PPV^{FTB} = 20%
Cohort size (N)	10000	10000	10000	10000	10000
Number diagnosed positive (N)	563 (313, 882)	396 (93, 687)	158 (37, 275)	79 (19, 137)	40 (9, 69)
Number completing treatment (N)	316 (176, 495)	222 (52, 386)	89 (21,154)	44 (10, 77)	22 (5, 39)
Number experiencing side-effects (N)	22.7 (12.6, 35.6)	16.0 (3.8, 27.7)	6.4 (1.5, 11.1)	3.2 (0.8, 5.5)	1.6 (0.4, 2.8)
Number of TB cases averted (N)	4.1 (1.0, 7.2)	4.1 (1.0, 7.2)	4.1 (1.0, 7.2)	4.1 (1.0, 7.2)	4.1 (1.0, 7.2)
Number of TB deaths averted (N)	0.27 (0.06, 0.47)	0.27 (0.06, 0.47)	0.27 (0.06, 0.47)	0.27 (0.06, 0.47)	0.27 (0.06, 0.47)
LTBI testing costs ($, 000s)	690 (690, 690)	690 (690, 690)	690 (690, 690)	690 (690, 690)	690 (690, 690)
LTBI treatment costs ($, 000s)	204 (114, 320)	144 (34, 249)	57 (14, 100)	29 (7, 50)	14 (3, 25)
Averted costs of TB disease ($, 000s)	184 (43, 320)	184 (43, 320)	184 (43, 320)	184 (43, 320)	184 (43, 320)
QALYs lost during LTBI treatment (N)	0.24 (0.13, 0.37)	0.17 (0.04, 0.29)	0.07 (0.02, 0.12)	0.03 (0.01, 0.06)	0.02 (0, 0.03)
QALYs gained through averted TB (N)	9.29 (2.19, 16.13)	9.29 (2.19, 16.13)	9.29 (2.19, 16.13)	9.29 (2.19, 16.13)	9.29 (2.19, 16.13)
Incremental costs of LTBI testing and treatment ($, 000s)	611 (514, 737)	550 (447, 657)	464 (297, 637)	435 (247, 630)	421 (222, 627)
Incremental costs versus base case ($, 000s)[b]	Reference	−61 (−85, −14)	−147 (−220, −95)	−176 (−270, −107)	−190 (−295, −110)
Incremental QALYs saved by LTBI testing and treatment (N)	9.05 (2.06, 15.76)	9.12 (2.15, 15.84)	9.22 (2.17, 16.01)	9.26 (2.18, 16.07)	9.27 (2.18, 16.1)
Incremental QALYs versus base case (N)	Reference	0.07 (0.02, 0.1)	0.17 (0.11, 0.26)	0.20 (0.12, 0.31)	0.22 (0.13, 0.34)

[a] Table shows mean across 6 sets of model results. Range across model results shown in parentheses. PPV^{FTB} represents the positive predictive value for LTBI that will progress to TB in the future. Each column shows incremental outcomes of LTBI testing and treatment with different test specificity for future TB, as compared to no testing or treatment. Analyses assume that other components of LTBI testing and treatment services (size and composition of cohort being tested, probability of starting and completing a regimen for those receiving a positive diagnosis, regimen effectiveness, test cost) are the same across scenarios. We did not consider the costs or benefits of identifying individuals with TB disease through LTBI screening. QALY estimates represent changes in quality of life and survival over the lifetime of cohort members. Costs reported in 2018 US dollars.

[b] Negative values represent reductions in societal costs. LTBI = latent TB infection. IGRA = interferon-gamma release assays. PPV = positive predictive value. QALY = quality-adjusted life year.