Online Appendix for “The Programmatic Benefits and Costs of Using MTD Nucleic Acid Amplification Testing to Diagnose Tuberculosis Disease in the U.S.”

Additional Description of Methods

Description of Patient Evaluation and MTD

Clinicians generally defined patients suspected of having pulmonary TB as persons who exhibited symptoms of respiratory TB disease or, if asymptomatic, had clinical and radiologic findings consistent with pulmonary TB (e.g., SP, abnormal chest radiograph, MTD positive) or were at moderate/high clinical suspicion for TB disease because of exposure and inclusion in a risk group (HIV infected, homeless, incarcerated, etc.). However, individual providers, hospitals, and laboratories use their own judgment in ordering or performing diagnostic tests. The State public laboratories in Georgia, Maryland, and Massachusetts all had protocols to conduct MTD on all smear-positive specimens. The study included only patients suspected of TB who were reported to the public health system from the project catchment areas of each participating site. Only sites that had full capture of AFB-smear and Mycobacterium-tuberculosis-culture results were eligible to participate in the evaluation study. Since data on patients suspected of TB are not reported to CDC, each site conducted specific procedures to obtain data, as described below.

Georgia collaborated with the epidemiology department at Grady Memorial Hospital, a public health hospital that cares for most TB patients in Fulton and DeKalb counties and sees a highly HIV-prevalent population, to obtain data on persons suspected of TB. MTDs are conducted at Grady on all SP respiratory specimens to help exclude TB and on high suspicion SN specimens to consider TB. For patients suspected of TB but not identified by Grady
Hospital, Georgia collaborated with the Georgia Department of Human Resources to obtain data.

In Hawaii, in accordance with Hawaii law, all persons suspected of TB, including those seen in the private sector, are reported to the Hawaii Department of Health (DOH) TB Branch within 24 hours. The majority (70%) of persons suspected of TB are reported to the DOH by the DOH TB Clinic, which also houses the TB Registry. Patients suspected of having TB by the DOH are identified through administrative screening, evaluation of recent immigrants, TB contact investigation, or through referrals to the DOH TB Clinic from private doctors. Clinical data of patients suspected of TB were abstracted from the DOH TB Clinic charts and/or electronic tracking system. Most specimens were analyzed for *M. tuberculosis* by one private commercial laboratory, which along with other laboratories sent specimen results to the DOH TB Registry.

In Massachusetts, the state laboratory conducted most MTD, with the remainder performed by individual hospitals or by commercial laboratories. Once a suspect was reported to the public health system, Massachusetts reviewed daily reports and gathered needed information by contacting multiple providers and laboratories.

Maryland officially defined persons suspected of TB as having a lab-confirmed AFB-positive smear or biopsy report consistent with active TB disease, an abnormal chest radiograph suggestive of active TB, or having initiated ≥ two anti-TB medications. Persons suspected of TB were immediately reported to the Maryland DOH and materials submitted. However, the
timing of suspect reporting varied according to clinician discretion and whether state or private laboratories were used. If private laboratories were used, the suspect was referred to the local DOH TB clinic where the provider collected new specimens if the patient had been treated for less than seven days and sent them to the Maryland State Laboratory for AFB testing followed by MTD on all SP specimens and decided whether to start anti-TB treatment. If the MTD was positive, then the suspect was reported; if the MTD was negative, then the clinician determined whether to report the patient as a suspect. Other activities (contact investigation, isolation, etc.) were started depending on clinical data and symptoms. Maryland had access to Maryland State Laboratory data; all DOH TB clinics used the State Laboratory, as well as some hospitals and private doctors.

Analysis

The following outcomes were analyzed: AFB smear result (positive or negative), MTD conducted and result (positive or negative), *Mycobacterium tuberculosis* culture result (positive or negative), MTD and no MTD positive predictive value (PPV), MTD and no MTD negative predictive value (NPV), MTD and no MTD sensitivity, and MTD and no MTD specificity, non-tuberculous mycobacterial disease diagnosis, TB-related hospitalization, and TB-related death.

To assess statistically significant associations at p<0.05 with dichotomous outcomes (MTD use, CP, NTM diagnosis), we used multivariable log-binomial regression (SAS Version 9.2, 9.3) including patient demographics and sites for final model determination. We defined substance abuse as a history of injection or non-injection illicit drug use or excess alcohol use within one year of suspect assessment. Patient demographics were: age groups 25-44, 45-64,
≥ 65 versus age < 25 as the referent; race/ethnicity Hispanic, black/African American (henceforth referred to as “black”), Asian, American Indian/Alaskan Native (AIAN), Native Hawaiian/Other Pacific Islander (NHPI) versus white; foreign-born versus US-born; HIV-infected versus HIV-uninfected; homelessness within the past year versus none; substance abuse within the past year versus none. Suspects missing any of the above characteristics were deleted from the models.

Outpatient days for patients never hospitalized were calculated as the product of the number of non-hospitalized patients and the average days to TB determination. For hospitalized patients, outpatient days were the product of the total number of persons hospitalized times the average outpatient days prior to determination. Contact investigation days were calculated as the average days of contact investigation per contact (average number of contact investigation days prior to TB determination per suspect divided by the average number of contacts per suspect) times the total number of contacts tested (average number of contacts per suspect times the number of suspects having contacts tested for latent TB infection).

Standard unit costs (presented in Table S2) were estimated as follows. The fee for the MTD (CPT Code 83898) was obtained from the Physicians’ Fee and Coding Guide\(^1\) and converted to a cost using the 0.5 cost-to-charge ratio the for pulmonary diagnostic group.\(^2\) Cost per person per day of TB-related hospitalization was obtained from a multisite U.S. study of TB hospitalization.\(^3\) To that cost, we added in physician fees initial hospital care for level 2 (CPT Code 99222),\(^1\) converted to a cost (multiplied by 0.5).\(^2\) Medicare reimbursements were used to estimate costs for respiratory isolation (CPT Code 94662), intensive care (CPT Code 99292),
mechanical ventilation (CPT Code 94003). To estimate the costs per day of outpatient management of a patient suspected of TB, we used an average daily personnel cost at health departments from a study at three U.S. sites, averaged after adjusting each site’s costs to a U.S. basis using Medicare Geographic Adjustment Factors (1.08 for New York City and Massachusetts and 0.94 for Texas), and updating the cost to 2010 dollars using the change in the U.S. Bureau of Labor Statistics average hourly earnings ratio (19.07/14.02). Medication costs of $3/dose (from unpublished citations of public health HRSA 340B Program negotiated TB medication costs) were added. The cost per person per day of contact investigation were obtained from a multisite U.S. study of contact investigation: costs of $180/contact in 1999 dollars from the study, divided by 130 for 6 months of 5-day weeks, to obtain a daily estimate, updated to 2010 dollars using the change in the medical care CPI. Productivity loss per day was estimated at $165 in 2000 dollars, updated to 2010 dollars by the change in average hourly earnings ratio.
Figure S1. Cohort Description

- Smear (+): 848 (40%)
  - No MTD: 168 (20%)
  - MTD: 680 (80%)
    - MTD (-): 313 (46%)
    - MTD (+): 367 (54%)
- Smear (-): 1292 (60%)
  - No MTD: 1052 (82%)
  - MTD: 240 (18%)
    - MTD (-): 200 (83%)
    - MTD (+): 40 (17%)

TB
- 129 (77%)
  - No TB: 39 (23%)
  - TB: 90 (6%)
  - No TB: 95 (94%)
  - TB: 9 (2%)

No TB
- 819 (78%)
  - TB: 25 (13%)
  - No TB: 175 (88%)
  - TB: 36 (90%)
  - No TB: 4 (10%)

(70% hosp)
(82% hosp)
(52% hosp)
**Figure S2. Analysis Methods**

- **Person days for service** = Total number of persons receiving service × Average number of days while TB suspect for service

- **Outpatient days for hospitalized suspects** = Total number of persons hospitalized × Average outpatient days prior to TB determination

- **Outpatient days for non-hospitalized suspects** = Total number of non-hospitalized suspects receiving TB treatment × Average number of days to TB determination

- **Contact investigation days** = Average days of contact investigation per contact** × Total number of contacts tested**

  - **(*) Average days of contact investigation per contact**
  - **(** Total number of contacts tested** = Average number of contacts per suspect × Number of suspects having contacts tested for LTBI**
### Table S1. Average Days from TB Suspicion to TB Treatment

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Treatment Started</th>
<th>% Started</th>
<th>Days to Treatment Start</th>
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<tbody>
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<td><strong>SP/MTD(+)</strong></td>
<td>367</td>
<td>355</td>
<td>97%*</td>
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<tr>
<td><strong>SP/MTD(-)</strong></td>
<td>313</td>
<td>73</td>
<td>23%*</td>
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<tr>
<td><strong>SP/No MTD</strong></td>
<td>168</td>
<td>147</td>
<td>88%</td>
<td>7</td>
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<tr>
<td><strong>SN/MTD(-)</strong></td>
<td>200</td>
<td>107</td>
<td>54%*</td>
<td>7</td>
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<tr>
<td><strong>SN/MTD(+)</strong></td>
<td>40</td>
<td>40</td>
<td>100%*</td>
<td>9</td>
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<td><strong>SN/No MTD</strong></td>
<td>1052</td>
<td>439</td>
<td>42%</td>
<td>12</td>
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<tr>
<td><strong>Total</strong></td>
<td>2140</td>
<td>1161</td>
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<tr>
<td>CPT Code</td>
<td>Cost Per Person Per Day</td>
<td>Source</td>
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<tr>
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<td>83898</td>
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<td>Reference #3: CDC 1996 TB Hospitalization Study average cost; added in physician fees converted to a cost, updated to 2010 dollars</td>
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<td>$33</td>
<td>Reference #5: TB suspect study average personnel costs per suspect for the 3 sites, cost-of-living adjusted to a US basis, divided by 40 days (8 weeks), updated 2010 dollars, plus estimated TB medication costs</td>
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<td>$2</td>
<td>Reference #8: CDC 1999 Outcomes of Contact Investigation Study $180/contact in 1999 dollars, updated to 2010 dollars, divided by 130 for 6 months of 5-day weeks</td>
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<td>$224</td>
<td>Reference #10: Value of a lost day of work of $165 in 2000 dollars, updated to 2010 dollars by the change in the average hourly earnings ratio</td>
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References


