LATENT TUBERCULOSIS INFECTION TESTING AND TREATMENT IN THE PRIVATE SECTOR:

EVIDENCE FROM COMMERCIAL HEALTH INSURANCE CLAIMS

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DISSERTATION

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Targeted identification and treatment of people with latent tuberculosis infection (LTBI) are key components of the US tuberculosis (TB) elimination strategy. Little research on LTBI testing and treatment has been conducted outside of public healthcare settings, so there is a dearth of information about the provision of LTBI-related services in the private sector environment. This gap was highlighted by recent health insurance-related regulatory changes that are expected to increase LTBI testing and treatment by private providers. Our research aimed to provide insight on the LTBI-related services provided to commercially insured individuals in the private sector setting. We analyzed a national sample of commercial insurance medical and pharmacy claims data from the Optum National Research Database for 4 million people ages 0 to 64; these data represented insurance-paid healthcare services received between January 2011 and December 2013 at minimum. We estimated private sector LTBI testing rates and examined patient characteristics associated with private sector LTBI testing. We also developed a claims-based method to identify LTBI treatment in the private sector and subsequently used this method to estimate treatment completion rates and identify clinical and system factors associated with treatment completion. We found that LTBI testing was not uncommon in the private sector and it is generally targeted to patients at the highest risk of TB/LTBI. Further, our claims-based

method to identify and evaluate LTBI treatment successfully identified such treatment occurring in the private sector. Private sector LTBI treatment completion rates were in the range of those found in public health settings. Additionally, we identified factors unique to the private healthcare system that are associated with LTBI treatment completion. Our results suggest that the commercial sector may be a valuable adjunct to more traditional venues for TB prevention. Moreover, medical and pharmacy claims data and the claims-based methods we developed offer a means to gain important insights and open new avenues to monitor, evaluate, and coordinate TB prevention.

CHAPTER I

STATEMENT OF THE PROBLEM

Background and Significance

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (*Mtb*). Globally, TB is one of the world's deadliest diseases (World Health Organization, 2016). Although TB is treatable, it has long-term health consequences and substantial mortality risk even after treatment is successfully completed (Hoger, Lykens, Beavers, Katz, & Miller, 2014; Miller, McNabb, Hilsenrath, Pasipanodya, & Weis, 2009; Miller et al., 2015). Further, treatment is lengthy, patients can experience adverse events from TB medications, or they may be lost to follow-up and not be cured (Centers for Disease Control and Prevention [CDC], 2016d). Because of the significant health impact of this disease, US health policy has long aimed for domestic TB elimination (CDC, 1989, 1999, 2000, 2015a; Institute of Medicine [IOM], 2000). Coordinated efforts towards that goal have yielded the current historically low rates of acute TB incidence and mortality in the US; however, the goal of TB elimination has not yet been achieved and progress towards it has slowed (Salinas et al., 2016). An important aspect of domestic TB elimination is more effectively ascertaining and reducing TB risk among the people in the US with latent tuberculosis infection (LTBI) (CDC, 2015a; IOM, 2000).

People with LTBI are infected with *Mtb* but their condition has not progressed to active TB disease. While these individuals have no symptoms and are unable to spread the bacteria to others, without treatment for LTBI they are at risk of developing active TB. Up to 13 million people in the US have LTBI (Mancuso, Diffenderfer, Ghassemieh, Horne, & Kao, 2016;

Miramontes et al., 2015) and between 5 to 10 percent of people with untreated LTBI will develop active TB disease (Kahwati et al., 2016); consequently, an estimated 650,000 to 1.3 million people in the US will develop and potentially spread TB if they do not receive LTBI treatment. Eighty-six percent of incident TB cases in the US have been attributed to reactivation of LTBI (Yuen, Kammerer, Marks, Navin, & France, 2016). Thus, identifying and treating the substantial population of people with LTBI in the US is a key focus of the US TB elimination strategy (CDC, 2015a).

TB prevention activities in the US have historically been conducted by public health agencies (Balaban et al., 2015; Ehman, Flood, & Barry, 2014; IOM, 2000; Sterling et al., 2006) but private sector healthcare is expected to take an increasingly important role. Due to regulatory changes and limited public health budgets, some LTBI testing and treatment activity previously occurring in public health departments may be shifting to private sector healthcare providers (Balaban et al., 2015; Bovbjerg, Ormond, & Waidmann, 2011; Ehman et al., 2014). This shift will likely be expedited with the US Preventive Services Task Force's (USPSTF) recent assignment of a "Grade B" rating to the practice of screening for LTBI in populations that are at increased risk of TB (US Preventive Services Task Force [USPSTF] et al., 2016). This grade indicates to primary care providers that targeted LTBI testing and treatment are best practices, as this practice affords moderate health benefit with little risk (USPSTF, 2014; USPSTF et al., 2016). Additionally, as a consequence of this rating the Affordable Care Act requires that TB/LTBI testing in these populations be covered by commercial health plans at no out of pocket cost to patients (H.R. 3590, 2010). It is likely that the USPSTF recommendation would promote increased testing and treatment even without these financial incentives because the

recommendations raise awareness and provide information regarding evidence-based practices.

The USPSTF's focus on screening individuals at increased risk of TB aligns with US Centers for Disease Control and Prevention (CDC) recommendations. There are pockets of higher LTBI prevalence within the generally low-risk US population, so the CDC recommends a screening strategy that involves identifying high-risk groups and targeting individuals in those groups for enhanced prevention efforts. Conversely, the CDC recommends against widespread LTBI testing of individuals in the general population who are at low risk of LTBI (CDC, 2000) Screening of low-risk people may be relatively common in the US, as LTBI testing may be done for administrative purposes (e.g., school physicals, pre-employment screening) (Brassard, Steensma, Cadieux, & Lands, 2006; CDC, 2000; Flaherman, Porco, Marseille, & Royce, 2007; Miller, Reading, Hilsenrath, & Weis, 2006; Reves & Nolan, 2012).

Despite the private sector's increasing role in TB prevention, little information is available about whether LTBI testing in the private sector is appropriately focused on high risk individuals. This knowledge gap is problematic, as testing within a low-risk population of individuals without known exposure to active TB represents an inefficient use of health care resources, which increases health care costs and diverts resources from more valuable activities (CDC, 2000). Additionally, harm is likely when low-risk people are tested (Blumberg & Ernst, 2016). False-positive results are likely (Dorman et al., 2014) and not all individuals with true positive results are good candidates for LTBI treatment. Traditional isoniazid treatments are of long duration and they carry a not insignificant risk of hepatotoxicity and other side effects (Fountain, Tolley, Chrisman, & Self, 2005; LoBue & Moser, 2003).

Further, the CDC recommends that LTBI testing only be done when a plan is in place for the patient to complete LTBI treatment if the test result is positive (CDC, 2000). However, it is unknown whether or how often LTBI treatment is occurring in the private sector because research examining this issue has focused only on select samples of providers or limited geographic areas (Sterling et al., 2006). Additionally, it is unknown whether patients treated in the private sector typically complete a full course of LTBI treatment.

Public health officials and policymakers must gain a greater understanding of the LTBI testing and treatment occurring across the US in the private sector in order to better direct TB prevention efforts. Unfortunately, they have little information on the LTBI testing and treatment activity occurring outside of the public health system by health care providers in communities across the country. Although providers are required to report cases of active TB to health departments or health officers (Centers for Law and the Public's Health, 2009) such requirements for LTBI are inconsistent. Thus, there is a dearth of data available to public health officials and policymakers on how LTBI is handled in the day-to-day practice of private sector medicine. Our research aimed to fill many of these knowledge gaps.

Research Aims

Our broad goal is to provide public health leaders with critical information about the spectrum and appropriateness of LTBI-related care occurring in the private sector healthcare setting. This information will enable public health leaders to effectively shape the delivery of this care and facilitates the development of evidence-based LTBI private sector treatment strategies. Our specific aims are as follows:

1. The first aim of this research was to determine whether TB/LTBI risk factors are associated an increased likelihood of LTBI testing (i.e., Interferon-Gamma Release Assay [IGRA] or Tuberculin Skin Testing [TST]) in the private sector.
2. Our second aim was to a) develop a methodology to identify long term daily-dose isoniazid treatment using medical and pharmacy claims data, and b) estimate LTBI treatment initiation and completion rates in the private sector.
3. Our third aim was to determine whether TB/LTBI risk factors are associated an increased likelihood of completion of daily dose isoniazid LTBI treatment in the private sector setting.

Methodological Overview

The aims above were met by analyzing medical and pharmacy claims data from commercial insurers. Although claims data have been used to study the diagnostic prevalence, treatment costs, treatment practices, and prevention practices for a myriad of health conditions treated in the private sector (Carroll, Fairman, & Lage, 2014; Cooper et al., 1999; Dunne, Stokley, Chen, & Zhou, 2015; Harris, Ward, & Schwab, 2015; Hebert et al., 1999; Helmers, Thurman, Durgin, Pai, & Faught, 2015; Kirson et al., 2015; Sullivan et al., 2015; Topol et al., 1993), we are aware of only one other study that has examined private sector LTBI testing using claims data (Owusu-Edusei, Stockbridge, Winston, Kolasa, & Miramontes, 2017). That study, which is currently in press, explored changes in LTBI testing rates over a 15 year period, but it did not examine the association between TB/LTBI risk factors and LTBI testing

(Owusu-Edusei, Stockbridge, et al., 2017). We identified no studies that used claims data to examine private sector LTBI treatment.

The majority of people in the US are covered by private health insurance (Barnett, 2016), so commercial claims data provide a valuable window into the private sector LTBI testing and treatment occurring in the majority of the general US population. We examined LTBI testing and LTBI treatment practices in the private sector by analyzing data from a sizable national sample of medical and pharmacy claims data. Specifically, we used a randomly selected, de-identified sample of 4 million people from the Optum Impact National Research Database. This database includes data for approximately 19% of the commercially insured US population (Optum, 2015). All persons in the sample were ages 0 to 64 and had continuous commercial insurance coverage between January 1, 2011 and December 31, 2013, at minimum. This large sample of claims data enabled us to gain new knowledge about the LTBI testing and treatment occurring across the nation in the private sector.

While we met all of our aims by conducting analyses of a single data source, the specific research methods for each aim varied. These specifics are discussed in detail in the following chapters. Each chapter focuses on a single aim and includes the methods, results, and discussion related to that aim. Chapter 2, “Tuberculosis Prevention in the Commercially Insured: Characteristics Associated with Private Sector Interferon-Gamma Release Assay or Tuberculin Skin Testing,” describes the research conducted to meet our first aim. We discuss our second aim in our third chapter, “Tuberculosis Prevention in the Private Sector: Using Claims-Based Methods to Identify and Evaluate Latent Tuberculosis Infection Treatment among the Commercially Insured.” Please note that a manuscript describing this method has been

provisionally accepted for publication in the Journal of Public Health Management and Practice. Please cite that journal article rather than this dissertation when referencing this method or the results (Stockbridge, Miller, Carlson, & Ho, 2017). The research conducted to meet our third aim is described in Chapter 4, “Private Sector Tuberculosis Prevention: Predictors of Latent Tuberculosis Infection Treatment Completion in Commercially Insured Individuals.” Our final chapter, Chapter 5, discusses the conclusions that can be drawn from this body of work and describes areas where future research is warranted.

CHAPTER II

CHARACTERISTICS ASSOCIATED WITH PRIVATE SECTOR INTERFERON-GAMMA RELEASE ASSAY OR TUBERCULIN SKIN TESTING

Introduction

Tuberculosis (TB), an infectious disease caused by *Mycobacterium tuberculosis* (*Mtb*), is one of the world's deadliest diseases (World Health Organization [WHO], 2016). Although TB is less prevalent in the US than in many other countries, nearly 10,000 new TB cases are diagnosed in the US annually (Dye, Glaziou, Floyd, & Raviglione, 2013; Salinas et al., 2016). TB is a debilitating and potentially deadly illness with long-term health consequences and substantially increased mortality risk even after treatment is completed (Miller et al., 2009; Miller et al., 2015). Further, TB in the US exacts great financial and societal costs (Laurence, Griffiths, & Vassall, 2015; Miller et al., 2010; Miller et al., 2009). Consequently, domestic TB elimination, defined as a rate of less than one incident TB case per million population, has long been a goal of US public health policy (Centers for Disease Control and Prevention [CDC], 1989, 2015a; Institute of Medicine [IOM], 2000).

It is generally accepted that this goal is achievable (CDC, 1989; Dye et al., 2013; Lewinsohn, 2016; Reves & Nolan, 2012), but the US falls well short of elimination, and advancement towards the goal has stalled (Salinas et al., 2016). This is in part due to persistent heightened risk of active TB among the estimated 13 million people in the US with latent TB infection (LTBI) (IOM, 2000; Mancuso et al., 2016; Miramontes et al., 2015). People with LTBI are infected with *Mtb* but do not have active TB disease. While they are asymptomatic and not

infectious, on average 5 to 10% will progress to active TB in their lifetime if they are not treated (Kahwati et al., 2016). Historically LTBI has been largely unaddressed, but well-targeted identification and treatment of people with LTBI have become important components of the domestic TB elimination strategy (CDC, 2015a).

Public health authorities have led a coordinated effort against TB in the US, including providing much of the direct patient care associated with diagnosis and treatment of patients with active TB and LTBI (IOM, 2000; Sterling et al., 2006). Private sector healthcare has played a less visible part of this work, but recent recommendations from the US Preventive Services Task Force (USPSTF) create new incentives that will likely result in a growing presence of commercial healthcare in the domestic fight against TB (Blumberg & Ernst, 2016; H.R. 3590, 2010; US Preventive Services Task Force [USPSTF] et al., 2016). Given the chronic constraints of public budgets, the potential to leverage commercial healthcare's considerable resources toward an important public health goal is very attractive. Unfortunately, little information exists to guide policy makers as they consider the benefits and limitations of this new opportunity.

A key knowledge gap exists around risk-targeted LTBI testing and treatment in the private sector. LTBI is distributed heterogeneously within the US population. While roughly 5.0% of the US population has been estimated to have LTBI, prevalence is higher in some subpopulations (e.g., foreign-born persons) (Mancuso et al., 2016; Miramontes et al., 2015). Similarly, the risk of progression to active TB among those with LTBI varies, with certain characteristics increasing the risk of progression (e.g., immunosuppression, diabetes) (Kahwati et al., 2016; Mazurek et al., 2010; USPSTF et al., 2016). Conversely, many people are at little risk of *Mtb* infection or disease progression. When low-risk people are tested, the harms may

outweigh the benefits (Blumberg & Ernst, 2016). There is a high probability of false-positive results (Dorman et al., 2014) and the most commonly used treatment regimen with isoniazid is long and carries a not insignificant risk of hepatotoxicity and other side effects (Fountain et al., 2005; LoBue & Moser, 2003). Thus, LTBI testing should be targeted toward individuals and populations with known risks (CDC, 2000). It is unknown whether the testing currently occurring in the private sector is well-targeted, but understanding the appropriateness of LTBI testing occurring in this increasingly important setting is necessary in order for public health leaders to shape the delivery of these services. We analyzed a large commercial claims dataset to determine whether TB/LTBI risk factors are associated with an increased likelihood of TST or IGRA testing.

METHODS

We used the Optum Impact National Research Database to examine pharmacy and medical insurance claims for a randomly selected, de-identified sample of 4 million people ages 0 to 64 who had continuous commercial insurance coverage between January 1, 2011 and December 31, 2013 (Optum, 2015). Approximately 19% of the commercially insured US population is represented in this database. The data included information about each individual's insurance-covered prescriptions filled and healthcare services received during that three-year period, at minimum. The sample roughly approximated the 2010 US population geographic distribution by Census division (U. S. Department of Commerce, 2012). Individuals with detailed geographic information missing were excluded from analysis.

Measures

Outcome variable. The outcome of interest was the receipt of at least one tuberculin skin test (TST) or interferon-gamma release assay (IGRA). We used current procedural terminology (CPT) codes to identify testing by TST or either of the IGRA methods (i.e., T-SPOT®.TB or QuantiFERON®–TB). In addition, we presumed that ICD-9-CM coding indicating "special screening examination for pulmonary tuberculosis, including diagnostic skin testing" represented a TST when not accompanied by a testing CPT code. They were counted as testing occurrences if they existed in the absence of a CPT code for a TST, IGRA, or another procedure potentially related to *Mtb* testing within ±3 days from the date of service. Presumptive TST screenings were not combined with CPT-coded TST screenings when testing methods were analyzed separately, but when testing methods were examined in total they were included in the total. Testing with TSTs or IGRAs is henceforth collectively referred to as "TST/IGRA testing."

Explanatory variables. We constructed explanatory variables from information in the medical and pharmacy claims data based on services occurring and prescriptions filled between 2011 and 2013. Socio-demographic variables included sex, age, census region, and urban-rural classification. Additional variables included insurance type (HMO, indemnity, POS, or PPO) and residence in a county designated as a geographic primary care physician health professional shortage area (PCP-HPSA). We incorporated indicators of asthma and COPD as well as variables associated with risk of LTBI or progression to active TB, including the state TB rate. The percentage of households living under the federal poverty level (FPL) in an individual's county was included as a proxy for household income (United States Census Bureau [USCB], 2015a). Country of birth was unknown, but the prevalence of foreign-born individuals in the county

served as a rough measure of nativity (USCB, 2015a). Clinical risk factors were incorporated, including HIV, use of immunosuppressive medication, contact with or exposure to TB, a history of TB, diabetes, evidence of tobacco use, leukemia or lymphoma, lung cancer, head or neck cancer, lung disease due to external agents (e.g., silicosis), gastrectomy or gastric bypass, end stage renal disease/dialysis, alcohol use disorder, and drug use disorder (CDC, 2000). We used a simple count of each individual's clinical risk factors to assign cumulative risk (i.e., 6 levels of risk representing 0 risk factors through ≥5 risk factors).

Statistical Analyses

We calculated the proportion of individuals receiving at least one test, examining each type of *Mtb* test separately (i.e., TST, presumptive TST, IGRA QFT, IGRA T-spot, IGRA in total) and with all methods combined. We estimated these proportions for two time periods: 1) January 2011 through December 2013 (the longest period for which complete data were available) and 2) January through December 2013 (a subperiod representing the most recent calendar year). The unit of measure for these proportions was individual people; those receiving >1 test in a given time period were only counted one time in the numerator. Additionally, testing rates were calculated based on a count of the total number of tests between 2011 and 2013 divided by person-years. All testing occurrences were represented in these testing rates; when an individual had multiple tests all of these tests were counted.

We examined the bivariate relationships between explanatory variables and TST/IGRA testing (all methods combined) between 2011 and 2013 using chi square tests for categorical variables and Spearman correlations for continuous variables. We then explored adjusted

associations between these variables and TST/IGRA testing with two logistic regression models. Model 1 includes the specific clinical risk factors as explanatory variables while Model 2 includes a count of clinical risk factors. To provide insight into effect sizes and practical significance of the observed statistically significant differences, the two models were used to generate the average adjusted probability of a TST/IGRA test for each level of the categorical explanatory variables and for the minimum, 25th percentile, median, 75th percentile, and maximum values of the continuous explanatory variables. These probabilities were expressed as percentages, and they represent the average predicted probability of a TST/IGRA test being performed conditional on all observations having the given value. All statistical testing used Stata 14.2 [StataCorp, College Station, TX], was two-sided, and significance was tested at $p < 0.001$.

RESULTS

Of 3,997,986 people with sufficiently detailed geographic data for inclusion in analyses, 172,253 (4.31%) received ≥1 TST/IGRA test between 2011 and 2013 and 67,792 (1.69%) received ≥1 TST/IGRA test in 2013 (Table 1, following page). The TST/IGRA testing rate was 1902.87/100,000 person-years. TSTs were more prevalent than IGRAs in both periods studied. Between 2011 and 2013, 3.83% of individuals received ≥1 TST but 0.39% received ≥1 IGRA. In 2013, 1.42% received ≥1 TST while 0.22% received ≥1 IGRA. Presumptive TST screening (inferred from ICD-9-CM codes but not coded with a CPT code) was identified at a rate of

Table 1: Rates of screening for *Mycobacterium tuberculosis* with tuberculin skin tests (TSTs) or interferon-gamma release assays (IGRAs) in commercially insured individuals ages 0 to 64, based on data from the Optum Impact National Research Database (N=3,997,986).

Method	# Tests, 2011-2013	Tests per 100,000 Person-Years, 2011-2013	% of Insured Persons with ≥ 1 Test, 2011-2013 (99.9% Confidence Interval)	% of Insured Persons with ≥ 1 Test, 2013 (99.9% Confidence Interval)
Tuberculin skin test (TST)	197,980	1650.66	3.83% (3.80-3.86%)	1.42% (1.40-1.44%)
Interferon-gamma release assay (IGRA)*	18,666	155.63	0.39% (0.38-0.40%)	0.22% (0.21-0.22%)
QuantiFERON	17,644	147.11	0.37% (0.36-0.38%)	0.20% (0.20-.021%)
T-SPOT	1,022	8.52	0.02% (0.02-0.03%)	0.01% (0.01-0.01%)
TST screening likely occurred but procedure code not specified**	11,584	96.58	0.21% (0.21-0.22%)	0.09% (0.08-0.09%)
Total (All combined)*	228,230	1902.87	4.31% (4.27-4.34%)	1.69% (1.67-1.72%)

* Percentage totals may be different from the sum of the individual screening percentages for two reasons: 1) Rounding, and 2) Some individuals were screened >1 time in a given time period.

** Based on the presence of the ICD-9-CM diagnosis code "V74.1: Special screening examination for pulmonary tuberculosis, including diagnostic skin testing" on a given date, excluding those with a current procedural terminology (CPT) procedure code for a TST, IGRA, or other procedure potentially related to *Mtb* screening occurring within ±3 days from that date.

96.58/100,000 person-years, representing 11,584 (5.08%; 99.9% Confidence Interval: 4.93, 5.22) of the 228,230 tests conducted.

Most observable clinical risk factors were independently and cumulatively associated with an increased likelihood of TST/IGRA testing (Tables 2, 3 and 4, pages 15, 19 and 24 respectively). These included HIV, use of immunosuppressive medications, contact with or

Table 2: Frequency distributions of variables describing commercially insured individuals ages 0 to 64 and the proportion of people with these characteristics who were screened for *Mycobacterium tuberculosis* with a tuberculin skin test (TST) or an interferon-gamma release assay (IGRA) between 2011 and 2013, based on data from the Optum Impact National Research Database (N=3,997,986).

		N	% or Mean of Total	No Screening (% or Mean)	Had Screening (% or Mean)	p-value
Sex	Female	2,021,984	50.58%	94.90%	5.10%	<0.001
	Male	1,976,002	49.42%	96.51%	3.49%	
Age	0-4	192,115	4.81%	91.40%	8.60%	<0.001
	5-9	284,868	7.13%	95.11%	4.89%	
	10-14	313,776	7.85%	95.03%	4.97%	
	15-19	325,691	8.15%	88.43%	11.57%	
	20-24	246,268	6.16%	91.87%	8.13%	
	25-29	207,736	5.20%	96.87%	3.13%	
	30-34	286,912	7.18%	96.76%	3.24%	
	35-39	320,717	8.02%	96.94%	3.06%	
	40-44	384,974	9.63%	97.21%	2.79%	
	45-49	416,863	10.43%	97.56%	2.44%	
	50-54	432,965	10.83%	97.76%	2.24%	
	55-59	390,435	9.77%	97.85%	2.15%	
	60-64	194,666	4.87%	98.04%	1.96%	
Census Division	New England	412,136	10.31%	96.61%	3.39%	<0.001
	Mid-Atlantic	660,516	16.52%	91.78%	8.22%	
	East North Central	660,596	16.52%	96.63%	3.37%	
	West North Central	373,219	9.34%	97.23%	2.77%	
	South Atlantic	568,544	14.22%	96.25%	3.75%	
	East South Central	137,765	3.45%	97.45%	2.55%	
	West South Central	694,018	17.36%	97.45%	2.55%	
	Mountain	198,636	4.97%	97.23%	2.77%	
	Pacific	292,556	7.32%	92.10%	7.90%	

		N	% or Mean of Total	No Screening (% or Mean)	Had Screening (% or Mean)	p-value
Rural-Urban Category	Large central metro	1,114,746	27.88%	94.49%	5.51%	<0.001
	Large fringe metro	1,518,188	37.97%	95.34%	4.66%	
	Medium metro	763,457	19.10%	96.59%	3.41%	
	Small metro	269,069	6.73%	97.54%	2.46%	
	Micropolitan	201,185	5.03%	97.70%	2.30%	
	Noncore	131,341	3.29%	97.92%	2.08%	
PCP Health Professional Shortage Area	Not an HPSA	3,854,171	96.40%	95.61%	4.39%	<0.001
	HPSA	143,815	3.60%	97.86%	2.14%	
Insurance Type	HMO	635,718	15.90%	95.13%	4.87%	<0.001
	Indemnity	1,585	0.04%	97.73%	2.27%	
	POS	2,712,259	67.84%	95.93%	4.07%	
	PPO	648,424	16.22%	95.26%	4.74%	
Percent of Households in County with Income under FPL		3,997,986	14.44	14.46	13.95	<0.001
Percent of Foreign-born Individuals in County		3,997,986	12.77	12.56	17.57	<0.001
State TB Rate		3,997,986	3.11	3.09	3.57	<0.001
Asthma	No diagnosis	3,768,168	94.25%	95.81%	4.19%	<0.001
	Had diagnosis	229,818	5.75%	93.76%	6.24%	
COPD	No diagnosis	3,956,823	98.97%	95.70%	4.30%	0.001
	Had diagnosis	41,163	1.03%	95.38%	4.62%	
Count of Clinical Risk Factors	0 clinical risk factors	3,523,528	88.09%	95.99%	4.01%	<0.001
	1 clinical risk factor	407,710	10.19%	94.02%	5.98%	
	2 clinical risk factors	57,922	1.45%	91.47%	8.53%	
	3 clinical risk factors	9,729	0.24%	88.93%	11.07%	
	4 clinical risk factors	998	0.02%	84.95%	15.05%	
	>=5 clinical risk factors	113	0.00%	76.22%	23.78%	

		N	% or Mean of Total	No Screening (% or Mean)	Had Screening (% or Mean)	p-value
HIV	No diagnosis	3,989,327	99.78%	95.73%	4.27%	<0.001
	Had diagnosis	8,659	0.22%	76.75%	23.25%	
Immuno-supressive Medications	No medication/procedure	3,955,046	98.93%	95.95%	4.05%	<0.001
	Had medication/procedure	42,940	1.07%	71.77%	28.23%	
Diagnosis of Contact with TB	No diagnosis	3,990,955	99.82%	95.83%	4.17%	<0.001
	Had diagnosis	7,031	0.18%	16.29%	83.71%	
History/Late Effects of TB	No diagnosis	3,997,034	99.98%	95.70%	4.30%	<0.001
	Had diagnosis	952	0.02%	79.83%	20.17%	
Diabetes	No diagnosis/medication	3,764,124	94.15%	95.62%	4.38%	<0.001
	Had diagnosis/medication	233,862	5.85%	96.89%	3.11%	
Tobacco	No diagnosis/medication	3,825,292	95.68%	95.65%	4.35%	<0.001
	Had diagnosis/medication	172,694	4.32%	96.62%	3.38%	
Leukemia or Lymphoma	No diagnosis	3,986,952	99.72%	95.70%	4.30%	<0.001
	Had diagnosis	11,034	0.28%	94.97%	5.03%	
Lung Cancer	No diagnosis	3,994,927	99.92%	95.69%	4.31%	0.148
	Had diagnosis	3,059	0.08%	95.16%	4.84%	
Head or Neck Cancer	No diagnosis	3,994,510	99.91%	95.69%	4.31%	<0.001
	Had diagnosis	3,476	0.09%	97.01%	2.99%	
Lung Disease Due to External Agents	No diagnosis	3,997,416	99.99%	95.69%	4.31%	<0.001
	Had diagnosis	570	0.01%	91.40%	8.60%	
Gastrectomy or Gastric Bypass	No diagnosis/procedure	3,978,496	99.51%	95.69%	4.31%	0.351
	Had diagnosis/procedure	19,490	0.49%	95.83%	4.17%	

		N	% or Mean of Total	No Screening (% or Mean)	Had Screening (% or Mean)	p-value
ESRD/ Dialysis	No diagnosis	3,991,465	99.84%	95.71%	4.29%	<0.001
	Had diagnosis	6,521	0.16%	84.45%	15.55%	
Alcohol Use Disorder	No diagnosis	3,964,501	99.16%	95.70%	4.30%	<0.001
	Had diagnosis	33,485	0.84%	94.68%	5.32%	
Drug Use Disorder	No diagnosis	3,965,294	99.18%	95.71%	4.29%	<0.001
	Had diagnosis	32,692	0.82%	93.50%	6.50%	

Table 3: Results of first logistic regression model examining associations between insurance enrollee characteristics and screening for *Mycobacterium tuberculosis* with either a tuberculin skin test (TST) or an interferon-gamma release assay (IGRA) between 2011 and 2013, based on data from the Optum Impact National Research Database (N=3,997,986). Clinical risk factors are examined individually in this model.

		Model #1: Includes Individual Clinical Risk Factors						
		Odds Ratio	p-value	99.9% Confidence Interval		Average Adjusted Prob-ability*	99.9% Confidence Interval	
Sex	Female	1.000				5.12%	5.07%	5.17%
	Male	0.645	<0.001	0.634	0.656	3.49%	3.45%	3.53%
Age	0-4	1.000				9.01%	8.80%	9.22%
	5-9	0.549	<0.001	0.527	0.572	5.42%	5.28%	5.55%
	10-14	0.569	<0.001	0.547	0.592	5.58%	5.45%	5.72%
	15-19	1.472	<0.001	1.423	1.522	12.35%	12.16%	12.54%
	20-24	0.926	<0.001	0.892	0.962	8.45%	8.27%	8.64%
	25-29	0.297	<0.001	0.282	0.312	3.16%	3.03%	3.28%
	30-34	0.299	<0.001	0.286	0.313	3.18%	3.08%	3.28%
	35-39	0.276	<0.001	0.264	0.289	2.96%	2.87%	3.05%
	40-44	0.247	<0.001	0.236	0.258	2.68%	2.60%	2.76%
	45-49	0.208	<0.001	0.199	0.218	2.30%	2.23%	2.37%
	50-54	0.188	<0.001	0.180	0.197	2.10%	2.04%	2.17%
	55-59	0.179	<0.001	0.170	0.187	2.01%	1.94%	2.08%
	60-64	0.158	<0.001	0.148	0.169	1.80%	1.71%	1.89%

		Model #1: Includes Individual Clinical Risk Factors						
		Odds Ratio	p-value	99.9% Confidence Interval		Average Adjusted Prob-ability*	99.9% Confidence Interval	
Census Division	New England	1.000				3.48%	3.38%	3.58%
	Mid-Atlantic	1.958	<0.001	1.889	2.030	6.25%	6.15%	6.35%
	East North Central	1.509	<0.001	1.444	1.577	4.99%	4.86%	5.13%
	West North Central	1.188	<0.001	1.133	1.246	4.05%	3.91%	4.19%
	South Atlantic	1.058	<0.001	1.015	1.103	3.66%	3.58%	3.74%
	East South Central	1.131	<0.001	1.055	1.212	3.88%	3.67%	4.08%
	West South Central	0.703	<0.001	0.671	0.736	2.54%	2.47%	2.60%
	Mountain	1.061	0.001	1.000	1.126	3.67%	3.51%	3.83%
	Pacific	1.473	<0.001	1.401	1.549	4.89%	4.75%	5.03%
Rural-Urban Category	Large central metro	1.000				4.30%	4.23%	4.37%
	Large fringe metro	1.049	<0.001	1.020	1.079	4.49%	4.42%	4.55%
	Medium metro	1.000	0.964	0.968	1.033	4.30%	4.21%	4.39%
	Small metro	0.857	<0.001	0.816	0.900	3.76%	3.61%	3.90%
	Micropolitan	0.799	<0.001	0.755	0.846	3.53%	3.37%	3.70%
	Noncore	0.805	<0.001	0.749	0.866	3.56%	3.34%	3.78%
PCP Health Professional Shortage Area	Not an HPSA	1.000				4.31%	4.28%	4.34%
	HPSA	0.925	<0.001	0.866	0.989	4.03%	3.80%	4.26%

		Model #1: Includes Individual Clinical Risk Factors						
		Odds Ratio	p-value	99.9% Confidence Interval		Average Adjusted Prob-ability*	99.9% Confidence Interval	
Insurance Type	HMO	1.000				4.18%	4.10%	4.26%
	Indemnity	0.756	0.110	0.425	1.344	3.27%	1.61%	4.93%
	POS	1.031	<0.001	1.004	1.060	4.29%	4.25%	4.34%
	PPO	1.088	<0.001	1.056	1.121	4.50%	4.41%	4.58%
Percent of Households in County with Income under FPL		0.998	0.004	0.996	1.000	**	**	**
Percent of Foreign-born Individuals in County		1.021	<0.001	1.020	1.022	**	**	**
State TB Rate		1.179	<0.001	1.165	1.193	**	**	**
Asthma	No diagnosis	1.000				4.23%	4.20%	4.27%
	Had diagnosis	1.305	<0.001	1.264	1.347	5.33%	5.19%	5.47%
COPD	No diagnosis	1.000				4.29%	4.26%	4.33%
	Had diagnosis	1.482	<0.001	1.357	1.619	6.02%	5.57%	6.46%
Count of Clinical Risk Factors	0 clinical risk factors	N/A				N/A	N/A	N/A
	1 clinical risk factor	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	2 clinical risk factors	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	3 clinical risk factors	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	4 clinical risk factors	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	>=5 clinical risk factors	N/A	N/A	N/A	N/A	N/A	N/A	N/A

		Model #1: Includes Individual Clinical Risk Factors						
		Odds Ratio	p-value	99.9% Confidence Interval		Average Adjusted Prob-ability*	99.9% Confidence Interval	
HIV	No diagnosis	1.000				4.26%	4.23%	4.30%
	Had diagnosis	11.017	<0.001	10.049	12.078	26.69%	25.19%	28.19%
Immuno-supressive Medications	No medication/ procedure	1.000				4.04%	4.01%	4.07%
	Had medication/ procedure	17.512	<0.001	16.794	18.262	34.42%	33.66%	35.18%
Diagnosis of Contact with TB	No diagnosis	1.000				4.18%	4.15%	4.21%
	Had diagnosis	108.876	<0.001	97.053	122.140	71.62%	69.57%	73.66%
History/Late Effects of TB	No diagnosis	1.000				4.30%	4.27%	4.34%
	Had diagnosis	4.468	<0.001	3.223	6.193	14.53%	11.02%	18.03%
Diabetes	No diagnosis/ medication	1.000				4.29%	4.25%	4.32%
	Had diagnosis/ medication	1.149	<0.001	1.099	1.202	4.84%	4.65%	5.02%
Tobacco	No diagnosis/ medication	1.000				4.29%	4.26%	4.33%
	Had diagnosis/ medication	1.120	<0.001	1.065	1.177	4.74%	4.53%	4.94%
Leukemia or Lymphoma	No diagnosis	1.000				4.31%	4.28%	4.35%
	Had diagnosis	0.545	<0.001	0.463	0.642	2.53%	2.16%	2.90%
Lung Cancer	No diagnosis	1.000				4.31%	4.27%	4.34%
	Had diagnosis	1.351	0.001	0.991	1.840	5.58%	4.11%	7.04%
Head or Neck Cancer	No diagnosis	1.000				4.31%	4.27%	4.34%
	Had diagnosis	1.010	0.923	0.709	1.440	4.35%	3.01%	5.68%
Lung Disease Due to External Agents	No diagnosis	1.000				4.31%	4.27%	4.34%
	Had diagnosis	1 800	<0.001	1.035	3.131	7.10%	3.84%	10.36%

		Model #1: Includes Individual Clinical Risk Factors						
		Odds Ratio	p-value	99.9% Confidence Interval		Average Adjusted Prob-ability*	99.9% Confidence Interval	
Gastrectomy or Gastric Bypass	No diagnosis/ procedure	1.000				4.30%	4.27%	4.33%
	Had diagnosis/ procedure	1.312	<0.001	1.156	1.488	5.43%	4.85%	6.02%
ESRD/ Dialysis	No diagnosis	1.000				4.30%	4.27%	4.33%
	Had diagnosis	1.396	<0.001	1.219	1.599	5.73%	5.07%	6.39%
Alcohol Use Disorder	No diagnosis	1.000				4.30%	4.27%	4.33%
	Had diagnosis	1.285	<0.001	1.171	1.410	5.33%	4.91%	5.75%
Drug Use Disorder	No diagnosis	1.000				4.30%	4.27%	4.34%
	Had diagnosis	1.062	0.020	0.975	1.157	4.54%	4.20%	4.87%

* Calculated as the average predicted probability of a test conditional on all observations being in the category represented by the row. The difference between the predicted probabilities for two categories of a given categorical variable represents the average marginal effect.

** Average predicted probability of *Mycobacterium tuberculosis* screening at the minimum, maximum, and quartile values of these variables can be found in Table 5.

Table 4: Results of second logistic regression model examining associations between insurance enrollee characteristics and screening for *Mycobacterium tuberculosis* with either a tuberculin skin test (TST) or an interferon-gamma release assay (IGRA) between 2011 and 2013, based on data from the Optum Impact National Research Database (N=3,997,986). A count of clinical risk factors is included in this model.

		Model #2: Includes a Count of Clinical Risk Factors						
		Odds Ratio	p-value	99.9% Confidence Interval		Average Adjusted Prob-ability*	99.9% Confidence Interval	
Sex	Female	1.000				5.20%	5.15%	5.25%
	Male	0.632	<0.001	0.622	0.643	3.43%	3.38%	3.47%
Age	0-4	1.00				9.73%	9.50%	9.96%
	5-9	0.551	<0.001	0.529	0.573	5.77%	5.61%	5.92%
	10-14	0.569	<0.001	0.548	0.592	5.94%	5.79%	6.09%
	15-19	1.408	<0.001	1.362	1.456	12.93%	12.74%	13.13%
	20-24	0.871	<0.001	0.839	0.904	8.65%	8.46%	8.84%
	25-29	0.292	<0.001	0.278	0.307	3.21%	3.08%	3.33%
	30-34	0.293	<0.001	0.280	0.306	3.21%	3.11%	3.32%
	35-39	0.271	<0.001	0.260	0.284	2.99%	2.89%	3.09%
	40-44	0.242	<0.001	0.232	0.253	2.68%	2.60%	2.77%
	45-49	0.204	<0.001	0.195	0.213	2.28%	2.20%	2.35%
	50-54	0.179	<0.001	0.171	0.187	2.01%	1.94%	2.08%
	55-59	0.167	<0.001	0.159	0.175	1.88%	1.81%	1.94%
	60-64	0.146	<0.001	0.137	0.155	1.65%	1.56%	1.74%

		Model #2: Includes a Count of Clinical Risk Factors						
		Odds Ratio	p-value	99.9% Confidence Interval		Average Adjusted Prob-ability*	99.9% Confidence Interval	
Census Division	New England	1.000				3.41%	3.31%	3.51%
	Mid-Atlantic	1.982	<0.001	1.913	2.053	6.35%	6.25%	6.45%
	East North Central	1.499	<0.001	1.436	1.566	4.95%	4.81%	5.09%
	West North Central	1.186	<0.001	1.132	1.243	3.99%	3.86%	4.13%
	South Atlantic	1.075	<0.001	1.032	1.120	3.65%	3.57%	3.73%
	East South Central	1.138	<0.001	1.063	1.218	3.84%	3.63%	4.05%
	West South Central	0.718	<0.001	0.687	0.752	2.50%	2.43%	2.56%
	Mountain	1.082	<0.001	1.021	1.146	3.67%	3.50%	3.83%
	Pacific	1.478	<0.001	1.407	1.553	4.88%	4.74%	5.03%
Rural-Urban Category	Large central metro	1.000				4.33%	4.26%	4.40%
	Large fringe metro	1.043	<0.001	1.015	1.072	4.50%	4.44%	4.57%
	Medium metro	0.978	0.022	0.947	1.010	4.25%	4.16%	4.33%
	Small metro	0.843	<0.001	0.803	0.884	3.70%	3.56%	3.85%
	Micropolitan	0.779	<0.001	0.737	0.824	3.45%	3.28%	3.61%
	Noncore	0.785	<0.001	0.731	0.844	3.47%	3.25%	3.69%
PCP Health Professional Shortage Area	Not an HPSA	1.000				4.31%	4.28%	4.35%
	HPSA	0.922	<0.001	0.864	0.984	4.00%	3.77%	4.24%
Insurance Type	HMO	1.000				4.19%	4.11%	4.27%
	Indemnity	0.731	0.068	0.416	1.285	3.14%	1.50%	4.79%
	POS	1.023	0.005	0.996	1.050	4.28%	4.23%	4.32%
	PPO	1.097	<0.001	1.066	1.130	4.56%	4.47%	4.64%

		Model #2: Includes a Count of Clinical Risk Factors						
		Odds Ratio	p-value	99.9% Confidence Interval		Average Adjusted Prob-ability*	99.9% Confidence Interval	
Percent of Households in County with Income under FPL		0.998	0.001	0.996	1.000	**	**	**
Percent of Foreign-born Individuals in County		1.022	<0.001	1.021	1.023	**	**	**
State TB Rate		1.176	<0.001	1.162	1.190	**	**	**
Asthma	No diagnosis	1.000				4.24%	4.21%	4.27%
	Had diagnosis	1.269	<0.001	1.230	1.309	5.25%	5.11%	5.39%
COPD	No diagnosis	1.000				4.30%	4.27%	4.33%
	Had diagnosis	1.155	<0.001	1.063	1.254	4.90%	4.54%	5.25%
Count of Clinical Risk Factors	0 clinical risk factors	1.000				3.80%	3.77%	3.84%
	1 clinical risk factor	2.818	<0.001	2.746	2.892	9.41%	9.22%	9.59%
	2 clinical risk factors	4.226	<0.001	4.014	4.449	13.01%	12.50%	13.51%
	3 clinical risk factors	4.912	<0.001	4.409	5.472	14.59%	13.41%	15.77%
	4 clinical risk factors	9.703	<0.001	7.353	12.803	23.57%	19.31%	27.84%
	>=5 clinical risk factors	18.509	<0.001	9.390	36.485	34.75%	21.84%	47.65%
HIV	No diagnosis	N/A				N/A	N/A	N/A
	Had diagnosis	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Immuno-supressive Medications	No medication/ procedure	N/A				N/A	N/A	N/A
	Had medication/ procedure	N/A	N/A	N/A	N/A	N/A	N/A	N/A

		Model #2: Includes a Count of Clinical Risk Factors						
		Odds Ratio	p-value	99.9% Confidence Interval		Average Adjusted Prob-ability*	99.9% Confidence Interval	
Diagnosis of Contact with TB	No diagnosis	N/A				N/A	N/A	N/A
	Had diagnosis	N/A	N/A	N/A	N/A	N/A	N/A	N/A
History/Late Effects of TB	No diagnosis	N/A				N/A	N/A	N/A
	Had diagnosis	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Diabetes	No diagnosis/ medication	N/A				N/A	N/A	N/A
	Had diagnosis/ medication	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Tobacco	No diagnosis/ medication	N/A				N/A	N/A	N/A
	Had diagnosis/ medication	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Leukemia or Lymphoma	No diagnosis	N/A				N/A	N/A	N/A
	Had diagnosis	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lung Cancer	No diagnosis	N/A				N/A	N/A	N/A
	Had diagnosis	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Head or Neck Cancer	No diagnosis	N/A				N/A	N/A	N/A
	Had diagnosis	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lung Disease Due to External Agents	No diagnosis	N/A				N/A	N/A	N/A
	Had diagnosis	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Gastrectomy or Gastric Bypass	No diagnosis/ procedure	N/A				N/A	N/A	N/A
	Had diagnosis/ procedure	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ESRD/ Dialysis	No diagnosis	N/A				N/A	N/A	N/A
	Had diagnosis	N/A	N/A	N/A	N/A	N/A	N/A	N/A

		Model #2: Includes a Count of Clinical Risk Factors						
		Odds Ratio	p-value	99.9% Confidence Interval		Average Adjusted Prob-ability*	99.9% Confidence Interval	
Alcohol Use Disorder	No diagnosis	N/A				N/A	N/A	N/A
	Had diagnosis	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Drug Use Disorder	No diagnosis	N/A				N/A	N/A	N/A
	Had diagnosis	N/A	N/A	N/A	N/A	N/A	N/A	N/A

* Calculated as the average predicted probability of a test conditional on all observations being in the category represented by the row. The difference between the predicted probabilities for two categories of a given categorical variable represents the average marginal effect.

** Average predicted probability of *Mycobacterium tuberculosis* screening at the minimum, maximum, and quartile values of these variables can be found in Table 5.

Table 5: Average adjusted probability of *Mycobacterium tuberculosis (Mtb)* screening with either a tuberculin skin test (TST) or an interferon-gamma release assay (IGRA) at the minimum, maximum, and quartile values of the continuous variables included in the two logistic regression models detailed in Tables 3 and 4. These models examine associations between insurance enrollee characteristics and screenings for *Mtb* between 2011 and 2013, based on data from the Optum Impact National Research Database (N=3,997,986).

		Percent of Foreign-born Individuals in County *Models 1 & 2 p<0.001*				Percent of Households in County with Income under FPL *Model 1 p=0.004, Model 2 p=0.001*				State TB Rate *Models 1 & 2 p<0.001*			
		% Foreign-born	Average Adjusted Prob-ability*	99.9% Confidence Interval		% Under FPL	Average Adjusted Prob-ability*	99.9% Confidence Interval		State TB Rate	Average Adjusted Prob-ability*	99.9% Confidence Interval	
Model #1: Includes Individual Clinical Risk Factors	Minimum	0.00%	3.22%	3.16%	3.27%	3.10%	4.38%	4.29%	4.48%	0.4	2.78%	2.69%	2.88%
	25th percentile	4.80%	3.51%	3.47%	3.56%	10.20%	4.33%	4.29%	4.38%	1.8	3.42%	3.36%	3.48%
	Median	9.33%	3.82%	3.78%	3.86%	13.90%	4.31%	4.28%	4.34%	3.2	4.19%	4.16%	4.22%
	75th percentile	18.96%	4.56%	4.52%	4.60%	18.20%	4.28%	4.23%	4.32%	4.4	4.97%	4.91%	5.04%
	Maximum	51.20%	8.08%	7.79%	8.37%	51.20%	4.06%	3.78%	4.34%	9.0	9.39%	8.87%	9.91%
Model #2: Includes a Count of Clinical Risk Factors	Minimum	0.00%	3.12%	3.06%	3.17%	3.10%	4.40%	4.30%	4.49%	0.4	2.74%	2.65%	2.83%
	25th percentile	4.80%	3.44%	3.39%	3.49%	10.20%	4.34%	4.29%	4.38%	1.8	3.39%	3.33%	3.45%
	Median	9.33%	3.77%	3.73%	3.81%	13.90%	4.31%	4.28%	4.34%	3.2	4.18%	4.15%	4.21%
	75th percentile	18.96%	4.58%	4.54%	4.62%	18.20%	4.27%	4.22%	4.32%	4.4	4.99%	4.92%	5.05%
	Maximum	51.20%	8.55%	8.24%	8.85%	51.20%	4.01%	3.72%	4.29%	9.0	9.53%	9.00%	10.06%

* Calculated as the average predicted probability of a test conditional on all observations being at the value represented by the row.

exposure to TB, a history of TB, diabetes, tobacco use, lung disease due to external agents, end stage renal disease/dialysis, and alcohol use disorder. Asthma, while not a risk factor, was also significantly associated with TST/IGRA testing.

Most non-clinical explanatory variables were also significantly associated with TST/IGRA testing in adjusted and unadjusted models (Tables 3, 4 and 5). Females were more likely to be tested than males. There was higher likelihood of testing among very young children and young adults with a decreasing trend as age increased beyond 24 years. Testing likelihood rose with the state TB rate, with increased population density, with larger relative populations of foreign-born persons in a county, and with less restrictive insurance. Living in a PCP-HPSA was associated with decreased testing likelihood.

Having COPD or a gastrectomy/gastric bypass was not significantly associated with TST/IGRA testing in the bivariate analyses but were associated with a higher likelihood of testing in the multivariable models. Conversely, having a drug use disorder was significantly associated with TST/IGRA testing in bivariate analyses but was non-significant in the multivariable model. Having leukemia or lymphoma was associated with an increased likelihood of testing in the unadjusted analysis but a decreased likelihood in the adjusted analysis. Head/neck cancer was associated with a lower likelihood of testing in the unadjusted analysis but was non-significant in the adjusted analysis. See Appendix 1 for additional information about the associations between TST/IGRA testing and COPD, gastrectomy/gastric bypass, drug use disorder, and leukemia/lymphoma. Lung cancer was not significantly associated with testing in either the unadjusted or adjusted analyses.

DISCUSSION

Our study provides evidence that the US commercial healthcare sector has actively participated in domestic TB prevention-related activities in recent years. Our results provide an important window into the relative likelihood of LTBI testing for given patient groups to identify those more or less likely to be tested by broadly observable characteristics. More than 1 in 25 (4.31%) commercially insured individuals in our sample received either a TST or IGRA during three years of observation, and likelihood of screening closely tracked important clinical and other risk factors.

The majority of the characteristics known to be associated with increased risk of *Mtb* infection or disease progression were found to be associated with an increased likelihood of TST/IGRA testing. However, there was great variation in the probability of testing across the different patient groups. A diagnosis indicating contact with or exposure to TB was associated with the highest adjusted probability of testing, followed by immunosuppressive therapy and HIV (71.62%, 34.42%, and 26.69%, respectively). These findings are heartening, as they suggest that guideline concordant testing is occurring in the private sector. Testing is strongly recommended for persons in these groups, since they are at the highest risk for developing active TB if they are infected with *Mtb* (CDC, 2000). We also found that as the number of clinical risk factors for a given person increased so did the likelihood that he or she would be tested. In combination, these results suggest that many private sector providers are aware of the factors most strongly associated with TB and they conduct TB/LTBI testing accordingly.

The clinical characteristics associated with an intermediate risk of *Mtb* infection or disease progression were also generally associated with a statistically significant increase in the likelihood of testing. However, the magnitude of the effects were not as striking as those seen when examining high-risk characteristics. For example, the average adjusted probability of testing for someone with end stage renal disease was 5.73% versus 4.30% for someone without, and the average adjusted probability of testing for someone with diabetes was 4.84% versus 4.29% for someone without. Additionally, some clinical risk factors were not associated with an increased likelihood of TST/IGRA testing (e.g., head/neck cancer, lung cancer). These mixed results align with providers' need for clear guidance regarding LTBI testing for US patients with intermediate-risk conditions (Blumberg & Ernst, 2016; US Preventive Services Task Force et al., 2016). US Centers for Disease Control and Prevention (CDC) guidelines indicate that diabetes, chronic renal failure, immunosuppressive therapy, alcohol abuse, and a number of other clinical conditions increase the risk of developing TB; thus individuals with these conditions are appropriate targets for LTBI testing and treatment programs (CDC, 2000; Mazurek et al., 2010). However, recent guidelines released by the World Health Organization (WHO) exclude some of these conditions (e.g., diabetes, alcohol use disorders). They indicate that individuals with these conditions should not be tested for LTBI unless additional risk factors are present (WHO, 2015). Clinical practice guidelines from American Thoracic Society (ATS) / Infectious Disease Society of America (IDSA) / CDC will specify who should be tested for LTBI and are in development and forthcoming (Lewinsohn, 2016). These guidelines should be well-received by private sector providers; the USPSTF received much feedback on their draft LTBI

screening recommendation requesting “clarification around risk assessment of populations who should receive screening” (USPSTF et al., 2016).

While the final USPSTF recommendation does not provide guidance regarding testing for specific clinical conditions, it does state that persons who were born in countries with increased TB prevalence are at increased risk of LTBI and recommends LTBI testing in this population (USPSTF et al., 2016). Our results suggest that many providers are aware of their foreign-born patients’ TB/LTBI risk and are conducting TST/IGRA testing accordingly. We found that as the percentage of foreign-born individuals in a person’s county increased, the likelihood of testing also increased. Similarly, as the state TB rate increased, so did the likelihood of TST/IGRA testing. This corresponds with a greater risk of TB exposure for patients living in high-incidence states and suggests a greater awareness of TB/LTBI in private sector providers practicing in these states.

We found increased likelihood of TST/IGRA testing in pre-kindergarten age (0-4 years) and college-entry age groups (15-19 and 20-24 years) (adjusted probabilities of 9.01%, 12.35% and 8.45%, respectively). These findings align with the practice of requiring that students be screened prior to or upon entry into school (Flaherman et al., 2007; Hennessey et al., 1998). Compared to other age groups, the college-entry years were associated with the highest likelihood of TST/IGRA testing. This is likely because targeted LTBI testing is especially important for colleges and universities. Many foreign-born students are at risk for TB, yet people entering the US on student visas are not required to be tested for TB; further, dormitories provide a congregate environment in which TB can be transmitted (CDC, 1990; Hennessey et al., 1998).

While targeted testing of at-risk children and young adults entering or attending school can effectively contribute to domestic TB prevention efforts and is cost-effective, school-related universal LTBI testing is not recommended (Taylor et al., 2005). Nevertheless, universal testing of this population has been widely conducted (Flaherman et al., 2007; Hennessey et al., 1998). Fortunately, there are signs that some local and organizational policies are changing to align with national screening guidelines. For example, Los Angeles County implemented a new testing policy in July 2012, discontinuing universally required pre-kindergarten LTBI testing and beginning risk assessment and targeted testing (County of Los Angeles Public Health [LAPH], 2012).

Although claims data provide a rich source of information about health conditions and TST/IGRA testing, these data have limitations. We cannot determine when TST/IGRA testing is for employment purposes or if persons tested are employed in high-risk environments. Similarly, while it is evident that TST/IGRA testing in the private sector is occurring at relatively high rates in age groups associated with school entry, we cannot determine whether universal testing or targeted testing was occurring in these groups because we cannot know if pre-testing risk assessments were conducted. Some risk factors of *Mtb* infection or progression are not evident in claims data, including homelessness, visiting areas with high TB prevalence, and residence in congregate settings (CDC, 2000; Mazurek et al., 2010). Country of birth and household income were also not available through billing data, although we incorporated county-level proxies of these important variables. While data limitations disallowed us from examining some risk factors, the current study provides insight into the TST/IGRA testing associated with many important clinical risk factors.

Further, we found that some persons tested in a three-year period were not tested in a one year subperiod. This demonstrates that the results of any study examining the proportion of individuals tested within a restricted span of time may underrepresent the likelihood that an individual has been tested. Persons not tested in our three-year study period may have been tested prior to that period. Similarly, health conditions are only reflected in claims data if they are diagnosed or treated, so undiagnosed and untreated risk factors are not reflected in these analyses. Additionally, claims data do not provide direct assessments of provider knowledge, so our conclusions regarding providers' awareness of TB risk are based on inference. Our methods do not examine temporality. That is, we do not determine if a TST/IGRA test was conducted before or after a diagnosis was assigned or a treatment occurred. We also do not examine the association between risk factors and the receipt of a TST versus an IGRA; we examine the two types of tests in combination.

While CPT codes are generally required for third party payer reimbursement for office-based services, there is not a strong incentive for providers to consistently request reimbursement for TSTs, given the low amount reimbursed for these tests (e.g., the 2012 Medicare Physician Fee Schedule amount for a TST was $7.83) (Centers for Medicare & Medicaid Services, 2016). It appeared that some providers did not include testing CPT codes on all claims in which testing was conducted. Consequently, we inferred some of the TST testing in our analyses using the "special screening examination for pulmonary tuberculosis, including diagnostic skin testing" diagnosis rather than observing the tests in service codes. That we found claims with that diagnosis code and no CPT procedure code accompanying it indicates that TST/IGRA coding is imperfect. It is possible that commercially insured patients are receiving

testing that is not documented at all in claims data. Thus, our results may be considered a low estimate of testing activity in the private sector. Our data also excludes testing not submitted to or reimbursed by commercial payers (e.g., testing conducted in workplaces or public health departments). Despite these limitations, commercial claims provide the public health community a window into the TST/IGRA testing occurring in the private sector, and the large sample size enables us to examine low-prevalence risk factors and identify subtle variations in testing practices.

While our study was specifically designed to determine whether TB/LTBI risk factors are associated with an increased likelihood of LTBI testing, our analyses generated additional questions that remain unexplored. We observed that some individuals received >1 TST/IGRA test in the two periods studied. It is plausible that patterns of routine testing required for administrative purposes may be evident in the claims data. Similarly, retesting after an initial positive test may also be apparent. Future research exploring retesting patterns and whether these patterns are associated with TB/LTBI risk factors is warranted.

Given changes in local screening requirements (CLAPH, 2012), the recently released USPSTF recommendations and WHO guidelines (WHO, 2015), and the forthcoming ATS/IDSA/CDC clinical practice guidelines (Lewinsohn, 2016), the period we studied reflects screening occurring during a time of shifting clinical practice and policies. This study serves as a baseline measure of LTBI screening in the private sector prior to USPSTF guidelines. The methods used in the current study can be applied to claims data from other time periods and our results can be used to assess whether TST/IGRA testing is increasing or decreasing in high-risk and intermediate-risk groups. Understanding these trends is especially important because

there is evidence that the prevalence of LTBI testing in some high-risk groups may be decreasing (Vozoris & Batt, 2016). Perhaps most importantly our findings give evidence of the value of the commercial healthcare sector as a powerful resource in the fight against TB. Commercial healthcare already has extended the reach of public health authorities farther than most appreciate, and the opportunities presented by a newly incentivized system with such massive capacity should not be ignored.

PUBLIC HEALTH IMPLICATIONS

We identified that LTBI testing in the private sector is not uncommon, and that private sector providers appear to have an awareness of TB risk factors. There is a need for clear clinical guidance regarding LTBI testing for US private sector patients with intermediate-risk conditions (Blumberg & Ernst, 2016; USPSTF et al., 2016). Additionally, our analysis indicates that LTBI screening of students prior to or upon entry into school remains common, suggesting that continued messaging regarding the inappropriateness of school-based universal testing is necessary. Our results provide public health leadership with important information about private sector LTBI testing practices, which facilitates the development of programs to shape TB prevention activities in this setting of increasing importance to domestic TB elimination efforts.

CHAPTER III

CLAIMS-BASED METHODS TO IDENTIFY AND EVALUATE LATENT TUBERCULOSIS INFECTION TREATMENT

Introduction

Domestic tuberculosis (TB) elimination is a longstanding component of US public health policy (Centers for Disease Control and Prevention [CDC], 1989, 1999; Institute of Medicine [IOM], 2000). Unfortunately, the goal of TB elimination, defined as a rate of newly diagnosed TB less than 1 case per million population (CDC, 1989) remains unmet and progress toward meeting the goal has slowed (Salinas et al., 2016). One important reason for this is the need to better address latent TB infection (LTBI) (IOM, 2000). People with LTBI are infected with *Mycobacterium tuberculosis (Mtb)* but do not have active TB disease, are not infectious, and are asymptomatic. LTBI represents a vast and largely unaddressed reservoir of future TB cases (IOM, 2000). The up to 13 million people in the US with LTBI remain at elevated risk for developing TB through their lifetime; without treatment, 5-10% of these individuals will develop active TB (Mancuso et al., 2016; Miramontes et al., 2015). Carefully targeted efforts to identify and treat people with LTBI are now a key focus of the US TB elimination strategy (CDC, 2015a).

The overwhelming majority of TB control and prevention, including LTBI treatment, has traditionally been provided by safety net and local public health agencies (Balaban et al., 2015; Ehman et al., 2014; IOM, 2000; Sterling et al., 2006). This may be changing with the Affordable Care Act's (ACA) deliberate move towards insurance-financed care, and some treatment for

LTBI previously occurring in public health departments is likely shifting to private sector healthcare providers (Balaban et al., 2015; Bovbjerg et al., 2011; Ehman et al., 2014). This shift will be expedited with the US Preventive Services Task Force's (USPSTF) recent assignment of a "Grade B" rating to the practice of screening for LTBI in populations that are at increased risk of TB (US Preventive Services Task Force [USPSTF] et al., 2016). With this rating, the ACA requires that TB/LTBI testing in these populations be covered by commercial health plans at no out of pocket cost to patients (H.R. 3590, 2010) which will likely drive increased LTBI treatment initiation in the private sector. As activity in the commercial setting grows it is important for public health authorities and health plans to consider how commercial claims data can be used to inform planning and evaluation of TB prevention.

We identified and evaluated LTBI treatment using commercial claims data to provide methods and inform planning around TB prevention occurring in the commercial healthcare sector. Our specific objectives were to 1.) develop methodology to identify LTBI related healthcare and specifically long term daily-dose isoniazid treatment using medical and pharmacy claims data, and 2.) estimate the treatment initiation and completion rates from a large commercial claims dataset.

Methods

Please note that a manuscript describing this method has been provisionally accepted for publication in the Journal of Public Health Management and Practice. Please cite that

journal article rather than this dissertation when referencing this method (Stockbridge, Miller, Carlson, & Ho, 2017).

Data Source

We analyzed a deidentified, randomly selected sample of paid medical and pharmacy claims and health insurance enrollment data for 4 million continuously commercially insured individuals ages 0-64 years from the Optum Impact National Research Database (Optum, 2015). This database includes claims data for approximately 30.6 million commercially insured people, which is roughly 19% of the commercially insured population in the US.

All people in the sample had continuous health insurance enrollment with both medical and pharmacy coverage beginning January 1, 2011 and ending no earlier than December 31, 2013. The data reflect insurance-paid services rendered and prescriptions filled from January 2011 through the end of each person's health insurance coverage period or March 31, 2015, whichever came first. Of the 4 million people in the sample, 2,390,112 (59.7%) were continuously enrolled through March 2015. In total, the sample represented 186,670,279 person/months of commercially insured healthcare utilization. The distribution of individuals in our sample roughly approximated the 2010 US population distribution based on Census divisions (U. S. Department of Commerce, 2012).

We developed an algorithm to identify people initiating and those completing 6-9 months of isoniazid, the overwhelmingly dominant regimens prescribed for LTBI (Horsburgh et al., 2010). This algorithm identifies billing codes suggestive of LTBI treatment within the claims data and then applies increasingly sensitive logic to retain only those episodes of care we can

confidently attribute to LTBI treatment for final analysis. For those meeting the inclusion criteria for final analyses, treatment completion and initiation rates were calculated. We defined "LTBI treatment" as 6-month or 9-month daily-dose isoniazid LTBI treatment regimens.

Process to Identify LTBI Treatment

Please note that a manuscript describing this process has been provisionally accepted for publication in the Journal of Public Health Management and Practice. Please cite that journal article rather than this dissertation when referencing this process (Stockbridge et al., 2017).

The algorithm we developed to identify individuals eligible to be included in the LTBI treatment completion analyses is depicted in Figure 1 on the following page. Specific billing codes are available upon request from the author. First, people with isoniazid prescriptions filled from the beginning through one year prior to the end of the time span of the Optum data sample were identified (January 2011 through March 2014; Figure 1 Cell 1). A prescription had to be filled at least one year before the end of the available data so that treatment completion (as defined in the "Completion Rate Calculation" section) could be determined. For the same reason, an individual's insurance coverage had to span for 1 year after the date of his/her first isoniazid prescription (the "post-period"; Figure 1 Cell 2).

We then established whether each individuals' first isoniazid prescription in the data could be deemed the beginning of treatment. This was done by ensuring that each person had continuous insurance coverage in the 6 months prior to the prescription (the "pre-period") and had no isoniazid prescriptions during the pre-period (Figure 1 Cell 3). With this 6 month pre-

Figure 1: Process identifying individuals initiating latent tuberculosis infection (LTBI) treatment with isoniazid (INH) for whom treatment completion can be assessed. The process was applied to Optum Impact National Research Database claims data for 4 million commercially insured people. The data represented services from January 2011 through March 2015.

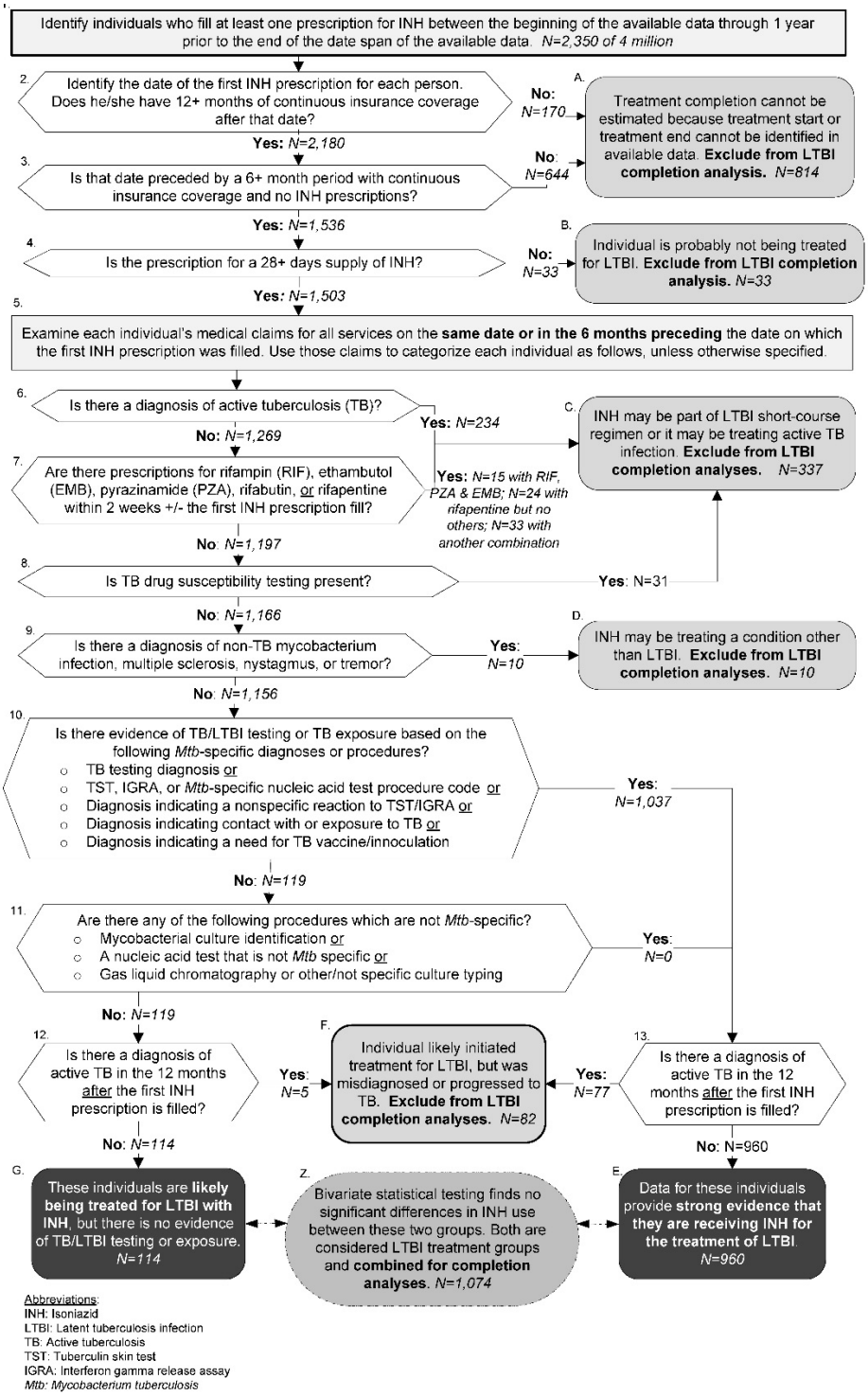
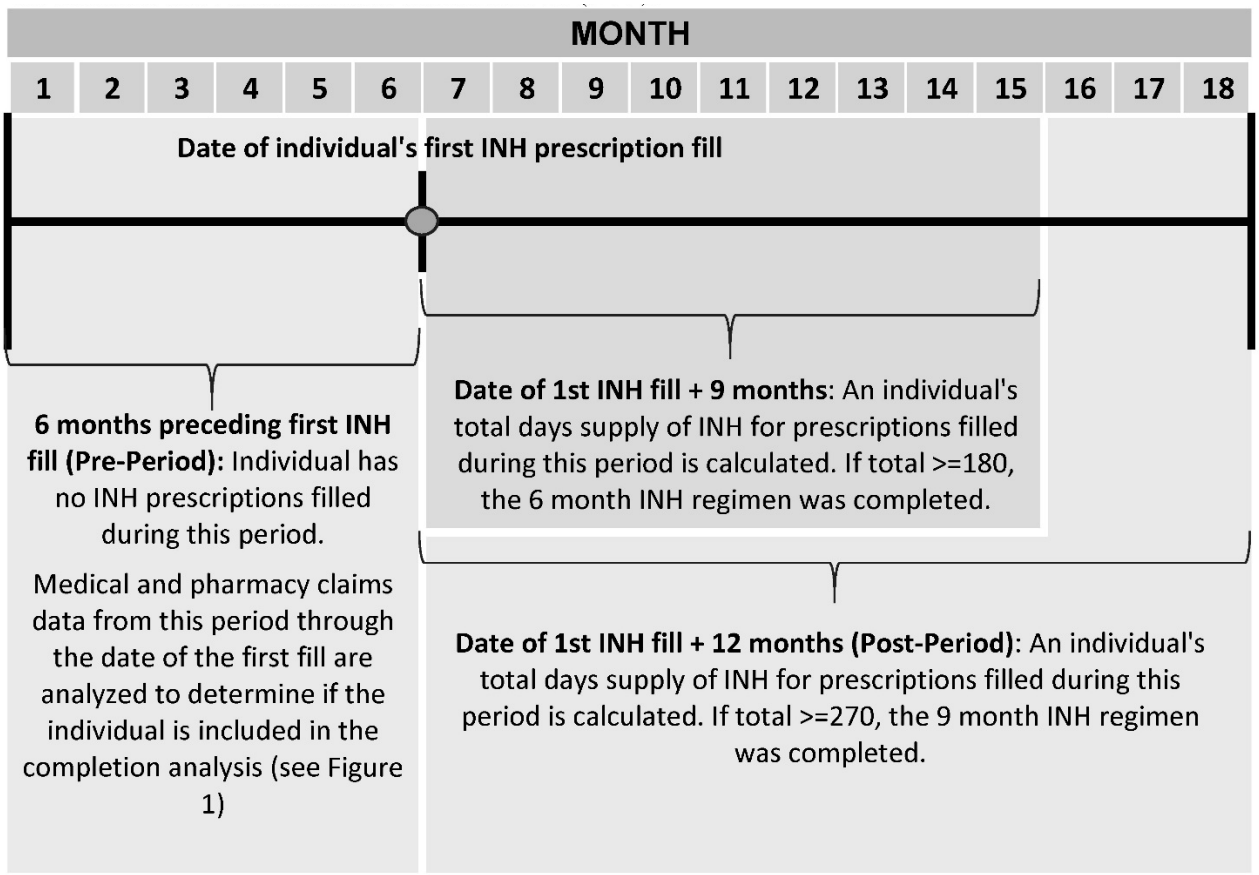


Figure 2: Illustration of how 18 months of each individuals' data were used to identify latent tuberculosis infection treatment with isoniazid (INH).



period plus the one year post-period required to assess treatment completion, 18 months of each individual's data were used (Figure 2, above).

Next, we excluded individuals whose data suggested that isoniazid was used for something other than daily dose LTBI treatment. Individuals with a first isoniazid prescription for less than 28 daily doses are excluded (Figure 1 Cell 4). Prescription medications used for ongoing treatments are typically filled for 1 or 3 month supplies (Liberman & Girdish, 2011). Consequently, a supply of less than 28 days suggests the isoniazid might have been prescribed for another condition. Then, individuals were excluded if they were receiving isoniazid as part

of a course of treatment for active TB or as part of the 12-dose weekly isoniazid and rifapentine LTBI regimen. These determinations were made based on the presence one of the following: 1) an active TB diagnosis in the pre-period, or 2) a concurrent prescription for a medication used in conjunction with isoniazid to either treat active TB or another rifamycin-containing LTBI regimen (Figure 1 Cells 6 and 7) (CDC, 2016d). Next we determined if TB drug susceptibility testing was conducted in the pre-period. Drug susceptibility testing is conducted for active TB but is not applicable to LTBI, so individuals with these tests are likely taking isoniazid for active TB (Figure 1 Cell 8) and are excluded. Further, individuals with diagnoses of non-tuberculosis mycobacterium or nystagmus/tremor from multiple sclerosis were excluded because isoniazid may be used to treat these conditions (Figure 1 Cell 9) (Griffith et al., 2007; Mills, Yap, & Young, 2007).

We determined if the remaining people were receiving isoniazid for LTBI treatment based on the presence of *Mtb* testing, a positive TB/LTBI test result diagnosis, or a TB exposure diagnosis (Figure 1 Cell 10). We also determined if any testing was conducted which was not *Mtb*-specific but which may be used to test for *Mtb* (Figure 1 Cell 11). Individuals who met all of the criteria preceding Cell 10 and had diagnoses and procedures that were indicative of TB exposure or TB/LTBI testing in Cells 10 or 11 were deemed as being treated for LTBI with isoniazid.

Individuals diagnosed with active TB in the 12 months after the first isoniazid prescription is filled were excluded as either people with active TB who were initially misdiagnosed with LTBI or they had LTBI which developed into active TB during their course of treatment (Figure 1 Cell 13; see Appendix 2 for sensitivity testing of this approach). The

remaining individuals were included in the completion analyses based on the strong evidence that they were receiving isoniazid-only LTBI treatment (Figure 1 Terminal Cell E).

Less frequently, individuals who fill prescriptions for isoniazid were not disqualified (Figure 1 Cells 1-9 &12), but their claims data histories contained no specific evidence that they were being treated for LTBI (Figure 1 Cells 10-11). No uses for isoniazid other than those previously noted (CDC, 2016d; Griffith et al., 2007; Mills et al., 2007) were identified so it is likely that the individuals in this group were being treated for LTBI.

Statistical Assessment of Group Equivalency

We used two statistical tests to compare the number of isoniazid prescriptions filled to determine whether 1) people without evidence of LTBI testing or diagnoses (Figure 1 Terminal Cell G), and 2) those with LTBI testing or diagnoses (Figure 1 Terminal Cell E) could both be considered as receiving LTBI treatment. First, we used a bivariate ordinal logit regression model to determine if there were differences in three levels of completion – completion of neither the 6-month nor the 9-month regimen, completion of the 6-month but not the 9-month regimen, and completion of the 9-month regimen. Second, we used a bivariate zero-truncated negative binomial model to determine if they differed in terms of the number of months of isoniazid prescriptions filled. A lack of significant differences based on both of these tests would be used as evidence that the two groups were equally likely to represent individuals being treated for LTBI. In that case, both groups would be included in the treatment initiation and completion analyses. Conversely, if significant differences were identified, LTBI treatment initiation and completion would only be calculated for the group of individuals with LTBI testing procedures or diagnoses. Additionally, we generated frequency distributions to examine the demographic

characteristics of individuals with any isoniazid prescription during the study period; individuals in the two groups potentially eligible to be included in the completion analysis; and individuals completing isoniazid treatment.

Completion and Initiation Rate Calculations

We calculated 6-month and 9-month completion rates. Claims data do not provide the information needed to determine whether a patient was prescribed a 6 or 9-month regimen of isoniazid, so both of these regimens were assessed for each individual. We defined completion of the 9-month and 6-month daily isoniazid treatment regimen as at least 270 and 180 doses received within 12 and 9-months respectively (Horsburgh et al., 2010). We calculated completion rates as the proportion of completed treatments among those individuals who initiated treatment in the final analyses.

In order to calculate the LTBI treatment initiation rate within commercially insured persons, we identified all treatment initiations, even where completion could not be evaluated, by re-running the algorithm depicted in Figure 1 but this time retaining individuals without 12 months of continuous insurance coverage in the post-period (Figure 1 Cells 2 & A). The result was used as the numerator, and the treatment initiation rate was denominated in person-years.

Results

Please note that a manuscript reporting the final analysis results has been provisionally accepted for publication in the Journal of Public Health Management and Practice. Please look to that article for final analysis results (Stockbridge et al., 2017).

We identified 1,197 LTBI treatments initiated during 9,555,858 commercially insured person-years over 33 months of observation, an annual treatment initiation rate of 12.5/100,000. We could evaluate completion for 1,074 of these and found 497 (46.3%; CI: 43.3, 49.3) completed at least the 6 month regimen. Of those, 243 (48.9%; CI: 44.5%, 53.3%) completed the 9 month regimen (Table 6, below). Thus, the 9 month treatment completion rate was 22.6% (243/1074; CI: 20.2%, 25.2%).

Table 6: Isoniazid-only latent tuberculosis infection treatment initiation and completion estimates, based on individuals in a sample of Optum National Research Database medical and pharmacy claims data with an initial isoniazid prescription filled between July 2011 and March 2014.

Measure Description	Measure Value
Person/years during which treatment initiation was assessed	9,555,856.6
Number initiating treatment	1,197
Annual treatment initiation rate per 100,000 insured persons	12.53
Number initiating treatment for which completion could be assessed	1,074
Number completing ≥6 months of isoniazid treatment	497
Percent completing ≥6 months of isoniazid treatment	46.3% (95% CI: 43.3, 49.3)
Of those completing ≥6 months of isoniazid treatment:	
Number completing ≥6 months but ≤9 months	254
Percent completing ≥6 months but ≤9 months	51.1% (95% CI: 46.7, 55.5)
Number completing ≥9 months	243
Percent completing at ≥9 months	48.9% (95% CI: 44.5, 53.3)

In our sample, slightly more females than males, a higher proportion of older persons than young persons, and more people in the Northeast and West versus those in the Midwest and South had any isoniazid prescription (Table 7, following page).

Table 7: Demographic information for individuals in the Optum National Research Database medical and pharmacy claims data sample who filled at least one isoniazid prescription between January 2011 and March 2014.

	All Individuals With ≥1 Isoniazid Prescription between Jan. 2011 and Mar. 2014 *(N=2,350)*			Qualified for Inclusion in LTBI Treatment Completion Analyses *(N=1,074)*			Completed At Least 6-Month Isoniazid LTBI Regimen *(N=497)*			Completed At Least 9-Month LTBI Isoniazid Regimen *(N=243)*		
	#	%	Confidence Interval	#	%	Confidence Interval	#	%	Confidence Interval	#	%	Confidence Interval
Sex												
Female	1,266	53.9	(51.9, 55.9)	575	53.5	(50.5, 56.5)	254	51.1	(46.7, 55.5)	127	52.3	(45.9, 58.5)
Male	1,084	46.1	(44.1, 48.1)	499	46.5	(43.5, 49.5)	243	48.9	(44.5, 53.3)	116	47.7	(41.5, 54.1)
Age												
0-14	233	9.9	(8.8, 11.2)	105	9.8	(8.1, 11.7)	59	11.9	(9.3, 15.0)	33	13.6	(9.8, 18.5)
15-29	567	24.1	(22.4, 25.9)	291	27.1	(24.5, 29.8)	120	24.1	(20.6, 28.1)	52	21.4	(16.7, 27.0)
30-44	719	30.6	(28.8, 32.5)	322	30.0	(27.3, 32.8)	149	30.0	(26.1, 34.2)	67	27.6	(22.3, 33.6)
45-64	831	35.4	(33.5, 37.3)	356	33.2	(30.4, 36.0)	169	34.0	(30.0, 38.3)	91	37.5	(31.5, 43.7)
Census Region												
Northeast	811	34.5	(32.6, 36.5)	354	33.0	(30.2, 35.8)	161	32.4	(28.4, 36.7)	88	36.2	(30.4, 42.5)
Midwest	378	16.1	(14.7, 17.6)	174	16.2	(14.1, 18.5)	83	16.7	(13.7, 20.2)	39	16.1	(11.9, 21.3)
South	320	13.6	(12,3, 15.1)	148	13.8	(11.8, 16.0)	57	11.5	(8.9, 14.6)	24	9.9	(6.7, 14.3)
West	841	35.8	(33.9, 37.7)	398	37.1	(34.2, 40.0)	196	39.4	(35.2, 43.8)	92	37.9	(31.9, 44.2)
Year 1st Isoniazid Prescription Was Filled												
2011	966	41.1	(39.1, 43.1)	230	21.4	(19.1, 24.0)	96	19.3	(16.1, 23.0)	43	17.7	(13.4, 23.1)
2012	651	27.7	(25.9, 29.5)	452	42.1	(39.2, 45.1)	207	41.7	(37.4, 46.1)	108	44.4	(38.3, 50.8)
2013	623	26.5	(24.8, 28.3)	346	32.2	(29.5, 35.1)	172	34.6	(30.5, 38.9)	81	33.3	(27.7, 39.5)
2014	110	4.7	(3.9, 5.6)	46	4.3	(3.2, 5.7)	22	4.4	(2.9, 6.6)	11	4.5	(2.5, 8.0)

Abbreviations:
LTBI – Latent Tuberculosis Infection

Comparing the two groups of individuals that were potentially eligible to be included in the completion analysis, 960 had LTBI testing procedures or diagnoses while 114 did not have these procedures or diagnoses. In the group with LTBI testing procedures or diagnoses, 46.8% (CI: 43.6%, 44.9%) completed at least the 6-month regimen. Of those, 49.2% (CI: 44.6%, 53.8%) completed the 9 month regimen. In the group without these procedures or diagnoses, 42.1% (CI: 33.4, 51.4) completed at least the 6-month regimen. Of those, 45.8% (CI: 32.2%, 60.0%) completed the 9 month regimen. The results of the bivariate ordinal logit model that examined differences in three levels of completion indicated that there were no significant differences between the two groups in the levels of treatment completion achieved (Odds ratio 1.28; Confidence interval [CI] 0.87, 1.86). A non-significant Brant test indicated that the parallel regression assumption of the ordinal logit model was not violated (p=0.90).

Similarly, the results of the bivariate zero-truncated negative binomial model indicated that there was no significant difference between the two groups in terms of the number of isoniazid prescriptions that they filled (Incidence rate ratio 1.14, CI: 0.98, 1.31). The conditional mean number of months of isoniazid prescriptions filled for the group with LTBI testing procedures or diagnoses was 5.2 months (CI: 5.0, 5.4) while the conditional mean for the group without these procedures or diagnoses was 4.7 months (CI: 4.1, 5.3).

Given the lack of statistically significant differences we concluded that both groups consist of people taking isoniazid for LTBI treatment. The groups were combined to estimate the proportion of these individuals who completed each of the two treatment regimens.

Discussion

We successfully used claims data to identify and evaluate LTBI treatment among a large national sample of commercially insured individuals. The 6-month LTBI treatment completion rates among patients initiating commercially insured LTBI treatment is on the lower end of the 39%-96% range of isoniazid-only LTBI treatment completion rates observed in retrospective studies conducted in public health settings (Sandgren et al., 2016; Young et al., 2016). Almost half of those initiating treatments in our sample completed a 6-month or longer regimen. Almost half of those, roughly one quarter of all those initiating treatment, completed 9 or more months. Just as importantly, we quantified LTBI treatment rates in the commercial sector based on a national sample of data that is roughly generalizable to the US commercially insured population. Previous research on LTBI treatment in the private sector has focused only on limited geographic areas or select samples of providers (Sterling et al., 2006).

We found that LTBI treatment is not uncommon in the commercial healthcare setting. Commercial healthcare is likely a valuable adjunct to more traditional venues for TB prevention efforts. An increasing proportion of the US population has commercial insurance, and currently over 70% of adults and over 56% of children in the US population are commercially insured (Cohen, Martinez, & Zammitti, 2016). The commercially insured US population includes many of the persons at highest risk of LTBI and TB, including foreign-born persons (Cain, Benoit, Winston, & MacKenzie, 2008). Over 59% of foreign-born individuals in the US have private health insurance, and this rate is increasing (Barnett, 2016). As more people become commercially insured and as healthcare financing and policy evolve, management of LTBI will likely become increasingly common within the commercial healthcare sector. It is important to

understand treatment patterns in the commercial sector for LTBI as much to identify opportunities as to assess care quality. Our work provides important evidence toward both. We cannot evaluate how well LTBI treatments in our sample were targeted to persons at risk for progression to active TB, and work should be done to gauge the potential effectiveness of those efforts. But our finding that the rates of completion of at least 6 months of isoniazid treatment are similar in commercial and public settings suggests that LTBI treatment through commercial healthcare is of comparable quality to that in public health setting by at least that common indicator.

Administrative claims data is ubiquitous and accessible. At the same time it is collected to facilitate payment, not to inform clinical decision making, and realizing its potential can be challenging (Virnig, 2001). Unlike data collected from disease reporting or ad hoc program evaluation in the public health setting, LTBI related healthcare is not directly identified in claims data. Instead, it must be inferred from claims data rather than simply counted, and we are unaware of prior work that either provides methods or that has done so. By designing and testing the logic and methodologies necessary to tap into this resource we enable public health researchers and health plans to explore their own data and build on our work.

We analyzed commercial insurance claims data, but the codes used to represent diagnoses, procedures, and medications found on medical and pharmacy claims are generally consistent across private and public third party payers (Cleverley, Cleverley, & Song, 2010). Our methods may be as useful to analyze public payer claims data from Medicare and Medicaid as from commercial payers. Healthcare claims data are available from CMS or directly from states, 6 states currently have all-payer claims databases available to researchers, and the majority of

the remaining states are developing or are interested in developing such databases (Burda, 2016; Manos, 2013; Porter, Love, Peters, Sachs, & Costello, 2014; Research Data Assistance Center [ResDAC], 2016). As public health departments and other safety net agencies begin to bill third party payers for services (Bovbjerg et al., 2011) our methods can guide them in program evaluation. Finally, as the coordinating discipline for protections against TB in the US, it is important that public health authorities use claims based methods to monitor TB related healthcare services taking place beyond their clinics and seek to include such data in their decision-making. In so doing the public health community will continue its important leadership role to encourage LTBI treatment in both the public and private sectors and more effectively drive progress toward US elimination goals.

Our study does have limitations. Only patients who fill at least one prescription become visible to medication adherence studies that rely on claims data, and we cannot assess non-acceptance of treatment or determine how many people accepted treatment but failed to fill their first prescription (McGinnis, Kauffman, Olson, Witt, & Raebel, 2014). The bias such missing data introduces limits our ability to make more broad comparisons to public sector quality on the basis of treatment acceptance, but would not challenge our basic findings of the initiated treatment rate and outcomes. We also cannot know if someone filled a prescription but did not ingest the medication, but this is true for any setting not using directly observed preventive therapy (McGinnis et al., 2014). Similarly, claims data do not contain information needed to determine whether a 6 or 9-month regimen was initiated. In the public sector the majority of patients are prescribed a 9-month regimen (Horsburgh et al., 2010); we cannot know if the same is true in the private sector. Also, for individuals who initiate LTBI treatment but are

subsequently diagnosed with active TB, it we cannot determine whether there was an initial misdiagnosis, a progression to active TB during treatment, or a progression to active TB after treatment completion or discontinuation. However, our algorithm is robust to variations in assumptions for these individuals (see Appendix 2). Additionally, our initiation rate is based on all commercially insured individuals rather than those at risk of TB/LTBI, tested for TB/LTBI, or offered LTBI treatment because data exploration indicated that testing and test results are inconsistently coded in claims and offers of treatment are not coded.

Finally, it is likely that at least some people receiving LTBI related medical care do so using a mix of public and commercial services. Presumably, some individuals' LTBI treatment in the commercial sector occurs only after interaction with the public sector (e.g., being identified by the health department as a contact to a person with infectious TB). Pharmacy claims in our sample did not contain information about the prescribing provider, so we were unable to discern between isoniazid prescribed by private and public sector practitioners. In our analysis, 10.6% of the people initiating LTBI treatment with isoniazid had no LTBI-related diagnoses or procedures in the medical claims. These individuals may have been prescribed isoniazid by public health departments but filled their prescription through private pharmacies using insurance benefits; conversely, private sector providers may have prescribed these individuals isoniazid for LTBI without coding associated diagnoses or procedures on medical claims. Still, while these limitations might cloud our understanding of how prevention efforts are distributed among public and private agencies they do not challenge our basic findings for insurance paid treatment incidence and completion rates.

Implications for Policy and Practice

We found that LTBI treatment is occurring in the private healthcare sector, with completion rates within the range of rates observed in public health settings. Both findings suggest a shared purpose between public and commercial health and the opportunity to develop commercial healthcare as a valuable adjunct to more traditional TB prevention venues. Additionally, the claims-based methods we developed offer a means to gain important insights and open new avenues to monitor, evaluate, and coordinate TB prevention. Thus, these methods facilitate our goal of domestic TB elimination.

CHAPTER IV

PREDICTORS OF LATENT TUBERCULOSIS INFECTION TREATMENT COMPLETION

Introduction

There are up to 13 million people in the US with latent tuberculosis infection (LTBI) (Mancuso et al., 2016; Miramontes et al., 2015). These people are infected with *Mycobacterium tuberculosis (Mtb)* yet do not have active tuberculosis (TB) disease. People with LTBI are asymptomatic and cannot transmit *Mtb*. However, without treatment 5-10% will develop TB over time, and progression risk is higher in immunocompromised persons (Kahwati et al., 2016). The nation's strategic plan to eliminate domestic TB includes risk-targeted identification and treatment of people with LTBI (Centers for Disease Control and Prevention [CDC], 2015a). This strategy is supported by the US Preventive Services Task Force's (USPSTF) recent "Grade B" rating for LTBI testing of people in high-risk populations which indicates to primary care providers that targeted LTBI testing and treatment afford moderate health benefit with little risk (US Preventive Services Task Force [USPSTF], 2014; USPSTF et al., 2016).

Public health agencies and authorities have traditionally provided most TB control and prevention services and monitoring (Balaban et al., 2015; Ehman et al., 2014; Institute of Medicine [IOM], 2000; Sterling et al., 2006). The USPSTF's rating and provisions of the Affordable Care Act will likely drive increased private sector involvement as health insurers are required to cover TB/LTBI testing in high risk populations with no patient cost share (H.R. 3590, 2010). At the same time, the uninsured rate in the US is decreasing (Barnett, 2016). Health

insurance coverage is associated with increased use of primary and other health care and facilitates “usual sources” of care, both considered important elements to more effective medical care (The Kaiser Commission on Medicaid and the Uninsured, 2013). These shifts present a valuable but challenging opportunity to coordinate public/private approaches to TB prevention. Factors associated with LTBI treatment completion are seldom studied outside of public health departments or specifically focused at-risk patient populations (Hirsch-Moverman; Stuurman et al., 2016). Substantial differences in patient risks, provider and patient incentives, and care processes in the private sector suggest a pressing need for more information about the factors associated with treatment completion in this increasingly important setting.

We used a national sample of commercial claims data to examine private sector LTBI treatment across the US as a step toward filling this gap. Insurance claims offer a rich and broadly available window into private healthcare practice patterns (Virnig, 2001). Our goal was to use these data to identify factors associated with the completion of daily dose isoniazid LTBI treatment in the private sector setting.

MATERIALS AND METHODS

Data Source and Analytic Sample

We analyzed a retrospective sample of de-identified medical and pharmacy claims from the Optum Impact National Research Database (Optum, 2015). This database includes claims for approximately 30.6 million commercially insured individuals – about 19% of the commercially insured US population. We analyzed data for a sample of 4 million people

randomly selected by Optum. The sample included people ages 0 to 64 who had continuous commercial insurance coverage beginning January 1, 2011 and ending no earlier than December 31, 2013. The data described insurance-paid prescriptions filled and services rendered from January 2011 through the end of each person's coverage period or March 31, 2015, whichever was earliest. Geographically, the sample roughly approximated the 2010 US population distribution by Census division (U. S. Department of Commerce, 2012).

We used our recently described algorithm to identify individual 6-9 month daily dose isoniazid treatments for LTBI, which was the most common LTBI treatment in use during the study period (Horsburgh et al., 2010). Inclusion criteria for final analysis required treatment initiation between July 2011 and March 2014, insurance coverage spanning a minimum of one year after treatment initiation, and complete geographic details.

Measures

Outcome variable. The outcome of interest was completion of daily isoniazid treatment for LTBI (CDC, 2013). The data do not indicate whether the 6 or 9-month regimen was prescribed, but we could determine how many doses of isoniazid were received. Thus, we used pharmacy data to categorize isoniazid treatments into three mutually exclusive ordinal categories: 1) non-completion (<180 doses received within a 9-month period), 2) completion of the 6-month regimen but not the 9-month regimen (180 to 269 doses received within a 9-month period), or 3) completion of the 9-month regimen (≥ 270 doses received within a 12-month period) (Horsburgh et al., 2010).

Explanatory variables. Explanatory variables were constructed from information in the medical and pharmacy claims data. Socio-demographic variables included sex, age, census region, and urban-rural classification (Centers for Disease Control and Prevention, 2014). The percentage of households living under the federal poverty level (FPL) in a patient's county served as a proxy for household income (United States Census Bureau, 2015b). Additional variables included insurance type (HMO, POS, or PPO), prescription size (the supply of isoniazid received when the first prescription was filled, categorized as <2 months vs. ≥2 months), the year of treatment initiation, and the type of LTBI diagnostic test received in the 6 months before LTBI treatment initiation. We incorporated variables related to risk of LTBI or progression to active TB, including the state TB rate. Country of birth was not available, but we included a gross measure of this important information as the prevalence of foreign-born individuals in the patient's county (United States Census Bureau, 2015a; United States Department of Agriculture, 2015). Clinical risk factors were identified from claims, including diabetes, HIV, use of immunosuppressive medications, a diagnosis code documenting contact with or exposure to TB, and a history of or late effects of TB (Centers for Disease Control and Prevention, 2000). We used a simple count of each patient's clinical risk factors to assign cumulative risk (i.e., 0 risk factors, 1 risk factor, >1 risk factor).

Statistical Analyses

We calculated the proportion of individuals in each of the three categories of treatment completion (i.e., <6 months, 6 to <9 months, ≥9 months). We then examined the bivariate relationships between the explanatory variables and completion using Kruskal-Wallis tests for categorical variables and Spearman correlations for continuous variables. We explored the

adjusted association between these variables and the three categories of treatment completion using multivariable generalized ordered logit models with partial proportional odds. Variables meeting the parallel-lines assumption were constrained to have equal effects; the odds ratios for the likelihood of non-completion versus completing ≥6 months of treatment and the odds ratios for the likelihood of completing <9 months of treatment versus ≥9 months of treatment were the same. Variables violating the assumption were not constrained and consequently have different odds ratios for completion category comparisons (Williams, 2006). We ran two multivariable models. In Model 1 we examined the relationship between treatment completion and cumulative risk based on the count of clinical risk factors. Model 2 explores the relationship between treatment completion and the individual clinical risk factors. To clarify differences between the results in our bivariate and multivariable analyses examining completion, we conducted additional post hoc bivariate analyses exploring the relationship between the explanatory variables and the type of LTBI diagnostic test, e.g. tuberculin skin test (TST) or interferon gamma release assay (IGRA). We used chi square tests for categorical variables and ANOVAs for continuous variables. All statistical testing used Stata 14.2 (StataCorp, 2016), was two-sided, and significance was tested at $p < 0.05$.

RESULTS

Of 1,072 individuals with identified isoniazid LTBI treatment, almost half (46.2%) completed ≥6 months of treatment. The balance (53.8%) began treatment but fell short of completing the minimum standard 6-months course. Roughly equal proportions completed ≥6 but < 9 months treatment or ≥9 months (23.6% and 22.6% of all patients, respectively; Table 8, following page).

Table 8: Completion of daily-dose isoniazid treatment for latent tuberculosis infection. N=1,072.

Isoniazid Treatment Completion	N	% of Total	95% Confidence Interval
Less than 6 months (Incomplete treatment)	577	53.82	50.82-56.79
At least 6 months	495	46.18	43.20-49.17
≥6 months but ≤9 months	253	23.60	21.15-26.24
≥9 months	242	22.57	20.17-25.18

Tables 9 and 10 (on pages 61 and 65, respectively) describe relationships between the explanatory variables and the likelihood of treatment completion from unadjusted bivariate and multivariable models, respectively. Significant unadjusted non-clinical factors associated with treatment completion included younger age, PPO insurance, larger prescription size, and residing in a county with <15% of households below FPL. Similarly, in the multivariable models people in older age groups each had lower odds of increasing levels of treatment completion compared to people ages 0-14 years. Compared to people in large central metro counties, those in large fringe metropolitan counties had lower adjusted odds of completing ≥6 months of treatment, although this association was not seen with completing ≥9 months of treatment. Residing in a county with ≥15% of households below FPL was significantly associated with lower adjusted odds of treatment completion. Insurance type and prescription size were also significantly associated with completion. The adjusted odds of a PPO-insured patient completing ≥6 months of treatment were 1.8-1.9 times that of an HMO-insured patient, and the odds of a PPO-insured patient completing ≥9 months were 2.8-2.9 times that of an HMO-insured patient. Larger prescription size was associated with higher adjusted odds of completing ≥9 months of treatment, although this association was not seen for completing ≥6 months of treatment.

Table 9: Frequency distribution of patient characteristic variables for people initiating daily-dose isoniazid treatment and the proportion of people completing treatment by each characteristic. Treatment completion was categorized as 1) less than 6 months completed, 2) at least 6 months but less than 9 months completed, and 3) 9 or more months completed.

		Distribution		% Achieving Each Level of Isoniazid Treatment Completion				% Completing ≥6 Mo.	
		N	% or Mean of Total	<6 Months Complete [% or Mean]	≥6 but < 9 Months Complete [% or Mean]	≥9 Months Complete [% or Mean]	p-value: 3 Completion Levels	≥6 Months Complete [% or Mean]	p-value: <6 vs ≥6 Months Complete
Sex	Female	575	53.6%	55.8%	22.1%	22.1%	0.232	44.2%	0.158
	Male	497	46.4%	51.5%	25.4%	23.1%		48.5%	
Age Group	1. 0-14	105	9.8%	43.8%	24.8%	31.4%	0.019	56.2%	0.064
	2. 15-29	291	27.1%	58.8%	23.4%	17.9%		41.2%	
	3. 30-44	321	29.9%	53.9%	25.2%	30.9%		46.1%	
	4. 45-64	355	33.1%	52.7%	22.0%	35.4%		47.3%	
Census Region	Northeast	352	32.8%	54.8%	20.5%	24.7%	0.148	45.2%	0.151
	Midwest	174	16.2%	52.3%	25.3%	22.4%		47.7%	
	South	148	13.8%	61.5%	22.3%	16.2%		38.5%	
	West	398	37.1%	53.8%	23.6%	22.6%		46.2%	
Rural-Urban Category of County	Large central metro county	484	45.1%	50.0%	26.7%	23.4%	0.169	50.0%	0.066
	Large fringe metro county	413	38.5%	57.6%	19.6%	22.8%		42.4%	
	Any smaller county	175	16.3%	55.4%	24.6%	20.0%		44.6%	
% of Households Under FPL in County	<15%	596	55.6%	51.7%	22.8%	25.5%	0.035	48.3%	0.115
	≥15%	476	44.4%	56.5%	24.6%	18.9%		43.5%	

		Distribution		% Achieving Each Level of Isoniazid Treatment Completion				% Completing ≥6 Mo.	
		N	% or Mean of Total	<6 Months Complete [% or Mean]	≥6 but < 9 Months Complete [% or Mean]	≥9 Months Complete [% or Mean]	p-value: 3 Completion Levels	≥6 Months Complete [% or Mean]	p-value: <6 vs ≥6 Months Complete
Insurance Type	HMO	188	17.5%	62.2%	21.3%	16.5%	0.005	37.8%	0.022
	POS	742	69.2%	52.8%	25.1%	22.1%		47.2%	
	PPO	142	13.2%	47.9%	19.0%	33.1%		52.1%	
INH Days Supply Received on Date of 1st Fill	<2 month supply	991	92.4%	54.5%	24.1%	21.4%	0.020	45.5%	0.126
	≥2 month supply	81	7.6%	45.7%	17.3%	37.0%		54.3%	
Year INH Regimen Started	2011 Q3-4	230	21.5%	58.3%	23.0%	18.7%	0.308	41.7%	0.298
	2012 Q1-4	450	42.0%	54.4%	21.8%	23.8%		45.6%	
	2013 Q1-4	346	32.3%	50.3%	26.3%	23.4%		49.7%	
	Q1 2014	46	4.3%	52.2%	23.9%	23.9%		47.8%	
State TB Rate		-		3.85	3.84	3.81	0.846	3.83	0.864
LTBI Diagnostic Test	TST	441	41.1%	53.5%	22.9%	23.6%	<0.001	46.5%	0.005
	IGRA	219	20.4%	45.2%	23.7%	31.1%		54.8%	
	Unknown/ Other	412	38.4%	58.7%	24.3%	17.0%		41.3%	
Percent Foreign Born in County		-		19.96	20.24	20.97	0.403	20.60	0.516
# of Clinical Risk Factors	None	662	61.8%	58.0%	22.2%	19.8%	0.011	42.0%	0.002
	1	304	28.4%	47.7%	27.0%	25.3%		52.3%	
	2 or more	106	9.9%	45.3%	22.6%	32.1%		54.7%	
Diagnosis of Contact w/ TB*	No diagnosis	923	86.1%	54.3%	23.8%	21.9%	0.296	45.7%	0.457
	Had diagnosis	149	13.9%	51.0%	22.2%	26.9%		49.0%	

		Distribution		% Achieving Each Level of Isoniazid Treatment Completion				% Completing ≥6 Mo.	
		N	% or Mean of Total	<6 Months Complete [% or Mean]	≥6 but < 9 Months Complete [% or Mean]	≥9 Months Complete [% or Mean]	p-value: 3 Completion Levels	≥6 Months Complete [% or Mean]	p-value: <6 vs ≥6 Months Complete
History of TB/ Late Effects	No diagnosis	1027	95.8%	54.2%	23.1%	22.7%	0.426	45.8%	0.197
	Had diagnosis	45	4.2%	44.4%	35.6%	20.0%		55.6%	
HIV Positive	No diagnosis	1030	96.1%	54.7%	23.4%	21.9%	0.004	45.3%	0.007
	Had diagnosis	42	3.9%	33.3%	28.6%	38.1%		66.7%	
Diabetes	No diagnosis	999	93.2%	54.5%	23.5%	22.0%	0.085	45.6%	0.126
	Had diagnosis	73	6.8%	45.2%	24.7%	30.1%		54.8%	
Tobacco	No diagnosis or medication	1004	93.7%	54.2%	23.7%	22.1%	0.237	45.8%	0.366
	Had diagnosis or medication	68	6.3%	48.5%	22.1%	29.4%		51.5%	
Immuno-supressive Medication	No medication	948	88.4%	55.1%	23.0%	21.9%	0.030	44.9%	0.025
	Had medication	124	11.6%	44.4%	28.2%	27.4%		55.6%	

*Based on an ICD-9-CM code of V01.1

Table 9 Abbreviations:
Mtb – Mycobacterium tuberculosis
INH – isoniazid

FPL – federal poverty level
TB – tuberculosis
TST – tuberculin skin test
IGRA – interferon-gamma release assays
LTBI – latent tuberculosis infection
HMO – health maintenance organization
POS – point of service
PPO – preferred provider organization

Table 10: Results of two multivariable generalized ordered logit models* with partial proportional odds which examine associations between patient characteristics and the completion** of daily-dose isoniazid treatment for latent tuberculosis infection (N=1,072).

		Model 1: Includes Number of Medical/Diagnostic Risk Factors				Model 2: Includes Specific Medical/Diagnostic Risk Factors			
Independent Variables		Adjusted Odds Ratio	95% Confidence Interval		p-value	Adjusted Odds Ratio	95% Confidence Interval		p-value
Sex	Female	1.000				1.000			
	Male	1.085	0.855	1.378	0.501	1.045	0.818	1.335	0.724
Age Group	0-14	1.000				1.000			
	15-29	0.547	0.351	0.854	0.008	0.552	0.353	0.863	0.009
	30-44	0.597	0.385	0.925	0.021	0.599	0.386	0.930	0.022
	45-64	0.584	0.370	0.920	0.020	0.574	0.362	0.909	0.018
Census Region	Northeast	1.000				1.000			
	Midwest	0.934	0.588	1.483	0.772	0.933	0.587	1.484	0.771
	South	0.716	0.466	1.102	0.129	0.692	0.449	1.069	0.097
	West	0.989	0.676	1.448	0.956	0.967	0.661	1.416	0.864
Rural-Urban Category of County	Neither regimen completed vs. ≥6 months completed (completed 6 or 9 month regimen)								
	Large central metro county	1.000				1.000			
	Large fringe metro county	0.600	0.414	0.868	0.007	0.592	0.408	0.858	0.006
	Any smaller county	0.767	0.495	1.189	0.235	0.776	0.500	1.203	0.256
	<9 months completed (neither regimen or 6 month regimen completed) vs. ≥9 months completed								
	Large central metro county	1.000				1.000			
	Large fringe metro county	0.800	0.537	1.193	0.275	0.791	0.530	1.182	0.253
	Any smaller county	0.767	0.495	1.189	0.235	0.776	0.500	1.203	0.256

Independent Variables		Model 1: Includes Number of Medical/Diagnostic Risk Factors				Model 2: Includes Specific Medical/Diagnostic Risk Factors			
		Adjusted Odds Ratio	95% Confidence Interval		p-value	Adjusted Odds Ratio	95% Confidence Interval		p-value
% of Households Under FPL in County	<15%	1.000				1.000			
	≥15%	0.628	0.469	0.841	0.002	0.609	0.454	0.817	0.001
Insurance Type	Neither regimen completed vs. ≥6 months completed (completed 6 or 9 month regimen)								
	HMO	1.000				1.000			
	POS	1.434	0.981	2.097	0.063	1.513	1.032	2.218	0.034
	PPO	1.817	1.147	2.878	0.011	1.864	1.174	2.961	0.008
	<9 months completed (neither regimen or 6 month regimen completed) vs. ≥9 months completed								
	HMO	1.000				1.000			
	POS	1.434	0.981	2.097	0.063	1.513	1.032	2.218	0.034
	PPO	2.840	1.745	4.622	<0.001	2.921	1.789	4.767	<0.001
Prescription Size	Neither regimen completed vs. ≥6 months completed (completed 6 or 9 month regimen)								
	<2 month supply	1.000				1.000			
	≥2 month supply	1.419	0.884	2.278	0.148	1.395	0.867	2.245	0.170
	<9 months completed (neither regimen or 6 month regimen completed) vs. ≥9 months completed								
	<2 month supply	1.000				1.000			
	≥2 month supply	2.268	1.383	3.720	0.001	2.233	1.359	3.670	0.002
Year INH Regimen Started	2011 Q3-4	1.000				1.000			
	2012 Q1-4	1.109	0.802	1.532	0.531	1.104	0.798	1.526	0.551
	2013 Q1-4	1.268	0.906	1.774	0.167	1.261	0.901	1.766	0.177
	Q1 2014	1.333	0.720	2.468	0.361	1.333	0.718	2.473	0.363
State TB Rate		0.905	0.793	1.033	0.138	0.913	0.800	1.042	0.178

Independent Variables		Model 1: Includes Number of Medical/Diagnostic Risk Factors				Model 2: Includes Specific Medical/Diagnostic Risk Factors			
		Adjusted Odds Ratio	95% Confidence Interval		p-value	Adjusted Odds Ratio	95% Confidence Interval		p-value
LTBI Diagnostic Test	TST	1.000				1.000			
	IGRA	1.255	0.897	1.757	0.185	1.171	0.829	1.653	0.371
	Unknown/ Other	0.813	0.616	1.071	0.141	0.812	0.615	1.071	0.141
Percent Foreign Born in County		1.004	0.989	1.019	0.612	1.004	0.989	1.019	0.636
# of Clinical Risk Factors	None	1.000							
	1	1.522	1.158	2.001	0.003	na	na	na	na
	2 or more	1.816	1.188	2.778	0.006	na	na	na	na
Diagnosis of Contact w/ TB	No diagnosis	na	na	na	na	1.000			
	Had diagnosis	na	na	na	na	1.289	0.916	1.814	0.145
History of TB/Late Effects	No diagnosis	na	na	na	na	1.000			
	Had diagnosis	na	na	na	na	1.152	0.655	2.027	0.624
HIV	No diagnosis	na	na	na	na	1.000			
	Had diagnosis	na	na	na	na	2.578	1.377	4.827	0.003
Diabetes	No diagnosis or medication	na	na	na	na	1.000			
	Had diagnosis or medication	na	na	na	na	1.458	0.902	2.355	0.124
Tobacco	No diagnosis or medication	na	na	na	na	1.000			
	Had diagnosis or medication	na	na	na	na	1.254	0.766	2.052	0.368
Immuno-suppressive Medications	No medication	na	na	na	na	1.000			
	Had medication	na	na	na	na	1.470	0.997	2.167	0.052

Table 10 Footnotes:
* Constraints for parallel lines were applied to all independent variables except rural-urban category, insurance type, and isoniazid days supply received.
** For both models, isoniazid treatment completion was categorized as 1) less than 6 months completed, 2) at least 6 months but less than 9 months completed, and 3) 9 or more months completed.

Table 10 Abbreviations:
Mtb – Mycobacterium tuberculosis
INH – isoniazid
FPL – federal poverty level
TB – tuberculosis
TST – tuberculin skin test
IGRA – interferon-gamma release assays
LTBI – latent tuberculosis infection
HMO – health maintenance organization
POS – point of service
PPO – preferred provider organization

Significant clinical factors associated with treatment completion on bivariate analysis included IGRA testing, HIV, and immunosuppressive medication use. In the adjusted model, people with HIV had 2.5 times greater adjusted odds of an increased level of treatment completion than those without HIV. Additionally, both unadjusted and adjusted likelihood of completion was significantly associated with cumulative clinical risk. Compared to people with no clinical risk factors, those with one risk factor had 1.5 times greater adjusted odds and those with more than one risk factor had 1.8 times greater adjusted odds of an increased level of treatment completion.

Post hoc analyses identified significant associations between LTBI diagnostic test type and our model's explanatory variables (Table 11, following page). Diagnostic test type was significantly associated with age, region, rural-urban category, insurance plan type, year, clinical risk factor count, history of or late effects of TB, HIV, diabetes, tobacco use, and immunosuppressive medication use.

DISCUSSION

We used commercial insurance claims data to identify important individual, clinical, and system factors associated with LTBI treatment completion. Most striking were associations between a patient's insurance plan type and LTBI treatment completion, suggesting that benefit design is a potential means to modify patient behaviors and ultimately TB risk. HMO plans, typically the most tightly managed insurance design, were associated with lower likelihood of completion compared to POS and PPO plans; PPO plans were associated with the highest. The lower completion rates for HMO-insured individuals suggest a need for HMOs to

Table 11: Bivariate associations between *Mycobacterium tuberculosis* test type and other patient characteristics. Includes people initiating daily-dose isoniazid treatment (N=1,072).

		Mycobacterium tuberculosis Test Type			
		Tuberculin Skin Test [% or Mean]	Interferon-Gamma Release Assay [% or Mean]	Other/ Unknown Test [% or Mean]	p-value
Sex	Female	42.1%	19.8%	38.1%	0.767
	Male	40.0%	21.1%	38.8%	
Age Group	0-14	75.2%	8.6%	16.1%	<0.001
	15-29	51.5%	11.0%	37.5%	
	30-44	36.1%	20.9%	43.0%	
	45-64	27.0%	31.3%	41.7%	
Census Region	Northeast	46.6%	12.8%	40.6%	0.001
	Midwest	36.8%	21.3%	41.9%	
	South	41.9%	21.6%	36.5%	
	West	37.9%	26.4%	35.7%	
Rural-Urban Category of County	Large central metro county	41.1%	23.4%	35.5%	0.033
	Large fringe metro county	44.1%	17.2%	38.7%	
	Any smaller county	34.3%	20.0%	45.7%	
% of Households Under FPL in County	<15%	41.9%	20.8%	37.3%	0.672
	≥15%	40.1%	20.0%	39.9%	
Insurance Type	HMO	38.8%	13.3%	47.9%	0.015
	POS	41.1%	22.5%	36.4%	
	PPO	44.4%	19.0%	36.6%	
Prescription Size	<2 month supply	41.5%	20.0%	38.5%	0.428
	≥2 month supply	37.0%	25.9%	37.0%	
Year INH Regimen Started	2011 Q3-4	49.1%	23.2%	38.7%	0.001
	2012 Q1-4	36.2%	21.8%	42.0%	
	2013 Q1-4	40.5%	24.9%	34.7%	
	Q1 2014	54.4%	15.2%	30.4%	
State TB Rate		3.9	3.9	3.8	0.363
Percent Foreign Born in County		21.1	20.5	19.2	0.058

(Table Continued on Next Page)

		Mycobacterium tuberculosis Test Type			
		Tuberculin Skin Test [% or Mean]	Interferon-Gamma Release Assay [% or Mean]	Other/ Unknown Test [% or Mean]	p-value
# of Clinical Risk Factors	None	46.8%	14.5%	38.7%	<0.001
	1	36.8%	26.0%	37.2%	
	2 or more	17.9%	41.5%	40.6%	
Diagnosis of Contact w/ TB	No diagnosis	39.8%	20.6%	39.6%	0.058
	Had diagnosis	49.7%	19.5%	30.9%	
History of TB/Late Effects	No diagnosis	42.0%	20.2%	37.9%	0.031
	Had diagnosis	22.2%	36.7%	51.1%	
HIV	No diagnosis	42.4%	19.0%	36.5%	<0.001
	Had diagnosis	9.5%	54.8%	35.7%	
Diabetes	No diagnosis or medication	42.3%	19.8%	37.8%	0.010
	Had diagnosis or medication	24.7%	28.8%	46.6%	
Tobacco	No diagnosis or medication	42.1%	19.6%	38.3%	0.011
	Had diagnosis or medication	26.5%	32.3%	41.2%	
Immuno-suppressive Medications	No medication	43.8%	16.7%	39.6%	<0.001
	Had medication	21.0%	49.2%	29.8%	

Abbreviations:
Mtb – Mycobacterium tuberculosis
INH – isoniazid
FPL – federal poverty level
TB – tuberculosis
LTBI – latent tuberculosis infection
HMO – health maintenance organization
POS – point of service
PPO – preferred provider organization

monitor and conduct quality improvement initiatives that improve enrollees' LTBI treatment completion rates. Such activities would not be unusual – HMOs in most states are required to operate quality assurance programs that involve monitoring and conducting activities to improve care processes and clinical outcomes, such as improving medication adherence rates (Alexander et al., 2011). As private sector LTBI treatment becomes more common, the National Committee for Quality Assurance (NCQA) should consider incorporating an LTBI treatment completion measure into its standard set of quality performance measures (Healthcare Effectiveness Data and Information Set [HEDIS]) (National Committee for Quality Assurance [NCQA], 2016b). Health plans' quality improvement activities often focus on improving HEDIS rates, as many states consider quality assurance requirements met if plans maintain NCQA accreditation (Alexander et al., 2011) and plans are required to calculate HEDIS measures to attain and maintain accreditation (NCQA, 2016a).

Pharmacy benefit design and prescribing offer similar opportunities to improve treatment adherence and thus decrease TB risk. Individuals filling larger prescriptions (≥ 2 months supply) had greater odds of completing a 9-month regimen. Although we cannot be certain given data limitations, superior completion of the longer regimen may be due to the use of mail order pharmacies with automatic refill programs. Many insurers disallow community pharmacies from providing a >1-month supply of a medication. However, enrollees may be able to use mail order pharmacies to receive up to a 90-day supply (Pharmacy Benefit Management Institute, 2015), and mail order pharmacies are more likely than community pharmacies to have automatic refill programs (Brown & Rickles, 2010), These programs address patient passivity and transportation barriers by mailing prescription refills at regular intervals. Thus, encouraging

patients to fill larger prescriptions and use automated mail order programs may increase 9-month LTBI completion rates so long as appropriate clinical monitoring to avoid hepatotoxicity and other complications is ensured (CDC, 2013).

Our analysis suggests that private sector providers are likely sensitive to and communicating the importance of treatment completion for LTBI patients at especially high risk of active TB. In particular we found that patients with serious known risk factors such as HIV and immunosuppressive medication treatment are more likely to complete treatment than others (CDC, 2000). Correspondingly, treatment completion was increasingly likely as the total number of clinical risk factors increased. Nevertheless, there are opportunities to improve completion in high-risk private sector patients, as nearly half of those with one clinical risk factor and 45.3% of those with ≥1 risk factor completed <6 months of LTBI treatment. We also found that TST is much more likely to be used among young children than IGRA. This is consistent with CDC guidelines (Lewinsohn, 2016) and suggests that private providers are receiving CDC messaging related to best practices (Centers for Disease Control and Prevention, 2013) and are following these practices in their clinical decision making.

Our finding that IGRA is associated with greater likelihood of treatment completion aligns with anecdotal reports that IGRA testing may yield greater diagnostic confidence for both patient and provider relative to TST. However, the association is only significant in our unadjusted analysis. LTBI diagnostic test type is also associated with many other variables, including clinical risk factors, census region, insurance plan type, and year. After adjusting for these other variables, there is no significant association between the receipt of an IGRA and

treatment completion. It is unclear if the use of IGRA facilitates completion or if IGRA testing is more common in patients with other characteristics associated with treatment completion.

Claims are a rich source of information about commercial insurance-reimbursed LTBI treatment occurring across the US, but they have limitations. These data generally accurately reflect diagnoses and treatment (Virnig, 2001), but accuracy varies with the clarity of coding instructions and guidelines (CDC, 1994). There is ambiguity in the diagnostic and procedure coding for LTBI. For example, providers may be using the "contact with or exposure to tuberculosis" diagnosis code to represent LTBI status rather than known recent contacts. This might explain inconsistencies between our findings and prior reports of better completion rates among TB contacts (Li, 2010; Nyamathi, Christiani, Nahid, Gregerson, & Leake, 2006). On the other hand, many of our findings regarding LTBI treatment completion are consistent with past research, including associations with younger age and higher income (Hirsch-Moverman; Stuurman et al., 2016).

Data limitations also left us unable to identify important TB risk factors. Information about whether patients are foreign-born is not available. While 59% of foreign-born people in the US have private health insurance (Barnett, 2016), claims data do not identify nativity. Further, patient-level income data were not available. However, county-level nativity and FPL rates were included as proxies. Additionally, we cannot precisely determine treatment intent or adherence, and conclusions about provider and patient behavior are based on inference, not direct report. For instance, it is unclear whether a 6 or 9-month treatment regimen was prescribed for a given patient, or if a filled prescription was actually consumed. Of course, the latter applies to all medication adherence research not involving direct observation (McGinnis

et al., 2014). Despite these limitations, claims data provide unique opportunities to better understand LTBI treatment occurring in a setting of increasing importance for TB prevention.

Patient risks, provider and patient incentives or barriers, benefits design, and care processes in private healthcare differ substantially from that of public health programs. Our findings provide insight into the effect of these factors on LTBI treatment completion, enabling the development of evidence-based LTBI private sector treatment strategies. Such work is critical as more private healthcare providers provide LTBI treatment and as public health authorities consider the opportunities and limitations of private healthcare as a partner to US TB elimination efforts.

CHAPTER V

DISCUSSION AND CONCLUSION

Discussion

The results of our research described in the preceding chapters show that private sector providers already take an active role in domestic tuberculosis (TB) prevention-related patient care. Interferon-Gamma Release Assays (IGRA) and Tuberculin Skin Tests (TSTs) are not uncommon; more than 1 in 25 commercially insured persons received one or more of these tests in a three-year period. Latent Tuberculosis Infection (LTBI) treatment is also occurring in private sector settings, and 6-month isoniazid LTBI treatment completion rates are no lower than those reported for public health settings (Sandgren et al., 2016; Young et al., 2016). Private sector providers' LTBI testing and treatment patterns suggest that they are aware of and generally direct care in accordance with TB/LTBI risk factors as specified in CDC guidelines (Centers for Disease Control and Prevention [CDC], 2000; Mazurek et al., 2010). Both the likelihood of LTBI testing and the likelihood of completing LTBI treatment increase in association with TB/LTBI risk factors. In combination, these findings provide evidence that private sector healthcare practitioners provide healthcare services that could forward the goal of domestic TB elimination and suggest that more deliberate partnership is an important opportunity to leverage private resources toward this public health effort.

Progress towards domestic TB elimination has slowed (Salinas et al., 2016), indicating that new approaches to TB prevention are needed. The time is ripe for public health leaders to actively engage private sector healthcare providers in TB prevention efforts and shape LTBI-

related care in the private sector. The non-insured rate in the US is decreasing (Barnett, 2016), and insurance facilitates access to private sector healthcare services. Further, the US Preventive Services Task Force (USPSTF) recently recommended that populations at increased risk of TB be screened for LTBI (US Preventive Services Task Force [USPSTF] et al., 2016). This recommendation will not only raise provider and patient awareness of the importance of LTBI testing of high-risk individuals; with this recommendation the Affordable Care Act requires that TB/LTBI testing in high-risk populations be covered by health plans at no out of pocket cost to patients (H.R. 3590, 2010). Even in the absence of explicit requirements it is likely that the USPSTF recommendation would promote increased testing. In addition to raising awareness, the recommendations provide information regarding best practices and evidence-based medicine which facilitate the provision of quality care. In combination, these factors are likely to result in an increase in private sector LTBI testing and treatment. Thus, our research is much-needed and timely. Our findings offer important insights into the strengths and limitations of LTBI testing and treatment in the private sector setting and enable the development of evidence-based LTBI private sector treatment strategies.

Our research also illustrates how medical and pharmacy claims data from third party payers can serve as a means to understand and monitor TB prevention activities occurring in the private sector setting. Claims data not only provided evidence that LTBI testing and treatment is occurring in the private sector, these data showed that LTBI testing and treatment completion are associated with important TB/LTBI risk factors. Further, the data enabled us to identify new drivers of LTBI treatment completion that are unique to the private sector setting. Given that we only identified one other study that used claims data to examine LTBI-related

healthcare services in the private sector (Owusu-Edusei, Stockbridge, et al., 2017), claims data sources represent a largely untapped trove of information about private sector LTBI testing and treatment.

That said, we also identified that third party payer administrative claims data have important limitations when it comes to examining LTBI testing and treatment. These stem from the fact that the data were not collected for the purposes of research. Rather, claims data are generated when healthcare providers bill third party payers for services that patients received. As a result, only services submitted for payment are represented in claims data, and these data only include the information needed for a third party payer to process reimbursement payments to providers (Virnig, 2001). Important variables related to TB/LTBI risk are not required by payers and thus are not available in claims data, including country of birth. Similarly, claims data do not provide information about LTBI testing or treatment offered by a provider but not accepted by a patient.

We found that some LTBI-related healthcare services rendered by private sector providers to patients with commercial insurance may not be consistently represented in claims data. Specifically, procedure codes representing LTBI testing may not always be included on claims, likely because there is not a strong incentive for providers to consistently request reimbursement for TSTs given the low reimbursement amounts for these tests (Centers for Medicare & Medicaid Services, 2016). Additionally, 10.6% of the individuals that we identified as initiating LTBI treatment with isoniazid had no LTBI-related diagnoses or procedures in the medical claims prior to treatment initiation. Claims data did not allow us to determine if these individuals were prescribed isoniazid by public health departments but filled their prescription

through private pharmacies using insurance benefits or if private sector providers prescribed these individuals isoniazid for LTBI without coding associated diagnoses or procedures on medical claims.

In addition, the predominantly public sector approach to TB prevention has left gaps in how LTBI-related procedure and diagnosis codes are used in practice, including problematic challenges around diagnostic codes related to LTBI. When medical claims are submitted to payers they must include one or more diagnosis codes. However, there is not a code that specifically indicates that a patient has been diagnosed with LTBI. Table 12 (on the following page) lists the diagnosis codes related to LTBI. These codes are located in the "Symptoms, Signs and Abnormal Clinical Findings" chapter of the diagnosis code sets (Optum360, 2015; Optum, 2012), and they indicate that the patient has tested positive with a TST or IGRA and active TB is not present. However, while these two tests both provide evidence that someone has been infected with *Mycobacterium tuberculosis*, neither can distinguish between active and latent disease; a chest radiograph is required to rule out active TB (Lewinsohn, 2016). Further, false-positives are not uncommon in low-risk individuals, so confirmatory testing may be warranted to rule out LTBI after an initial positive TST or IGRA (Lewinsohn, 2016). It is unclear if providers are consistently ruling out active TB or false positive test results prior to assigning these codes. Ideally, an "abnormal clinical findings" diagnosis code would be included on claims after positive TST or IGRA test results, indicating to payers that further examinations are needed to rule out false positive results and active TB. Then, an LTBI-specific diagnosis code would be assigned after LTBI is diagnosed – but no such code exists.

Table 12: Diagnostic codes related to latent tuberculosis infection (LTBI) (Optum, 2012). These codes are located in the "Symptoms, Signs and Abnormal Clinical Findings" chapter of the code sets (Optum360, 2015; Optum, 2012). Medical claims for services rendered on or after October 1, 2015, are required to include one or more ICD-10-CM diagnosis codes, whereas medical claims from prior to that date included ICD-9-CM codes (Centers for Disease Control and Prevention, 2016b).

Version	Code	Description
ICD-9-CM	795.51	Nonspecific reaction to tuberculin skin test without active tuberculosis
ICD-9-CM	795.52	Nonspecific reaction to cell mediated immunity measurement of gamma interferon antigen response without active tuberculosis
ICD-10-CM	R76.11	Nonspecific reaction to tuberculin skin test without active tuberculosis
ICD-10-CM	R76.12	Nonspecific reaction to cell mediated immunity measurement of gamma interferon antigen response without active tuberculosis

The US recently transitioned from ICD-9 to ICD-10 diagnostic and procedural coding (CDC, 2016b). This change is expected to improve the quality of research and surveillance that relies on claims and other administrative data, as the newer code set better reflects the current understanding of medical conditions and more thoroughly captures diseases of public health interest (Bowman, 2008; Watzlaf, Garvin, Moeini, & Anania-Firouzan, 2007). Unfortunately, no ICD-10-CM diagnosis code representing LTBI was created. Thus, research and surveillance focused on LTBI, and subsequently the domestic TB elimination effort, will not reap the potential benefits of the change from ICD-9 to ICD-10. This is a lost opportunity. Additionally, many third party payers use algorithms which deny claims that do not contain appropriate diagnostic coding to justify the clinical necessity of treatments. It is plausible that private systems may avoid providing LTBI-related services if they have concerns that those services may be denied due to imprecise diagnostic coding. Improved diagnostic coding would result in

better administrative data quality and promote billable prevention activities, both of which are useful in forwarding domestic TB elimination.

Although the ICD-10 transition has passed, it is not too late for an LTBI diagnosis code to be created for use in the future. There are regular updates to the ICD-10 code sets. Two organizations, the Centers for Disease Control and Prevention (CDC) National Center for Health Statistics (NCHS) and the Centers for Medicaid and Medicare Services (CMS), share responsibility for the maintenance of ICD-10. NCHS has lead responsibility for ICD-10-CM, the diagnostic code set. Representatives from the two organizations co-chair the ICD-10 Coordination and Maintenance Committee which accepts suggestions for ICD-10 modifications from the public and private sectors (CDC, 2016a). We recommend that a proposal be submitted to this this committee requesting that an LTBI diagnosis code be added. As the CDC Division of Tuberculosis Elimination (DTBE) is part of the same organization as NCHS, this proposal is well suited for submission by DTBE leaders. Given the potential benefits to the domestic TB elimination efforts, such a proposal would align with the DTBE's strategic plan (CDC, 2015a).

If an LTBI diagnosis code were to be created, it would be appropriate for it to be located in the "Certain Infectious and Parasitic Diseases" chapter of the ICD-10-CM code set. Having an LTBI-specific code located within this chapter near or among the codes for active Tuberculosis (ICD-10-CM codes A15-A19) (Optum360, 2015) would be consistent with the code structure for other latent infectious diseases. For example, codes used for latent syphilis infection (see Table 13 on the following page) are located in the infectious disease chapter with the other syphilis ICD-10-CM codes (A50-A53) (Optum360, 2015; Optum, 2012). Additionally, if an LTBI diagnosis code is created, we recommend that the CDC release official guidelines for coding and reporting

LTBI-related diagnoses and services as was done when HIV-related ICD-9-CM codes were revised in 1994 (CDC, 1994). Such guidelines would facilitate the use of these codes and improve the accuracy of the information gleaned from administrative data.

Table 13: Diagnostic codes related to latent syphilis (Optum, 2012). These codes are located in the "Certain Infectious and Parasitic Diseases" chapter of the code sets.(Optum360, 2015; Optum, 2012) Medical claims for services rendered on or after October 1, 2015, are required to include one or more ICD-10-CM diagnosis codes, whereas medical claims from prior to that date included ICD-9-CM codes (Centers for Disease Control and Prevention, 2016b).

Version	Code	Description
ICD-9-CM	090.1	Early congenital syphilis, latent
ICD-9-CM	090.6	Late congenital syphilis, latent
ICD-9-CM	092.0	Early syphilis, latent, serological relapse after treatment
ICD-9-CM	092.9	Early syphilis, latent, unspecified
ICD-9-CM	096	Late syphilis, latent
ICD-9-CM	097.1	Latent syphilis, unspecified
ICD-10-CM	A50.1	Early congenital syphilis, latent
ICD-10-CM	A50.6	Late congenital syphilis, latent
ICD-10-CM	A51.5	Early syphilis, latent
ICD-10-CM	A52.8	Late syphilis, latent
ICD-10-CM	A53.0	Latent syphilis, unspecified as early or late

Despite the current limitations of administrative claims data and the code sets used therein, even today these data enable public health leaders to gain important insights about private sector LTBI-related healthcare provided to broad populations over long periods of time. Our research serves as an example; medical and pharmacy claims data allowed us to examine commercial insurance-covered LTBI testing and treatment services received by four million people located across the US, and we were able to track these and other healthcare services for each person over a period of ≥3 years. Additionally, these data enabled us to determine if and to what degree important clinical variables are associated with LTBI testing and treatment

completion. Primary data collection on a similar scale would be resource intensive and cost prohibitive (Virnig, 2001). Thus, claims data open new avenues to monitor, evaluate, and ultimately shape LTBI-related healthcare services.

Future Research

Much additional information about private sector TB prevention-related services could be gleaned from further analysis of medical and pharmacy claims data. One opportunity for future research involves exploring the differences in the characteristics of those receiving a TST versus an IGRA. The recent release of the American Thoracic Society (ATS) /Infectious Diseases Society of America (IDSA)/CDC clinical practice guidelines specify some groups of people for whom an IGRA is preferable and others for whom a TST is preferable (Lewinsohn, 2016). While we examined the characteristics associated with the receipt of one or more TSTs or IGRAs in our research described in Chapter 2, the results of that analysis do not explore who is receiving each type of test. We also explored bivariate associations between the test type used to diagnose LTBI and the characteristics of patients initiating LTBI treatment (see Chapter 4), but this group represents a small subset of all persons receiving a test. An analysis exploring testing practices prior to the release of the ATS/IDSA/CDC guidelines would provide insight into areas where private sector providers may benefit from additional messaging. Moreover, the impact of these guidelines on private sector clinical practice could be assessed by comparing which individuals were more or less likely to receive each type of test before and after the release of the guidelines.

Additionally, we observed some people receiving more than one test; some received both a TST and an IGRA while others were tested multiple times with the same type of test. Further analyses might explore how frequently individuals are getting >1 test, in what time period (e.g., does it appear to be annual testing or does a second test follow soon after the first), with which test type(s), and what are the characteristics of the patients being retested. The results of these analyses might provide a way to quantify the volume of the testing in the private sector that is occurring for routine, administratively required purposes. These data would permit a quantification of potentially wasteful testing. Further, we may see a stronger relationship between TB/LTBI risk factors and TST/IGRA testing (as was explored in Chapter 2) if individuals with apparent administrative testing are identified and removed from analysis. This finding would suggest that we likely underestimated the robustness of risk-targeted testing in those persons who are not getting routine testing.

The research described in Chapter 2 examines TST and IGRA testing occurring within a three-year period and explores whether that testing is associated with specific health conditions, healthcare services, and medications described in claims for the same three-year period. While the results of that research provide important information about targeted testing in the private sector, this method did not examine the point in time that the testing occurred relative to these conditions/services/prescriptions. To more thoroughly understand testing patterns, future research could incorporate temporality when examining LTBI testing. For example, patients should be evaluated for *Mycobacterium tuberculosis* infection prior to initiating treatment with immunosuppressive medications (Winthrop, Siegel, Jereb, Taylor, & Iademarco, 2005). While the research described in Chapter 2 establishes that TST/IGRA testing

is common in patients taking immunosuppressive medications, our results do not indicate whether the testing is typically occurring prior to, shortly after, or long after the first time the immunosuppressive medication is prescribed or administered. Similarly, testing might be expected to occur shortly after a patient is newly diagnosed with a medical condition associated with a risk of progression from LTBI to active TB (e.g., HIV, diabetes). Examining temporality would provide additional insight into care quality.

Other areas of research involve exploring testing trends over time using medical claims data. Analyses of the Truven Health MarketScan® Commercial Claims Database provide evidence that LTBI testing is becoming more common in private practice, with IGRA use increasing and TST use decreasing (Owusu-Edusei, Stockbridge, et al., 2017). Replicating this past study with the commercial health insurance data from the Optum Impact National Research Database (Optum, 2015) used in the research described in the previous chapters would lend insight into the robustness of those findings. Further, the study conducted on the Marketscan data did not identify tests that were coded using only the diagnosis code for "special screening examination for pulmonary tuberculosis, including diagnostic skin testing" which we identified and discussed in Chapter 2 (Optum, 2012). Incorporating that code would provide a more accurate measure of the volume of LTBI testing occurring in the commercially insured US population.

Future research using medical and pharmacy claims data could also further explore LTBI treatment occurring in the private sector. We developed a claims-based method to identify and assess treatment completion in persons being treated for LTBI with isoniazid (see Chapter 3), but shorter-course regimens also exist and claims-based methods to identify treatment with

those regimens are needed. These shorter regimens include: 1) a three month course of isoniazid and rifapentine administered weekly via directly observed therapy (DOT), and 2) a four-month course of daily self-administered rifampin (CDC, 2016c). While these regimens have not been used in practice as commonly as isoniazid (Horsburgh et al., 2010) there is increasing interest in these shorter course options because they are associated with higher rates of treatment completion (Sandgren et al., 2016; Young et al., 2016). We are currently finalizing a claims-based algorithm to identify rifampin LTBI treatment initiation and completion. Because rifampin and isoniazid are both self-administered, the rifampin algorithm will be somewhat similar to the isoniazid regimen in that both will identify the medication of interest within the pharmacy claims data. Conversely, because the three month course of isoniazid and rifapentine is administered via DOT, pharmacies are likely not dispensing these medications and thus there will likely be no pharmacy claims. Consequently, a different approach will be needed in order to identify this regimen within claims data. More research is necessary to determine if or how a claims-based method could examine treatment initiation and completion of the three month course of isoniazid and rifapentine administered via DOT.

Other applications of claims data include disease outcome modeling. LTBI treatment reduces the risk of progression to active TB (Kahwati et al., 2016). The decreasing risk of disease progression has been quantified at increasing levels of LTBI treatment completion (International Union Against Tuberculosis: Committee on Prophylaxis, 1982). This information could be combined with the information gleaned from the claims data regarding the prevalence and duration of LTBI treatment in order to estimate the number of TB cases averted through private sector LTBI treatment. Additionally, treatment prevalence and duration could be varied

in the model to quantify the potential benefits of more widespread private sector LTBI treatment or improvements in treatment completion. Similarly, risk-related clinical variables (e.g., HIV, diabetes) could be incorporated to determine potential differences in outcomes with different risk-targeting strategies.

Claims data could also be used to examine expenditures for LTBI services in the private sector. Such data have been used previously to examine expenditures for inpatient TB treatment in the US (Owusu-Edusei, Marks, Miramontes, Stockbridge, & Winston, 2017), but we identified no prior research that used claims data to examine expenditures for LTBI treatment. Expenditures would be expected to vary by regimen because the different regimens involve different medications. Further, a course of LTBI treatment ranges from three to nine months depending on the regimen (CDC, 2016c), and each of the regimens requires at least monthly clinical assessments (CDC, 2000, 2011). The results of this expenditure research could then be used in future studies examining the costs versus the benefits of LTBI treatment in the private sector. Further, information about expenditures, clinical risk, and reductions in the risk of progression, given the degree of treatment completion, could be combined to conduct cost effectiveness analyses, the results of which would provide insight on how to efficiently focus private sector healthcare resources to maximize value.

Clearly medical and pharmacy claims data could provide a great deal of information about distinct facets of LTBI testing and treatment in the private sector. However, there is also a need to examine the different steps of the LTBI identification and treatment process as a whole. The steps of this process, from identification of at-risk populations to the completion of LTBI treatment, are collectively referred to as the LTBI cascade of care (Alsdurf, Hill, Matteelli,

Getahun, & Menzies, 2016; Dheda, 2016). Researchers using medical and pharmacy claims data can monitor the healthcare services received by individual patients over time, so these data may provide insight into the volume of individuals in private sector care who are flowing through the different steps of the LTBI cascade of care. While it is likely that not all steps in the care cascade will be evident within claims data, it would be worthwhile to explore what can and cannot be learned from these data given the importance of the LTBI care cascade to domestic TB elimination.

The research and methods described in the previous chapters were based on commercial insurance claims; consequently, only commercially insured individuals were represented. However, medical and pharmacy claims data would also be of use in examining LTBI-related services in other US populations. The codes used to represent diagnoses, procedures, and medications are generally consistent across claims for private and public third party payers (Cleverley et al., 2010) so the methods we developed may be useful in analyzing claims data from Medicare and Medicaid. Additionally, the research we have already conducted could be replicated on public payer data and the claims-based research proposed above could also be conducted on public payer data.

LTBI research on publicly insured individuals is of great importance; it is probable that LTBI is more prevalent in this population as compared to commercially insured individuals given that many characteristics associated with LTBI are also associated with a higher likelihood of having public insurance. For example, education level, poverty, and race/ethnicity are each associated with insurance coverage type and LTBI risk (Barnett, 2016; Miramontes et al., 2015). However, we identified no studies which specifically examine LTBI prevalence by insurance

type. National Health and Nutrition Examination Survey (NHANES) data have been used to examine LTBI prevalence previously (Bennett et al., 2008; Mancuso et al., 2016; Miramontes et al., 2015) and the data also includes self-reported insurance type (CDC, 2015b). Consequently, NHANES data could be used to examine whether there is varying LTBI prevalence rates in persons with private insurance, Medicare, Medicaid, and dual Medicare/Medicaid coverage. This information would assist in prioritizing claims-based research for these different populations, and it would provide insight to public health leaders who might wish to partner with third party payers on TB prevention efforts.

Conclusions

Private sector providers already take an active and effective role in domestic tuberculosis (TB) prevention efforts. LTBI testing is not uncommon in the private sector setting, and LTBI treatment is occurring as well. LTBI testing and treatment completion patterns suggest that private sector providers are aware of and generally direct care in accordance with TB/LTBI risk factors as specified in CDC guidelines. In combination, these findings provide evidence that private sector healthcare providers can effectively work alongside public health leaders to forward the goal of domestic TB elimination. There is a great opportunity to develop commercial healthcare as a valuable adjunct to the traditional public health TB prevention venues. Additionally, claims-based methods offer a means to gain important insights and open new avenues to monitor, evaluate, and coordinate TB prevention. Medical and pharmacy claims data from private and public third party payers represent a largely untapped trove of information about private sector TB prevention activities. The information we have gleaned

from claims data, the methods we have developed which leverage claims data, and the light we have shined on the promise of claims data all serve to forward the important goal of domestic TB elimination.

APPENDIX 1

FURTHER EXPLORATION OF ASSOCIATIONS BETWEEN TST/IGRA TESTING AND COPD, GASTRECTOMY/GASTRIC BYPASS, DRUG USE DISORDER, AND LEUKEMIA/LYMPHOMA

COPD, gastrectomy/gastric bypass, drug use disorder, and leukemia/lymphoma had associations with TST/IGRA testing that differed in significance and/or direction in the adjusted and unadjusted analyses. Further analyses were conducted to understand these differences. The key variables driving the differences in associations are described in Table 14 below.

Table 14: Exploration of relationship between select variables and TST/IGRA testing (N= 3,997,986)

Variable	Relationship with TST/IGRA Testing	Data Exploration Results
COPD	No significant association with TST/IGRA testing in unadjusted analysis, significantly associated with increased likelihood of TST/IGRA testing in adjusted model.	Age is associated with both TST/IGRA testing and COPD. When age is not taken into consideration, the association between COPD and TST/IGRA testing no longer exists.
Gastrectomy/ Gastric bypass	No significant association with TST/IGRA testing in unadjusted analysis, significantly associated with increased likelihood of TST/IGRA testing in adjusted model.	Age is associated with both TST/IGRA testing and gastrectomy/gastric bypass. The association between gastrectomy/gastric bypass and TST/IGRA testing is no longer significant when age is held constant.

Variable	Relationship with TST/IGRA Testing	Data Exploration Results
Drug Use Disorder	Significantly associated with increased likelihood of TST/IGRA testing in unadjusted analysis, non-significant in adjusted analyses.	Alcohol use disorders are associated with both drug use disorders and TST/IGRA testing. When alcohol use disorders are excluded from the multivariable model, the relationship between drug use disorders and TST/IGRA testing remains significant.
Leukemia/ Lymphoma	Associated with significant increase in likelihood of TST/IGRA testing in unadjusted model, but associated with a significant decrease in likelihood of testing in adjusted model.	Age is associated with both TST/IGRA testing and leukemia/lymphoma. When age is taken into account, there is a lower likelihood of TST/IGRA testing for people with leukemia/lymphoma.

APPENDIX 2

SENSITIVITY OF COMPLETION RATE ESTIMATES TO VARYING ACTIVE TUBERCULOSIS EXCLUSION LOGIC

Individuals diagnosed with active TB in the 12 months after the date that the first isoniazid prescription was filled were excluded from the latent tuberculosis infection (LTBI) treatment completion analyses (Figure 1 Cell 13). These people likely had active TB but were initially misdiagnosed with LTBI or they had LTBI which developed into active TB during their course of treatment. The 12 month time period was selected because people who initiate LTBI treatment with isoniazid are given 12 months to complete a 9 month course of treatment (Horsburgh et al., 2010).

However, due to the limitations of claims data there is a degree of uncertainty about when the active TB developed, and changes in assumptions would result in changes in the inclusion or exclusion of a subset of these individuals who have an active tuberculosis diagnosis in this 12 month period. This appendix explores how the inclusion and exclusion of various groups based on different assumptions affects the obtained completion rates. The groups of interest are as follows:

- **Groups A1 & A2**: Individuals who did not complete 6 or 9 months of treatment, respectively, who have a diagnosis of active tuberculosis after their last day of isoniazid medication (i.e., the prescription fill date plus the days supply of isoniazid obtained on that date) but before the end of the 12 month period. These people might be included in the completion analyses if one assumes that 1) the active tuberculosis did not develop until after the treatment was discontinued, and 2) tuberculosis might have been prevented had the treatment not been discontinued. Including these individuals would decrease the obtained completion rate.

- **Groups B1 & B2**: Individuals who completed 6 or 9 months of treatment, respectively, who have a diagnosis of active tuberculosis after their last day of isoniazid medication but before the end of the 12 month period. These people might be included in completion analyses if one assumes that active tuberculosis did not develop until after the treatment was completed. Including these individuals would increase the obtained completion rate.

In order to determine the magnitude of the change in the completion rate estimates under these different assumptions, we recalculated the completion rates a number of different ways. The results are shown in Table 15 below.

Table 15: Exploration of varying latent tuberculosis infection (LTBI) treatment completion rate estimates under different assumptions about tuberculosis diagnosed after the initiation of LTBI treatment.

	# in Denominator	# Completing 6 Months of Isoniazid	6 Month Completion Rate & 95% Confidence Interval	# Completing 9 Months of Isoniazid	9 Month Completion Rate & 95% Confidence Interval
No change to logic	1,074	497	46.3% (43.3, 49.3)	243	22.6% (20.2, 25.2)
Group A1* not excluded	1,085	497	45.8% (42.8, 48.8)	243	22.4% (20.0, 25.0)
Group A2** not excluded	1,087	499	45.9% (43.0, 48.9)	243	22.3% (20.0, 24.9)
Group B1† not excluded	1,077	500	46.4% (43.5, 49.4)	244	22.7% (20.2, 25.3)
Group B2‡ not excluded	1,075	498	46.3% (43.4, 49.3)	244	22.7% (20.3, 25.3)
Groups A1-B2 not excluded	1,088	500	45.9% (43.0, 48.9)	244	22.4% (20.0, 25.0)

* Group A1: Individuals who did not complete 6 months of treatment and who have a diagnosis of active tuberculosis after their last day of isoniazid medication but before the end of the 12 month period.

** Group A2: Individuals who did not complete 9 months of treatment and who have a diagnosis of active tuberculosis after their last day of isoniazid medication but before the end of the 12 month period.

† Group B1: Individuals completed 6 months of treatment and who have a diagnosis of active tuberculosis after their last day of isoniazid medication but before the end of the 12 month period.

‡ Group B2: Individuals completed 9 months of treatment and who have a diagnosis of active tuberculosis after their last day of isoniazid medication but before the end of the 12 month period.

The 6 and 9 month completion rates calculated with varying logic differ less than 1% from the completion rates obtained with no change to the logic. These results indicate that the completion rates based on our algorithm are robust to excluding or including certain patients who have a TB diagnosis given after the initiation of isoniazid treatment for LTBI. Given these findings, and given the added complexity of the alternative options which would affect future users of the algorithm, the original logic was retained.

Please note that a manuscript describing this sensitivity testing has been provisionally accepted for publication in the Journal of Public Health Management and Practice. Please cite that journal article rather than this dissertation when referencing this testing (Stockbridge, Miller, Carlson, & Ho, 2017).

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