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MAJOR ARTICLE

Prior Screening for Latent Tuberculosis Among Patients Diagnosed With Tuberculosis Disease: Missed Opportunities?

Heidi Fischer,[1] Lei Qian,[1] Zhuoxin Li,[1] Saadiq Garba,[2] Katia J. Bruxvoort,[1,3] Jacek Skarbinski,[4,5] Jennifer H. Ku,[1] Bruno J. Lewin,[6,7] Parag S. Mahale,[1] Sally F. Shaw,[1] Brigitte C. Spence,[1] and Sara Y. Tartof[1,2]

[1]Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, California, USA, [2]Department of Health Systems Science, Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, California, USA, [3]Department of Epidemiology, University of Alabama at Birmingham, Birmingham, Alabama, USA, [4]Division of Research, Kaiser Permanente Northern California, Oakland, California, USA, [5]Department of Infectious Diseases, Oakland Medical Center, Kaiser Permanente Northern California, Oakland, California, USA, [6]Department of Family Medicine, Kaiser Permanente Los Angeles Medical Center, Los Angeles, California, USA, and [7]Department of Clinical Science, Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, California, USA

Background. California has the largest number of tuberculosis (TB) disease cases in the United States. This study in a large California health system assessed missed opportunities for latent tuberculosis (LTBI) screening among patients with TB disease.

Methods. Kaiser Permanente Southern California patients who were ≥18 years old with membership for ≥24 months during the study period from 1 January 2008 to 31 December 2019 were included. Prior LTBI test (tuberculin skin test or interferon-γ release assay) or diagnosis code prior to TB disease diagnosis was assessed among patients with observed TB disease (confirmed by polymerase chain reaction and/or culture). In the absence of current treatment practices, more patients screened for LTBI may have developed TB disease. We estimated hypothetical TB disease cases prevented by multiplying LTBI progression rates by the number of LTBI-positive patients prescribed treatment.

Results. A total of 1289 patients with observed TB disease were identified; 148 patients were LTBI positive and 84 were LTBI negative. Patients not prescreened for LTBI made up 82.0% of observed TB disease cases (1057/1289). Adding the hypothetical maximum estimate for prevented cases decreased the percentage of patients who were not prescreened for LTBI to 61.7% [1057/(1289 + 424)].

Conclusions. One-fifth of patients were screened for LTBI prior to their active TB diagnosis. Assuming the upper bound of cases prevented through current screening, almost 62% of TB disease patients were never screened for LTBI. Future work to elucidate gaps in LTBI screening practices and to identify opportunities to improve screening guidelines is needed.

Tuberculosis (TB) disease, caused by *Mycobacterium tuberculosis* (*Mtb*), results in substantial morbidity and mortality [1]. *Mtb* infection is spread from person to person through airborne droplets. Although some persons exposed to *Mtb* will immediately develop TB disease, most persons who become infected with *Mtb* are able to contain their infection [2]. These people have latent tuberculosis (LTBI), an asymptomatic infection. TB disease can later progress from LTBI through a complex spectrum of conditions, and those with LTBI have an estimated lifetime risk of 5%–10% of developing TB disease from LTBI progression [3–5]. California has the largest number of TB disease cases in the United States (US), with 22% of TB cases in 2021 originating in California [6]. As a state meeting thresholds for the highest level of TB incidence and cases, California has been highlighted by the Centers for Disease Control and Prevention as an area where prevention efforts must be expanded [7]. More than 2 million Californians are estimated to have LTBI, and 87% of TB disease cases in 2021 were attributed to progression from LTBI [8]. In 2019, total medical and societal costs of TB in California exceeded $210 million [9].

Screening and treatment are highly effective at preventing progression from LTBI [10–12]. Current screening guidelines developed by the California Department of Public Health (CDPH) provide a framework for providers to conduct LTBI screening, recommending screening for those with birth, travel, or residence in a country with high TB incidence ("HTBIC"; definition used by the CDPH that includes all individuals born outside of the US, Northern or Western Europe, Canada, or Australia/New Zealand), planned or current immunosuppression, or close contact with a person with TB disease during their lifetime [13]. However, providers face challenges

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Correspondence: Heidi Fischer, PhD, MS, Department of Research and Evaluation, Kaiser Permanente Southern California, 100 S. Los Robles Ave, Pasadena, CA 91505 (heidi.fischer@kp.org); Sara Y. Tartof, PhD, MPH, Department of Research and Evaluation, Kaiser Permanente Southern California, 100 S. Los Robles Ave, Pasadena, CA 91505 (sara.y.tartof@kp.org).

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in implementing guidelines, as many of these risk factors are not readily identifiable in patients' electronic health records (EHRs) and providers have competing priorities in the limited time of a medical encounter. This may result in failures to identify patients with LTBI before progression to TB disease, leading to unnecessary health and financial burdens. This study in a large California health system aims to describe missed opportunities for LTBI screening among patients with TB disease to aid in future LTBI screening policies.

METHODS

Study Setting

The study was conducted at Kaiser Permanente Southern California (KPSC), which provides healthcare coverage and services to >4.8 million racially and socioeconomically diverse members across California [14]. Members are enrolled through employer-provided, prepaid, or federally sponsored plans. KPSC has comprehensive EHRs, which capture details of care received during ambulatory, emergency department, and inpatient encounters, including diagnoses, procedures, laboratory tests, and pharmacy records. Although members have incentive to seek care at facilities within KPSC, care received at outside facilities is generally captured as part of claims reimbursement and integrated into the EHR.

Patient Consent Statement

This study was approved by the KPSC Institutional Review Board, with a waiver of informed consent, as this data-only study posed minimal risk to study participants.

Population

The study population consisted of KPSC members aged ≥18 years with KPSC membership for a minimum of 24 consecutive months at any point between January 2008 through December 2019, allowing for a 45-day gap. The index date was defined as the first day of consecutive membership. TB disease was defined by a positive culture or nucleic acid amplification for *Mtb*. Patients were excluded if there was indication of TB disease before index date. Patients who tested positive for TB disease at any point between the index date and 31 December 2019 were considered to have TB disease.

Other Variables

Demographic and clinical characteristics identified a priori were collected from the EHR for the study population. These included age at index date (18–35, 36–49, 50–64, 65–74, ≥75 years), sex (male, female), race/ethnicity (White, Asian, Black, Hispanic, Hawaiian/Pacific Islander, other/unknown), country of birth (born in HTBIC or not born in HTBIC, with missing values imputed using a previously published algorithm) [15], language preference (prefers to speak a language associated with an HTBIC, yes or no), Neighborhood Deprivation Index quintile of patient's census tract, immunocompromised status before TB disease (defined as solid organ transplantation including heart, lung, heart-lung, kidney, liver, pancreas, and intestine; use of high-dose steroid; use of tumor necrosis factor–α inhibitor; use of chemotherapy/immunomodulator; head and neck cancer; leukemia; or human immunodeficiency virus infection), Charlson Comorbidity Index score (0, 1–3, or ≥4), travel to an HTBIC for >30 days prior to TB disease [16], and recorded exposure to someone with TB disease prior to TB disease as defined by *International Classification of Diseases* diagnosis code (*ICD-9* V01.1, *ICD-10* Z20.1). To understand screening patterns by CDPH-recommended screening criteria, a composite variable was created to indicate if a patient was born in an HTBIC, traveled to an HTBIC for >30 days, was immunosuppressed, or had recorded exposure to someone with TB disease ("CDPH screening recommended").

Analyses

Patients with TB disease were categorized by whether they received a prior LTBI test, defined as either a tuberculin skin test (TST) or an interferon-γ release assay (IGRA), or in the absence of an LTBI test, an LTBI diagnosis code (Supplementary Table 1) during the study period. For patients receiving consistent care at KPSC, positive LTBI laboratory results from tests outside of KPSC that may not be part of claims data (such as from a federal immigration authority) or from within KPSC before the study period are typically captured in subsequent encounters during the study period through diagnosis codes.

LTBI tests and diagnoses can occur as part of advanced screening for LTBI or as part of the clinical diagnostic strategy for a patient with suspicion of having TB disease. We categorized patients who received LTBI tests/diagnoses into 2 groups. The first group received their first LTBI test/diagnosis >60 days before testing positive for TB disease; these individuals were screened in advance for LTBI, found to be LTBI positive or negative, and most likely acquired TB disease later due to progression or recent exposure, respectively ("prescreened for LTBI"). The second group received their LTBI test/diagnosis within 60 days of, or after, testing positive for TB disease; these individuals were tested for or diagnosed with LTBI simultaneously with or after testing positive for TB disease, so they were not screened in advance for LTBI ("not prescreened for LTBI"). Due to the slow nature of TB progression, a 60-day period was selected to allow for diagnostic workup of suspected TB disease [17, 18]. Patients who did not have an LTBI test/diagnosis at any time in the study period were also considered not prescreened for LTBI.

Patients who were prescreened for LTBI were further categorized into whether they ever tested positive or only tested negative for LTBI, with patients receiving either a positive LTBI test or a diagnosis code categorized as testing positive ("LTBI positive") and patients with only negative LTBI tests categorized as testing negative ("LTBI negative"). LTBI-positive patients were further categorized by whether or not they had

ever filled an LTBI treatment prescription (isoniazid [INH], rifampin, or rifamycin-INH short-course combinations [INH + rifampin or INH + rifapentine]) before testing positive for TB disease ("prescribed LTBI treatment").

To provide a more complete picture of LTBI screening among patients with TB disease, it is useful to understand the number of TB disease cases that may have been averted due to current LTBI treatment practices. Since this quantity is nonobservable, we estimated a range for the number of TB disease cases averted during the study period. We estimated this range by first categorizing those LTBI positive in the overall KPSC study population (including those who never developed TB disease) into those who were and those that were not prescribed LTBI treatment. We then defined a lower and upper bound for the hypothetical TB disease progression rate during the study period, supported by data and literature. We calculated the lower bound for the progression rate as the ratio of the number of TB disease cases in the LTBI-positive population not prescribed LTBI treatment during the study period to the full population not prescribed LTBI treatment, making the lower bound estimate a data-driven progression estimate from our LTBI-positive population. To estimate an upper bound for cases averted, we utilized 95 percentile estimates for age-specific lifetime risks of TB progression from nonconversion positive skin tests as described by Horsburgh [19]. Using the age-specific rates, we calculated the risk of TB progression for each LTBI-positive patient prescribed LTBI treatment (had they not been treated) by adjusting the average study period for each patient's remaining life-years. A step-by-step explanation of this calculation can be found in Supplementary Table 2. We arrived at the upper bound estimate by averaging estimated risks across the full population. We calculated the range of averted cases through current treatment practices by multiplying a range of rates from the lower to upper bound estimates by the number in the full LTBI-positive population not prescribed LTBI treatment who did not have TB disease during the study period (Figure 1).

We then added these hypothetical averted TB disease cases to the category of prescreened LTBI-positive patients with TB disease. We explored how the percentage of TB disease cases that were not prescreened for LTBI changed as we varied the number of averted cases estimated from the lower to upper bound estimates of TB disease progression.

Demographic and clinical characteristics were presented descriptively for patients with observed TB disease in the study population by each testing pattern grouping, as well as for LTBI-positive patients without TB disease who were prescribed treatment for LTBI during the study period.

RESULTS

We identified 1289 (0.032%) patients with TB disease among 4 016 699 patients meeting the inclusion criteria during the study period. Figure 2 shows how the 1289 patients with observed TB disease were categorized into each testing group as well as illustrating how averted TB disease cases calculated in Figure 1 are integrated into the analysis (orange box in Figure 2). Considering only the 1289 observed TB disease cases ($r = 0$ in Figure 2), 937 (72.7%) of these patients were tested or given a diagnosis code for LTBI during the study period. However, 705 of these 937 (75.2%) received their first LTBI test or diagnosis within 60 days prior to their TB disease diagnosis and thus were not prescreened for LTBI. Patients prescreened for LTBI who identified as being LTBI positive made up 11.5% (148/1289) of observed TB disease cases, with 18 of these 148 (12.2%) being prescribed treatment for LTBI before onset of TB disease, leaving 130 cases who were not prescribed treatment.

Before incorporating averted TB disease cases through current screening and treatment practices (assuming $r = 0$ in Figure 2), 1057 of 1289 TB disease cases (82.0%) were not prescreened for LTBI. To estimate hypothetical TB disease cases averted, we considered the lower bound estimate for r as the ratio of TB disease cases observed among LTBI-positive patients who were not prescribed treatment for LTBI (n = 130) to the full population not prescribed LTBI treatment (n = 114 171, adding the 130 patients with TB disease to the 114 041 patients without TB disease in Figure 1), to arrive at $r = 0.11\%$. To estimate our upper bound, we averaged across the study period adjusted 95th percentile upper bound TB progression risks for each patient in our patient population receiving an LTBI prescription to give an upper bound for the progression rate risk estimate of 1.99%. We identified 21 329 patients prescribed LTBI treatment who were LTBI positive and did not develop TB disease during the study period (Figure 1). Assuming 21 329 * r patients will progress to TB disease in the absence of treatment, our lower and upper bounds for progression rates led us to estimate between 24 and 424 cases averted.

Figure 3 shows how progression rates between the upper and lower bounds change the percentage of TB disease cases not prescreened for LTBI. At the lower bound for r where 24 cases were averted, 80.5% of TB disease cases are not prescreened for LTBI (1057 cases not prescreened divided by 1289 + 24 total cases), while at the upper bound where 424 cases were averted, 61.7% of cases are not prescreened for LTBI (1057 divided by 1289 + 424 total cases).

Table 1 presents demographic characteristics for patients with observed TB disease by testing group (n = 1289), as well as characteristics of LTBI-positive patients prescribed LTBI treatment in the study population who did not develop TB disease (n = 21 329). A total of 18 LTBI-positive patients who were prescribed LTBI treatment and did develop TB disease were included in the prescreened, LTBI-positive category (18 of 148 patients).

Patients recommended to be screened by the CDPH made up 66% (n = 14 138) of LTBI-positive patients prescribed LTBI

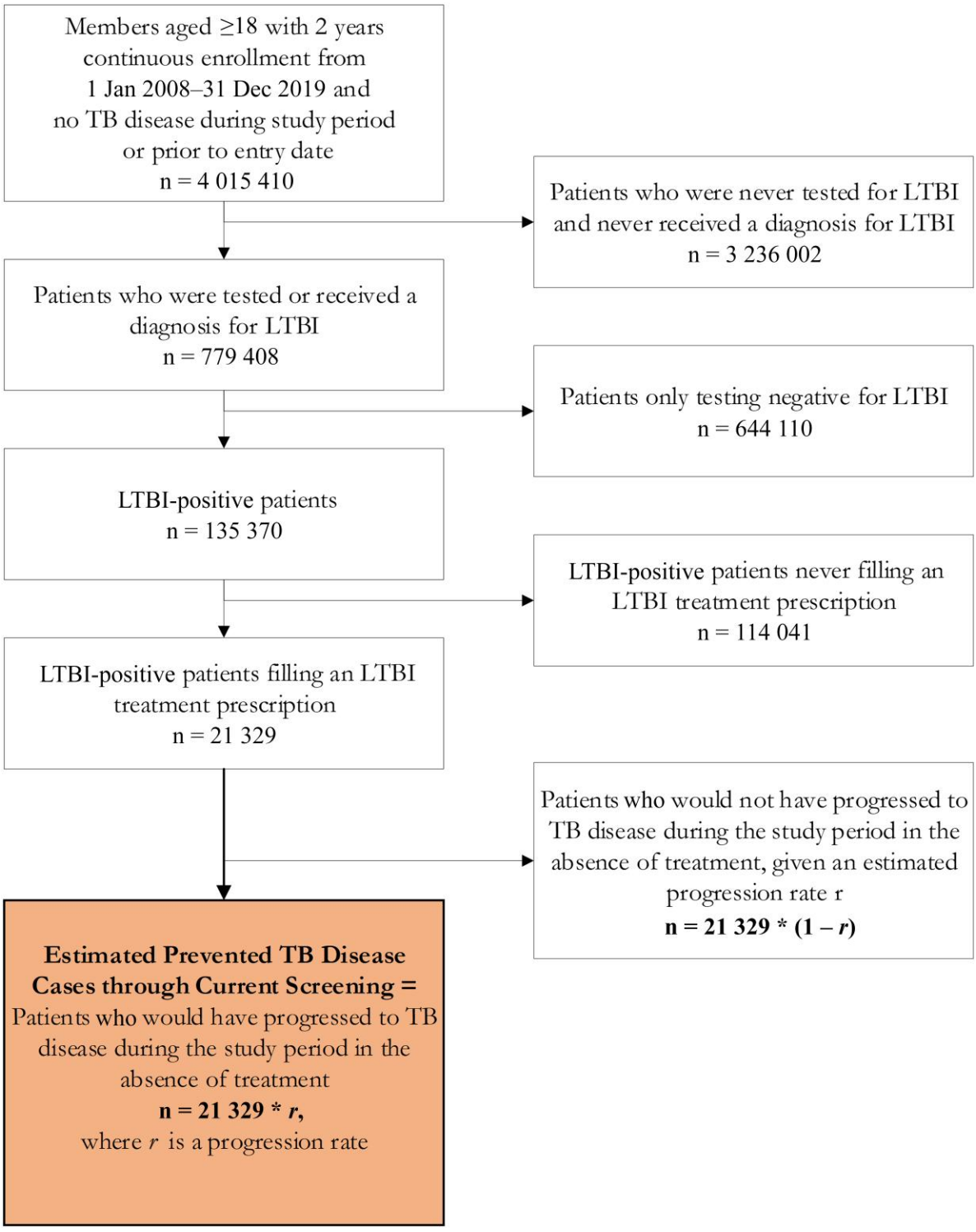

Figure 1. Algorithm to estimate prevented tuberculosis disease cases through current screening. Abbreviations: LTBI, latent tuberculosis infection; TB, tuberculosis.

treatment, compared to 77% (n = 810) of patients with TB disease not prescreened for LTBI and 83% (n = 123) and 85% (n = 71) of those who were screened who were LTBI positive and negative, respectively. For patients with TB disease who were prescreened for LTBI, 22% (n = 33) of LTBI-positive and 33% (n = 28) of LTBI-negative patients were immunosuppressed, compared to only 9.1% (n = 96) of patients with TB disease who were not prescreened for LTBI and 17%

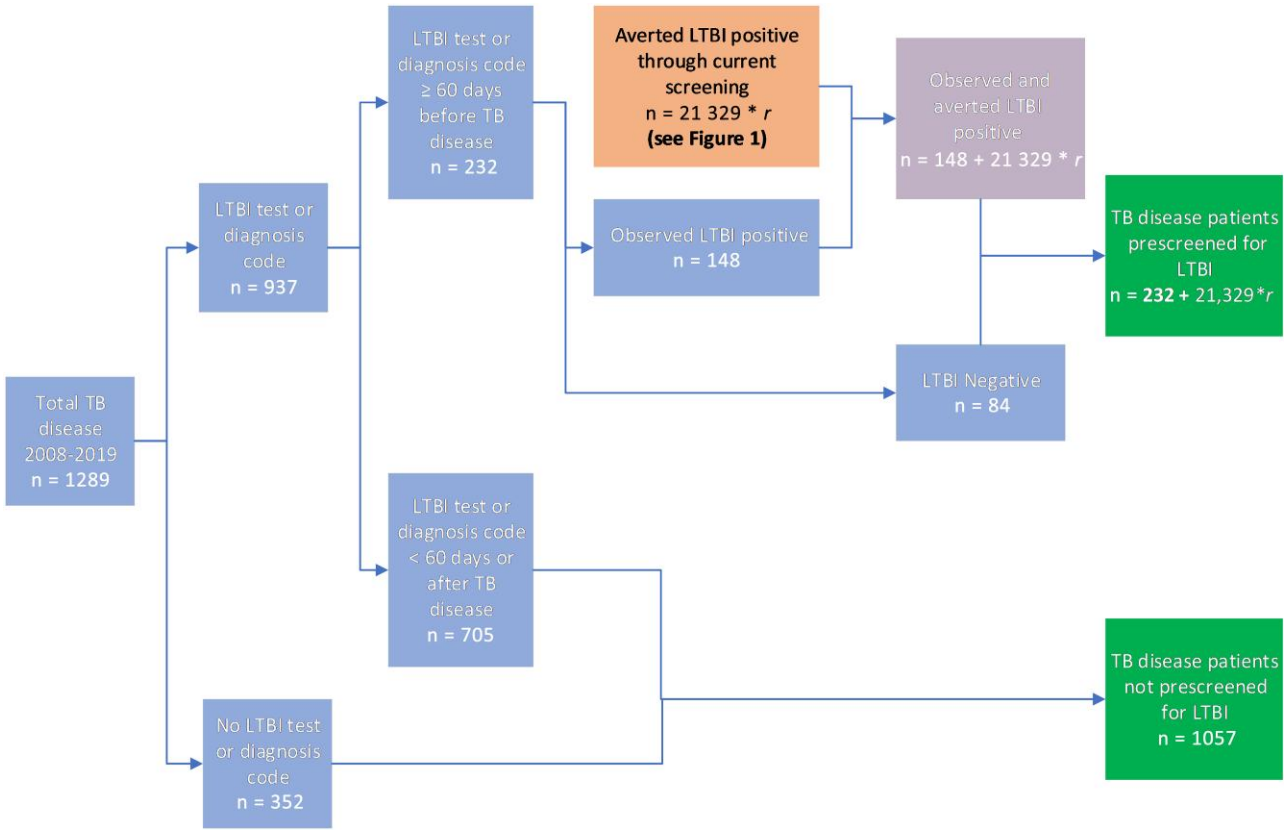

Figure 2. Observed and prevented tuberculosis (TB) disease cases, 2008–2019, by latent tuberculosis infection (LTBI) testing and diagnosis patterns.

(n = 3680) of treated patients overall. While 58% (n = 12 330) of patients prescribed LTBI treatment were born in an HTBIC, 74% (n = 952) of patients with TB disease, regardless of prescreening status, were born in an HTBIC. Travel for >30 days to an HTBIC was low and recent exposure to TB disease was less common across groups. Only 7.0% (n = 1493) of patients prescribed treatment for LTBI were ≥65 years of age, compared to 30% (n = 316) of patients with TB disease who were not prescreened for LTBI. Patients identifying as Asian/Pacific Islander made up 22% (n = 4785) of patients prescribed treatment for LTBI, compared to 49% (n = 638) of patients with TB disease during the study period. Forty-four percent (n = 467) of patients with TB disease who were not prescreened for LTBI had a Charlson score of 4 or higher, compared to 20% (n = 4185) of patients prescribed treatment for LTBI.

DISCUSSION

Our analyses showed that 1057 of 1289 observed TB disease cases (82%) from KPSC between 2008 and 2019 occurred in patients never screened for LTBI. Even in a hypothetical scenario using the upper bound for age-specific TB progression rates [19], we showed that almost 62% of TB disease cases would still not be screened for LTBI.

Our lower bound estimate for progression of TB disease from LTBI used our observed TB progression rate for patients not prescribed LTBI treatment testing positive for LTBI ($r = 0.11\%$). It is reasonable to assume that the progression rate among patients prescribed LTBI treatment (if otherwise untreated) could be higher than patients not prescribed LTBI treatment, since physicians may decide to treat patients deemed to be at a higher risk for progression to TB disease, implying a higher progression rate than our estimated lower bound estimate. However, our upper bound estimate using the 95th percentile estimates of literature supported progression rates over the study period still found that 62% of TB disease cases were not prescreened for LTBI.

We were unable to differentiate whether observed cases not screened for LTBI prior to testing positive for TB disease occurred due to recent exposure or progression from LTBI. However, because suspected TB disease exposure in this population is rare and because 87% of TB disease cases in 2021 were attributed to LTBI progression in California [8], we estimate that the vast majority of these cases were due to progression.

We did not require consecutive membership during the study period to occur prior to TB disease. However, TB disease diagnosis was made >1 year after cohort entry for 93% of nonscreened patients, 2 years for 86% of patients, and 5 years for 66% of patients.

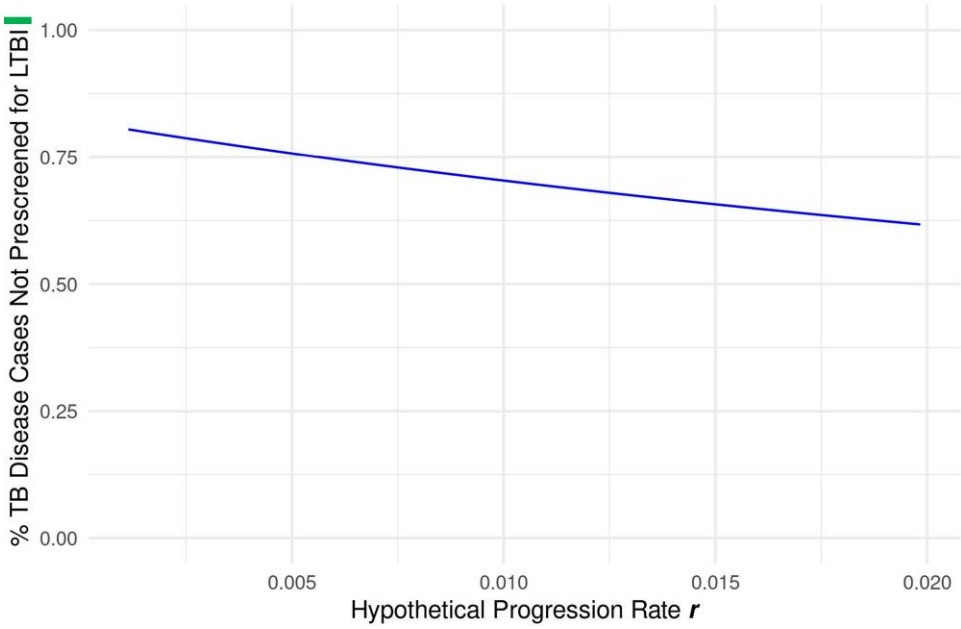

Figure 3. Percentage of tuberculosis (TB) disease cases not prescreened for latent tuberculosis infection (LTBI), as a function of the hypothetical progression rate.

Although LTBI screening may be less feasible for those with <1 year of KPSC membership prior to TB disease onset, for the 93% of patients with >1 year of membership prior to TB disease, the failure to prescreen for LTBI represents a missed opportunity for TB disease prevention. This is particularly true given 89% of patients in our cohort had at least 1 primary care encounter during the study period; moreover, 83% had at least 2 and 60% had at least 6 primary care encounters. As observed in previous studies, patients did have screening opportunities, but were not necessarily receiving a TST or IGRA [20].

In 2019, California reported 2115 TB disease cases, which resulted in >$210 million in medical and societal costs [9]. This missed opportunity to prevent 1057 TB disease cases at KPSC likewise resulted in significant avoidable costs, in addition to preventable mortality and morbidity, regardless of its magnitude in percentage terms among total TB disease.

We found that 66% of patients treated for LTBI met CDPH recommended screening criteria, compared to 77% of patients not prescreened for LTBI who acquired TB disease. We note that 57% of patients testing positive for LTBI who were not prescribed any LTBI treatment met CDPH screening criteria, so LTBI-positive patients do appear more likely to receive treatment if meeting CDPH-recommended screening criteria. However, 31% of the 3 236 000 patients (n = 1 015 030) never screened for LTBI during the study period met CDPH screening criteria, meaning collectively there are still many patients meeting CDPH criteria not being screening or treated for LTBI.

Patients with TB disease not prescreened for LTBI were much less likely to be immunosuppressed compared to patients with TB disease who were prescreened for LTBI and to LTBI patients prescribed treatment for LTBI, indicating that screening for immunosuppression may be effectively implemented. Possible mismatches between screening, treatment, and TB disease that may warrant further attention include older age, higher Charlson score, birth in an HTBIC, and persons identifying as Asian/Pacific Islander. However, differences observed by testing group may be influenced by LTBI testing and treatment patterns not examined here. Therefore, we present differences descriptively and defer to future work to more clearly delineate causal associations. It should also be noted that characteristics of the KPSC population at risk for LTBI and TB disease may be different than the general population.

We also note the low LTBI treatment initiation rate of 15.8% observed among screened LTBI-positive patients, which clearly contributes to missed opportunities to prevent progression to TB disease. The 130 LTBI-positive patients who progressed to TB disease who were not prescribed LTBI treatment during the study period could have been included in our estimate of prevented active TB disease had they completed LTBI treatment. Furthermore, improvements in LTBI screening will not be meaningful without more comprehensive treatment programs. Previous work by Bruxvoort et al highlighted the challenges and possible barriers to uptake and completion of treatment in our population, another extremely important aspect of TB disease prevention [21].

The 1057 TB disease cases not screened for LTBI came come from the population of 3 236 354 patients not tested for or diagnosed with LTBI during the study period. Screening all

Table 1. Patient Characteristics of Tuberculosis (TB) Disease–Positive Patients by Latent Tuberculosis Screening Pattern Compared With Latent Tuberculosis (LTBI)–Positive Patients Prescribed LTBI Treatment Who Did Not Develop TB Disease During the Study Period

Characteristic	Patients With TB Disease			Patients Prescribed LTBI Treatment[a] (n = 21 329)
		Screened		
	Not Screened (n = 1057)	LTBI Negative (n = 84)	LTBI Positive (n = 148)	
CDPH screening recommended[b]	810 (77%)	71 (85%)	123 (83%)	14 138 (66%)
Immunosuppressed[c]	96 (9.1%)	28 (33%)	33 (22%)	3680 (17%)
Country of birth[d]				
Not born in an HTBIC	276 (26%)	21 (25%)	29 (20%)	8892 (42%)
Born in an HTBIC	772 (73%)	63 (75%)	117 (79%)	12 330 (58%)
Unknown	9 (0.9%)	0 (0%)	2 (1.4%)	107 (0.5%)
Language preference				
Does not prefer to speak a language associated with an HTBIC	776 (73%)	63 (75%)	109 (74%)	15 296 (72%)
Prefers to speak a language associated with an HTBIC	262 (25%)	20 (24%)	33 (22%)	5873 (28%)
Unknown	19 (1.8%)	1 (1.2%)	6 (4.1%)	160 (0.8%)
Travel >30 days to an HTBIC	15 (1.4%)	2 (2.4%)	3 (2.0%)	394 (1.8%)
Contact with or suspected exposure to TB	26 (2.5%)	7 (8.3%)	4 (2.7%)	938 (4.4%)
Sex				
Female	457 (43%)	37 (44%)	79 (53%)	12 670 (59%)
Male	600 (57%)	47 (56%)	69 (47%)	8659 (41%)
Age, y				
18–34	208 (20%)	12 (14%)	27 (18%)	7546 (35%)
35–49	208 (20%)	16 (19%)	48 (32%)	7299 (34%)
50–64	325 (31%)	32 (38%)	42 (28%)	4991 (23%)
65–74	201 (19%)	19 (23%)	26 (18%)	1220 (5.7%)
≥75	115 (11%)	5 (6.0%)	5 (3.4%)	273 (1.3%)
Race/ethnicity				
White	108 (10%)	12 (14%)	5 (3.4%)	2607 (12%)
Asian/Pacific Islander	507 (48%)	40 (48%)	91 (61%)	4785 (22%)
Black	56 (5.3%)	2 (2.4%)	7 (4.7%)	1884 (8.8%)
Hispanic	373 (35%)	28 (33%)	43 (29%)	11 474 (54%)
Other/multiple/unknown	13 (1.2%)	2 (2.4%)	2 (1.4%)	579 (2.7%)
Neighborhood Deprivation Index quintile				
1	145 (14%)	15 (18%)	18 (12%)	2562 (12%)
2	203 (19%)	17 (21%)	33 (22%)	4097 (19%)
3	264 (25%)	19 (23%)	36 (24%)	5097 (24%)
4	256 (24%)	20 (24%)	37 (25%)	5181 (24%)
5	179 (17%)	11 (13%)	24 (16%)	4212 (20%)
Unknown	10	2	0	180
BMI category, kg/m^2				
<18.5: underweight	53 (5.0%)	8 (9.5%)	7 (4.7%)	296 (1.4%)
18.5–24.9: healthy weight	513 (49%)	30 (36%)	79 (53%)	6178 (29%)
25.0–29.9: overweight	322 (30%)	31 (37%)	47 (32%)	7793 (37%)
30–34.9: moderately obese	129 (12%)	12 (14%)	10 (6.8%)	4354 (20%)
≥35.0: severely obese	40 (3.8%)	3 (3.6%)	5 (3.4%)	2689 (13%)
Unknown BMI measure	0 (0%)	0 (0%)	0 (0%)	19 (<0.1%)
Weighted CCI Score				
0	189 (18%)	8 (9.5%)	32 (22%)	8415 (39%)
1–3	401 (38%)	24 (29%)	59 (40%)	8729 (41%)
≥4	467 (44%)	52 (62%)	57 (39%)	4185 (20%)

Data are presented as No. (%).

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; CDPH, California Department of Public Health; HTBIC, born in a country with high tuberculosis incidence; LTBI, latent tuberculosis infection; TB, tuberculosis;.

[a]Patients receiving a treatment prescription for LTBI during the study period who did not develop TB disease. See Figure 1 for more details.

[b]Birth or travel in a country with elevated TB, immunosuppression, exposure to TB disease.

[c]Defined as patients with solid organ transplantation (heart, lung, heart-lung, kidney, liver, pancreas, intestine), use of high-dose steroid, use of tumor necrosis factor–α inhibitors, use of immunosuppressants (chemotherapy/immunomodulators), head and neck cancer, leukemia, or human immunodeficiency virus infection.

[d]Patients missing country of birth had this information imputed using a previously published algorithm if input used in that algorithm was available.

patients meeting CDPH criteria may not be feasible in many health systems, and even so, many patients may be LTBI positive who do not meet these criteria. Screening programs to efficiently identify the patients most likely to advance to TB disease in such large populations is not a trivial matter. Still, given the enormous health and societal costs even a small number of TB disease cases bring, it is important to continually strive for improvements. Furthermore, in recent years, more TB diagnoses in the US among persons born in countries with higher TB incidence occurred ≥10 years after arrival in the US than among those in the US <10 years [22]. In 2021, half of TB cases in non-US-born persons occurred >20 years after arrival in the US [8]. This development indicates that the onus of LTBI screening and treatment will continue to fall to a greater degree on healthcare providers rather than on immigration departments, and efficient screening programs will be even more important [22–24]. Developing a prediction algorithm to identify those most at risk of TB disease in the near term, as well as harnessing decision support tools in the EHR, may be a valuable undertaking to improve LTBI screening practices in health systems.

In conclusion, one-fifth of patients were prescreened for LTBI prior to their TB disease diagnosis during the study period. Even assuming the upper bound of cases prevented through current screening, almost 62% of TB disease patients were never screened for LTBI. Future work to elucidate gaps in LTBI screening practices and to identify opportunities to improve screening guidelines are needed.

Supplementary Data

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

Notes

Author contributions. H. F., L. Q., J. S., S. G., K. J. B., B. J. L., S. Y. T.: concept and design. H. F., L. Q., Z. L., J. S., K. J. B., B. J. L., P. S. M., S. G., J. H. K., S. Y. T.: acquisition, analysis, or interpretation of data. H. F.: drafting of the manuscript. H. F., L. Q., Z. L., J. S., S. F. S., K. J. B., J. H. K., B. J. L., P. S. M., S. Y. T.: critical revision of the manuscript for important intellectual content. H. F., Z. L., L. Q., S. G.: statistical analysis. S. Y. T.: obtained funding, supervision. S. F. S., B. C. P.: administrative, technical, or material support.

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