Title

Association of Rapid Molecular Testing With Duration of Respiratory Isolation for Patients With Possible Tuberculosis in a US Hospital

Journal

JAMA Internal Medicine, 178(10)

ISSN

2168-6106

Authors

Chaisson, Lelia H
Duong, David
Cattamanchi, Adithya
et al.

Publication Date

2018-10-01

DOI

10.1001/jamainternmed.2018.3638

Peer reviewed

HHS Public Access

Author manuscript

JAMA Intern Med. Author manuscript; available in PMC 2019 October 01.

Published in final edited form as:

JAMA Intern Med. 2018 October 01; 178(10): 1380–1388. doi:10.1001/jamainternmed.2018.3638.

Rapid molecular testing to reduce duration of respiratory isolation for patients with possible tuberculosis in a U.S. hospital

Lelia H. Chaisson, MSc[1], **David Duong, MD**[2], **Adithya Cattamanchi, MD**[8], **Marguerite Roemer, BA**[9], **Margaret A. Handley, PhD**[3,5,10], **Dean Schillinger, MD**[5,10], **Matthew Sur, BS**[11], **Phong Pham, CLS**[9], **Mary Ann Lin, BS**[9], **L. Elizabeth Goldman, MD**[5], **Judy Quan, PhD**[5,10], **Saida Perez, MS**[8], **Michael Healy, MD**[7], **Julie Higashi, MD**[12], **Lisa Winston, MD**[6], **Barbara Haller, MD**[4,9], **Anne F. Luetkemeyer, MD**[6], and **J. Lucian Davis, MD**[13,14]

[1]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland [2]Departments of Emergency Medicine, University of California, San Francisco, San Francisco, California [3]Departments of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, California [4]Departments of Pathology, University of California, San Francisco, San Francisco, California [5]Divisions of General Internal Medicine, University of California, San Francisco, San Francisco, California [6]HIV/AIDS, Infectious Diseases, and Global Medicine, University of California, San Francisco, San Francisco, California [7]Hospital Medicine, University of California, San Francisco, San Francisco, California [8]Pulmonary & Critical Care Medicine, Department of Medicine, University of California, San Francisco, San Francisco, California [9]Division of Microbiology, Department of Laboratory Medicine, San Francisco, California [10]UCSF Center for Vulnerable Populations, Zuckerberg San Francisco General Hospital and Trauma Center, San Francisco, California [11]San Francisco Department of Public Health, San Francisco, California [12]Department of Public Health, Los Angeles County, Los Angeles, California [13]Department of Epidemiology of Microbial Diseases, Yale School of Public Health, New Haven, Connecticut [14]Pulmonary, Critical Care, and Sleep Medicine Section, Department of Medicine, Yale School of Medicine, New Haven, Connecticut

Abstract

Importance—New guidelines recommend that molecular testing replace sputum-smear microscopy to guide discontinuation of respiratory isolation in patients undergoing evaluation for active tuberculosis(TB) in health-care settings.

Objective—To evaluate the implementation and impact of a molecular-testing strategy to guide discontinuation of isolation.

Design—Prospective cohort study with a pragmatic, before-and-after-implementation design.

Setting—Zuckerberg San Francisco General Hospital and Trauma Center.

Contact Information: J. Lucian Davis, MD, Department of Epidemiology of Microbial Diseases, Yale School of Public Health, 60 College Street, New Haven, CT 06510, Lucian.Davis@yale.edu.

Participants—621 consecutive hospitalized patients undergoing sputum examination for evaluation for active pulmonary TB from January 2014—January 2016.

Intervention—Implementation of a sputum molecular-testing algorithm using GeneXpert MTB/RIF(Xpert) to guide discontinuation of isolation.

Main Outcomes and Measures—We measured the proportion of patients with molecular testing ordered and completed; the accuracy of the molecular-testing algorithm in reference to mycobacterial culture; the duration of each component of the testing and isolation processes; length of stay; mean days in isolation and in hospital; and mean cost. We extracted data from hospital records and compared measures before and after implementation.

Results—Among 320 patients evaluated in the post-implementation period, clinicians ordered molecular testing for 234(73%) patients and received results for 295/302(98%) tests ordered. Median age was 54(interquartile range 44–63), and 161(26%) were women. The molecular-testing algorithm accurately diagnosed all seven patients with culture-confirmed TB and excluded TB in all 251 *Mtb*-culture-negative patients. Compared to the pre-implementation period, there were significant decreases in median times to final rapid-test result(39.1 vs. 22.4 hours, p<0.001), discontinuation of isolation(2.9 vs. 2.5 days, p=0.001), and hospital discharge(6.0 vs 4.9 days, p=0.003), on average saving $13,347 per isolated non-TB patient.

Conclusions and Relevance—A sputum molecular-testing algorithm to guide discontinuation of respiratory isolation for patients undergoing evaluation for active TB was safe, feasible, widely and sustainably adopted, and provided substantial clinical and economic benefits. Molecular testing may facilitate more efficient, patient-centered evaluation for possible TB in U.S. hospitals.

INTRODUCTION

Nosocomial transmission of tuberculosis(TB) is one of the most feared public health consequences of a delayed TB diagnosis. Following several hospital outbreaks in the 1980s[1–3], the U.S. Centers for Disease Control and Prevention (CDC) issued guidelines on risk-stratification and infection-control measures to prevent such events[4]. Last updated in 2005, these guidelines recommend use of administrative screening measures, personal-protective equipment including high-efficiency particulate respirators, and environmental controls including airborne infection isolation until highly infectious TB can be excluded[5]. These procedures are resource-intensive, requiring private rooms with negative-pressure ventilation systems. While these policies have helped reduce nosocomial TB transmission[6,7], prolonged stays in isolation rooms are common because conventional rapid diagnostic testing for TB requires serial sputum collection for microscopic examination over two or more days.

A novel approach employs nucleic-acid amplification testing to guide discontinuation of respiratory isolation[8]. Following introduction of a semi-automated, cartridge-based molecular-testing assay(GeneXpert MTB/RIF, Cepheid, Sunnyvale, California, USA; henceforth called “Xpert”)[9] that provides testing results in under two hours, we and others have identified the potential to substantially decrease the duration of isolation[10–12] and hospital costs[13,14] required to evaluate inpatients for active TB. Based on high-quality diagnostic accuracy and modeling studies[10,11,13–15], regulatory authorities[16] and

professional societies[17] have endorsed molecular-testing strategies employing one or two sputum Xpert tests, but little is known about their impact in routine practice. Therefore, we introduced an Xpert-based strategy to guide discontinuation of respiratory isolation for patients undergoing evaluation for active pulmonary TB at a public hospital. We evaluated implementation outcomes, including adoption, feasibility, and safety[18], and impact on time to completion of TB evaluation, time in isolation and in hospital, and hospital costs.

METHODS

Study Setting

About 300 patients a year initiate and 250 patients complete rapid TB testing and respiratory isolation during evaluation for active TB at Zuckerberg San Francisco General Hospital and Trauma Center(ZSFG), a public teaching hospital serving the City and County of San Francisco, California. Prior to introducing molecular testing, ZSFG TB infection-control policies required all possible TB patients to stay in isolation for collection of ≥2 expectorated or induced sputa over two separate days for concentrated acid-fast bacilli smear microscopy and mycobacterial culture. Sputum concentration, smear preparation, and slide examination were carried out in a single batch once-daily. Patients with a high clinical probability of TB were placed in airborne infection isolation; patients considered to have a low clinical probability of TB could be placed in respiratory isolation in conventional private rooms without negative-pressure ventilation systems if no airborne infection isolation rooms were available. Isolation could be discontinued for non-TB patients when ≥2 sputa tested smear-negative. Hospital discharges of possible TB patients required ≥3 negative and no positive smear results; ≥3 pending mycobacterial cultures; and authorization from the San Francisco TB Control Program.

Implementation Strategy

In 2015, leaders from multiple departments at ZSFG and from the San Francisco TB Control Program developed a revised algorithm for discontinuing respiratory isolation incorporating sputum molecular testing. In constructing the new algorithm, stakeholders placed the highest priority on avoiding false-negative results and the next highest priority on shortening the time to final test results and the duration of respiratory isolation. The final algorithm recommended clinical assessments to guide how many sputum Xpert tests should be ordered and required that individuals be isolated for collection of ≥2 sputa for mycobacterial culture on two separate days. The algorithm allowed discontinuation of isolation after negative smear and/or Xpert examination of two sputa for patients with low-probability clinical presentations, or of three sputa for patients with high-probability clinical presentations, as determined by the bedside clinicians(Figure 1). Finally, the algorithm recommended that clinicians assess the public health risk of TB transmission to determine whether two(if low-risk) or three(if high-risk) negative sputum examinations would be required before hospital discharge. We disseminated this algorithm to clinicians and bedside nurses via information sessions, handouts, wall posters in clinician work areas, a website[19], and prompts in the electronic order-entry system. Laboratory staff completed training on Xpert MTB/RIF procedures; there were no other laboratory interventions. Two physicians with expertise in TB(AL, JLD) and an emergency medicine physician(DD) worked with stakeholders and

with facilitators from the UCSF Caring Wisely Initiative(MAH, DS, LG) to plan implementation.

Study design and population

From January 28, 2014—January 27, 2016, we performed a prospective, pragmatic, before-and-after implementation study to evaluate the molecular-testing strategy introduced on January 28, 2015. We also assessed program sustainability from January 1—December 31, 2017. We evaluated consecutive adults(≥18 years-old) undergoing sputum examination for *Mtb* in the ZSFG Emergency Department or on the Inpatient Medicine or Family Medicine Services. We excluded rapid TB test-positive patients from our analyses of clinical efficiency and impact because they were not the target population for our intervention; discontinuing isolation for active TB patients follows a longer process not reducible by Xpert testing. We included all medical inpatients admitted January 28, 2014—January 27, 2016 in assessments for underlying temporal trends in study outcomes. All ordering, testing, and decision-making were carried out by routine clinical and laboratory staff. All data were collected through routine hospital-information systems.

Procedures

In the post-implementation period, a clinical laboratory scientist performed Xpert MTB/RIF testing on unprocessed sputum according to manufacturer instructions using a GeneXpert XVI(Cepheid, Sunnyvale, CA, USA) instrument already in routine use for a variety of microbiologic assays. Previously developed laboratory protocols required two separate sputum samples of ≥1.0 mL each for molecular and conventional microbiologic testing by concentrated acid-fast bacilli smear microscopy and mycobacterial culture[10]. If the number or volume of samples was insufficient, staff prioritized available specimens for molecular testing. Laboratory operating procedures stated that Xpert would be performed and reported in the electronic medical record as soon as specimens were received in the laboratory on weekdays during daytime working hours. After hours and on weekends, Xpert testing would be completed by the on-duty clinical laboratory scientist as soon as possible pending other requests for rapid microbiologic testing. As in the pre-implementation period, smear microscopy results were entered into the electronic medical record once-daily as soon as they became available.

Measurements

We calculated the proportion of patients with ≥1 Xpert ordered in the post-implementation period as a measure of *adoption* of molecular testing by clinicians. We recorded the proportion of samples with adequate volume for analysis to determine the *feasibility* of simultaneously collecting two separate sputa for molecular and conventional microbiologic testing. We defined the final smear result as positive if there was any positive result among the first three sputa collected and negative if there were ≥2 negative results by smear examination and no positive smear results. We defined the final Xpert result as positive if there was any positive result among the sputa examined and negative if all sputa examined were negative. We excluded patients who had <2 sputa examined by microscopy, if negative or missing, or <1 sputum Xpert result for having an incomplete TB exam. We determined the accuracy of the microscopy and molecular-testing strategies in reference to a gold

standard of serial sputum mycobacterial culture, excluding those with <2 culture results unless culture-positive. We compared frequencies of false-negative results to assess the relative *safety* of each strategy.

To measure *clinical efficiency* and *clinical impact*, we calculated time intervals from the hospital admission order to several important time points in the TB evaluation process: 1) sputum collection, 2) sputum receipt in the laboratory, 3) reporting of first and final test results, and 4) hospital discharge. In addition, we calculated time spent in isolation from the order for its initiation until the order for its discontinuation. To measure impact on bed utilization, we calculated the mean number of 1) days in isolation and 2) days in hospital per rapid TB test-negative patient. We estimated mean costs per day for all participants using the U.S. Centers for Medicare and Medicaid Services' Principles of Reasonable Cost Reimbursement[20]. Finally, using these mean values, we projected annual hospital savings in isolation days, hospital days, and total costs, assuming 250 patients complete TB evaluation each year.

We defined time to first test result using the reporting time for the first smear result in the pre-implementation period and the reporting time for the first Xpert result(if Xpert was performed) or the first smear result(if Xpert was not performed) in the post-implementation period(eTable 1). We defined the time to final result in the pre-implementation period using the reporting time for the second negative smear result. In the post-implementation period, we defined the time to final result using the reporting time for the second smear result if only microscopy was performed, for the second Xpert result if ≥2 Xpert tests were performed, or for the second rapid test result(Xpert or smear) if only one Xpert test was performed.

Statistical analysis

We compared clinical and demographic characteristics; median time intervals for each component of the sputum testing process, respiratory isolation, and hospitalization; and measures of clinical efficiency and impact between the pre- and post-implementation periods. We evaluated statistical significance using chi-squared tests, Wilcoxon rank-sum tests, or t-tests, as appropriate. We performed linear regression to assess trends in time in isolation and hospital length of stay in the pre-implementation period.

Ethics approval

The University of California San Francisco Committee on Human Research approved the study protocol as quality improvement research and waived the requirement for informed consent. The Yale University Human Investigation Committee approved the study for analysis only. Cepheid was not involved in study design or analysis.

RESULTS

Adoption and feasibility of rapid-testing strategies

Clinicians ordered sputum testing for TB for 621 patients at ZSFG during the two-year study period(Figure 2). Of 301 patients in the pre-implementation period with ≥1 sputum

microscopy and culture ordered, clinicians completed the rapid TB testing evaluation process for 233(77%). A similar proportion(259/320, 81%) had TB evaluation terminated prior to completion during the post-implementation period(p=0.28). After introduction of molecular testing, clinicians ordered Xpert testing for 234(73%) patients and smear microscopy without Xpert testing for 86(27%) patients. Of those with Xpert testing ordered, 172(74%) had one, 56(24%) had two, and six(3%) had three, for a total of 302 tests ordered. Results were reported for 295(98%) tests; six(2%) samples had insufficient sputum for testing, and one sample provided indeterminate results. Overall, 228(71%) patients received Xpert results.

Study population and *microbiologic testing results*

Median age was similar in the two periods(54 years vs. 53 years, p=0.76), as were the proportions of women(26.6% vs. 21.6%, p=0.20), homeless patients(19.7% vs. 24.7%, p=0.19), and persons living with HIV(34.3% vs. 32.8%, p=0.45; Table 1). Ten(4.3%) patients before implementation and nine(2.7%) after were rapid TB test-positive, including six(2.3%) Xpert-positive and eight(3.7%) smear-positive after implementation. Eight(3.4%) patients evaluated before implementation and seven(2.7%) evaluated after were *Mtb* culture-positive. Forty-three(18%) patients evaluated before implementation and 58(22%) evaluated after had sputum that grew non-tuberculous mycobacteria. One *Mtb* culture-positive patient with a high clinical probability of TB initially tested Xpert-negative and scanty smear-positive, but subsequent sputa tested Xpert-positive(eResults). Among 168 patients who completed both smear and Xpert evaluation, one Xpert-positive, smear-negative patient was *Mtb* culture-positive and one Xpert-negative, smear-positive patient was culture-positive for *Mycobacterium kansasii*(eTable 2).

Clinical efficiency and clinical impact on hospital length of stay

Median time from hospital admission until initial sputum collection was 19.1 hours(interquartile range(IQR) 10.3–40.3) before implementation and 18.0 hours(IQR 9.2–41.8) after(p=0.62, Table 2). Median time to first test result after sputum collection decreased from 18.4 hours(IQR 15.5–23.6) before implementation to 4.6 hours(IQR 3.4–6.9) after(p<0.001). Median time to final test result after sputum collection decreased from 39.1 hours(IQR 35.6–42.9) before implementation to 22.4 hours(IQR 13.7– 30.6) after(p<0.001). Median time to hospital discharge after final test results were reported was 66.5 hours(IQR 26.6–160.3) before implementation and 49.6 hours(IQR 21.5–139.8) after(p=0.08). Median hospital length of stay decreased from 6.0 days(IQR 3.8–10.9) before implementation to 4.9 days(IQR 2.9–8.9) after(p=0.003). There were no significant temporal trends in hospital length of stay during the pre-implementation period for patients who were rapid TB test-negative(p=0.17). Moreover, median length of stay for all medical inpatients did not change from the pre-(3 days, IQR 2–4, n=11,287) to the post-implementation period(3 days, IQR 2–4, n=10,950).

Clinical efficiency and clinical impact on respiratory isolation

Respiratory isolation data were available for 207(93%) patients with negative rapid TB testing results before implementation and 226(90%) after(p=0.34). Median time from hospital admission to initiation of respiratory isolation was 2.4 hours(IQR 1.2–15.7) before

implementation and 1.8 hours(IQR 1.0–9.0) after(p=0.06, Table 3). Median time between initiation of isolation and sputum collection was 12.9 hours(IQR 6.6–19.3) before implementation and 13.5 hours(IQR 5.1–29.1) after(p=0.50). Median time from initial sputum collection to reporting of a final negative rapid TB test result decreased from 39.3 hours(IQR 36.3–43.4) before implementation to 21.9 hours(IQR 13.4–30.0) after(p<0.001). Median time from a final negative rapid TB test result until discharge from isolation was 13.9 hours(IQR 1.7–32.3) before implementation and 15.9 hours(IQR 2.3–34.4) after(p=0.52). Median duration of respiratory isolation decreased from 2.9 days(IQR 2.0–3.7) before implementation to 2.5 days(IQR 1.7–3.4) after(p=0.001). There were no significant trends in length of stay in isolation in the pre-implementation period(p=0.29).

Impact on utilization and cost

Among rapid TB test-negative patients, mean time in isolation decreased 29%, from 3.9 days per patient before implementation to 2.8 days after(p=0.03), and mean hospital length of stay decreased 27%, from 10.4 days before implementation to 7.5 days after(p=0.01). Mean hospital costs per rapid TB test-negative patient decreased from $46,921 before implementation to $33,574 after, providing average savings of $13,347 per patient. Estimating utilization and costs for approximately 250 inpatients completing TB evaluation each year, we project total annual savings to the hospital of 278 inpatient days in isolation, 705 inpatient days in hospital, and $3.3 million.

Sustainability

From January—December 2017, 293 patients had sputum examination for active TB ordered, including 205(70%) with Xpert testing. Compared with the post-implementation period, the proportion with Xpert ordered was unchanged(−3.2%, 95%CI −10 to +4.0%, p=0.39).

DISCUSSION

Respiratory isolation is effective for reducing nosocomial TB transmission, but delays care and places a considerable burden on patients, health-care providers, and hospitals. Molecular testing is simpler, faster, and more accurate than conventional microbiologic testing and has been deemed a public health priority, although it has not been widely adopted[21–23]. In this implementation study, we demonstrated that using an Xpert-based molecular-testing algorithm to guide discontinuation of isolation for patients undergoing evaluation for active TB was safe and associated with meaningful reductions time in respiratory isolation and in length of hospital stay compared to the conventional, microscopy-based testing strategy.

We documented favorable implementation outcomes and changes in several important process measures that emphasize the key role Xpert testing had in increasing clinical efficiency and clinical impact. First, a large proportion of clinicians adopted the molecular-testing strategy and usage was sustained two years after implementation. Second, we found that implementing Xpert to reduce turn-around time for testing, isolation, and hospital length of stay was highly feasible and did not affect the ability to complete culture-based evaluation. Finally, the molecular-testing algorithm was cost-saving compared to the

conventional microscopy-based testing strategy. Together, these measures of impact place rapid molecular testing for TB among a select group of interventions that have been shown to advance the “quadruple aim”: improved population health, a better patient experience, a better health worker experience, and lower costs[24].

We previously predicted in a hypothetical study in the same setting that use of Xpert could reduce time in respiratory isolation by approximately two days[10]. During this real-world implementation study, however, we observed more modest reductions (median 0.4 days, mean 1.1 days). There are several possible explanations for these differences. First, clinicians did not order Xpert testing in about one-quarter of admissions, for reasons we did not evaluate. Second, our algorithm for discontinuing isolation required not one negative test by Xpert as in the prior modeling study, but two negative tests by Xpert and/or smear on two separate days, as well as completion of sputum collection within isolation. These more stringent requirements were intended to provide a margin of safety because rare false-negative Xpert results have been reported[11,15]. For similar reasons, current guidelines require two negative Xpert results[17].

Among 168 patients who completed both smear and Xpert testing, we observed only one patient with a false-negative Xpert result, and risk-stratification within the molecular-testing algorithm allowed this individual to be safely diagnosed on an additional sputum sent for Xpert testing. The algorithm also detected one smear-negative TB patient, who would have otherwise gone undetected. There were no false-positive Xpert results. These results support the labeling of Xpert as safe and accurate for guiding discontinuation of isolation[16]. Furthermore, they support the findings of multiple prior diagnostic accuracy studies[10–12,14,15] showing that one Xpert is likely sufficient in almost all patients, especially those with a low clinical probability of active TB. Given the low yield and substantial delays we observed when two Xperts were performed instead of one, the recommendation from professional societies that all patients undergo two Xpert tests prior to discontinuation of isolation may be overly conservative[17]. Our data, along with additional high-quality implementation studies to identify molecular-testing algorithms that are not only safe but also patient-centered, should inform revision of TB infection control guidelines from the CDC. Revision is urgently needed, because these guidelines have not been updated since the introduction of semi-automated testing with GeneXpert[5]. Because these guidelines determine the policies enforced by hospital accreditation agencies, updating them would likely help advance CDC’s longstanding goal of increasing the proportion of possible TB patients undergoing molecular testing[22,25]. In the interim, collecting sputum samples eight hours apart as recommended by professional societies and the CDC may reduce the time to a final rapid TB test result[17,22]. Clinical efficiency and clinical impact of molecular-testing algorithms may be further enhanced by increasing clinician adoption of molecular testing, and by decreasing time from hospital admission to sputum collection and from final results reporting to discontinuation of isolation, each of which delayed completion of TB evaluation by two-thirds of a day.

Our study had several limitations. First, it was conducted at a single academic center where clinicians have substantial experience with TB evaluation, potentially limiting generalizability. Nevertheless, our interdisciplinary approach of involving clinicians,

laboratory leaders, and public health leaders from the TB and hospital infection control programs provides a model for implementation in different contexts. Second, before-and-after implementation designs are susceptible to false inferences if underlying temporal trends are driving changes attributed to the intervention. To reduce this risk, we compared two twelve-month periods before and after implementation to minimize the effects of seasonal variations in hospital census or experience among physicians-in training. Furthermore, we identified no significant underlying temporal trends before implementation. Finally, we may have misestimated local cost savings, since the reasonable costs methodology accounts for average rather than individual costs for services. Thus, we were unable to provide line-item comparisons of costs. However, we have previously used empirical costing to show that a shorter length of stay leads to cost savings (-$2,483) for the molecular strategy ($15,285) compared to the microscopy strategy ($17,768), and that these savings outweigh the higher testing costs (+$203) for the molecular strategy ($218) compared to the microscopy strategy ($15, all costs in 2009 USD)[22,25]. Moreover, the reasonable costs methodology may provide more relevant estimates of cost savings for hospital administrators than empirical costing because it is the approach recommended by the Centers for Medicare and Medicaid Services for determining cost-based reimbursement[20].

Our study had numerous strengths. First, we provide what we believe are the first published data on actual impact and implementation outcomes[18] of molecular testing to guide discontinuation of isolation in a U.S. hospital. Second, we employed a pragmatic, real-world study design that included consecutive, unselected patients referred by usual clinicians[26,27]. Clinicians were free to decide whether to use Xpert to guide discontinuation of isolation or not, and we extracted data on process measures, implementation outcomes, and service outcomes from routine hospital records. These design features enhance generalizability. Finally, we assessed outcomes important to both patients and hospital leaders, including clinical impact, safety, clinical efficiency, and costs.

In conclusion, introducing Xpert testing to guide discontinuation of respiratory isolation for patients undergoing evaluation for active TB appears to be effective for reducing time spent in isolation for patients in a U.S. hospital where the frequency of active TB is low. Routine use of Xpert should be strongly considered to provide faster, more patient-centered care to hospitalized patients undergoing evaluation for TB in the U.S. and other low TB-burden settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

The authors thank the patients, physicians, and staff of Zuckerberg San Francisco General Hospital and Trauma Center, especially the many individuals who contributed to the design and implementation of the molecular-testing strategy for evaluating patients for possible TB.

FUNDING

We acknowledge the support of grants from the University of California San Francisco / San Francisco Department of Public Health Caring Wisely Program(AL, JLD); the San Francisco Hearts Foundation(BH, JLD); and the Johns Hopkins HIV Epidemiology and Prevention Sciences Training Program(LHC, T32AI102623). We also acknowledge Cepheid for donating GeneXpert MTB/RIF test kits.

REFERENCES

1. Nosocomial transmission of multidrug-resistant tuberculosis among HIV-infected persons--Florida and New York, 1988–1991. MMWR Morb Mortal Wkly Rep 1991;40(34):585–591. [PubMed: 1870559]
2. Beck-Sague C, Dooley SW, Hutton MD, et al. Hospital outbreak of multidrug-resistant Mycobacterium tuberculosis infections. Factors in transmission to staff and HIV-infected patients. JAMA 1992;268(10):1280–1286. [PubMed: 1507374]
3. Edlin BR, Tokars JI, Grieco MH, et al. An outbreak of multidrug-resistant tuberculosis among hospitalized patients with the acquired immunodeficiency syndrome. N Engl J Med 1992;326(23): 1514–1521. doi:10.1056/NEJM199206043262302 [PubMed: 1304721]
4. Guidelines for preventing the transmission of Mycobacterium tuberculosis in health-care facilities, 1994. Centers for Disease Control and Prevention. MMWR Recomm Rep 1994;43(RR-13):1–132.
5. Jensen PA, Lambert LA, Iademarco MF, Ridzon R. Guidelines for preventing the transmission of Mycobacterium tuberculosis in health-care settings, 2005. MMWR Recomm Rep 2005;54(RR-17): 1–141.
6. Maloney SA, Pearson ML, Gordon MT, Del Castillo R, Boyle JF, Jarvis WR. Efficacy of control measures in preventing nosocomial transmission of multidrug-resistant tuberculosis to patients and health care workers. Ann Intern Med 1995;122(2):90–95. [PubMed: 7993001]
7. Cook S, Maw KL, Munsiff SS, Fujiwara PI, Frieden TR. Prevalence of tuberculin skin test positivity and conversions among healthcare workers in New York City during 1994 to 2001. Infect Control Hosp Epidemiol 2003;24(11):807–813. doi:10.1086/502141 [PubMed: 14649767]
8. Campos M, Quartin A, Mendes E, et al. Feasibility of shortening respiratory isolation with a single sputum nucleic acid amplification test. Am J Respir Crit Care Med 2008;178(3):300–305. doi: 10.1164/rccm.200803-381OC [PubMed: 18467509]
9. Boehme CC, Nabeta P, Hillemann D, et al. Rapid molecular detection of tuberculosis and rifampin resistance. N Engl J Med 2010;363(11):1005–1015. doi:10.1056/NEJMoa0907847 [PubMed: 20825313]
10. Chaisson LH, Roemer M, Cantu D, et al. Impact of GeneXpert MTB/RIF assay on triage of respiratory isolation rooms for inpatients with presumed tuberculosis: a hypothetical trial. Clin Infect Dis 2014;59(10):1353–1360. doi:10.1093/cid/ciu620 [PubMed: 25091300]
11. Lippincott CK, Miller MB, Popowitch EB, Hanrahan CF, Van Rie A. Xpert MTB/RIF assay shortens airborne isolation for hospitalized patients with presumptive tuberculosis in the United States. Clin Infect Dis 2014;59(2):186–192. doi:10.1093/cid/ciu212 [PubMed: 24729506]
12. Poonawala H, Leekha S, Medina-Moreno S, et al. Use of a Single Xpert MTB/RIF Assay to Determine the Duration of Airborne Isolation in Hospitalized Patients With Suspected Pulmonary Tuberculosis. Infect Control Hosp Epidemiol 3 2018:1–6. doi:10.1017/ice.2018.25
13. Millman AJ, Dowdy DW, Miller CR, et al. Rapid molecular testing for TB to guide respiratory isolation in the U.S.: a cost-benefit analysis. PLoS One 2013;8(11):e79669. doi:10.1371/journal.pone.0079669 [PubMed: 24278155]
14. Cowan JF, Chandler AS, Kracen E, et al. Clinical Impact and Cost-effectiveness of Xpert MTB/RIF Testing in Hospitalized Patients With Presumptive Pulmonary Tuberculosis in the United States. Clin Infect Dis 2017;64(4):482–489. doi:10.1093/cid/ciw803 [PubMed: 28172666]
15. Luetkemeyer AF, Firnhaber C, Kendall MA, et al. Evaluation of Xpert MTB/RIF Versus AFB Smear and Culture to Identify Pulmonary Tuberculosis in Patients With Suspected Tuberculosis From Low and Higher Prevalence Settings. Clin Infect Dis 2016;62(9):1081–1088. doi: 10.1093/cid/ciw035 [PubMed: 26839383]
16. Revised device labeling for the Cepheid Xpert MTB/RIF assay for detecting Mycobacterium tuberculosis. MMWR Morb Mortal Wkly Rep 2015;64(7):193. [PubMed: 25719683]

17. National TB Controllers Association and the Association of Public Health Laboratories. Consensus Statement on the Use of Cepheid Xpert MTB/RIF® Assay in Making Decisions to Discontinue Airborne Infection Isolation in Healthcare Settings.; 2015.

18. Proctor E, Silmere H, Raghavan R, et al. Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. Adm Policy Ment Health 2011;38(2): 65–76. doi:10.1007/s10488-010-0319-7 [PubMed: 20957426]

19. Acosta L. Introducing Xpert MTB/RIF Testing for Active Pulmonary TB at Zuckerberg San Francisco General | San Francisco Health Network (SFHN). San Francisco Health Network (SFHN).

20. Centers for Medicare and Medicaid Services. Principles of Reasonable Cost Reimbursement: 42 C.F.R. § 413.20 and 413.24 https://www.gpo.gov/fdsys/pkg/CFR-2002-title42-vol2/xml/CFR-2002-title42-vol2-part413-subpartB.xml. Published 2002. Accessed April 5, 2018.

21. Steingart KR, Sohn H, Schiller I, et al. Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev 2013;(1):CD009593. doi: 10.1002/14651858.CD009593.pub2 [PubMed: 23440842]

22. Centers for Disease Control and Prevention (CDC). Updated guidelines for the use of nucleic acid amplification tests in the diagnosis of tuberculosis. MMWR Morb Mortal Wkly Rep 2009;58(1): 7–10. [PubMed: 19145221]

23. Medicine I of. Leading Health Indicators for Healthy People 2020: Letter Report; 2011. doi: 10.17226/13088

24. Bodenheimer T, Sinsky C. From triple to quadruple aim: care of the patient requires care of the provider. Ann Fam Med 2014;12(6):573–576. doi:10.1370/afm.1713 [PubMed: 25384822]

25. Healthy People. 2020. IID-32 Data Details | Healthy People 2020. https://www.healthypeople.gov/node/4702/data_details.Accessed May 22, 2018.

26. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. BMJ 2015;350:h2147. [PubMed: 25956159]

27. Gaglio B, Phillips SM, Heurtin-Roberts S, Sanchez MA, Glasgow RE. How pragmatic is it? Lessons learned using PRECIS and RE-AIM for determining pragmatic characteristics of research. Implement Sci 2014;9:96. doi:10.1186/s13012-014-0096-x [PubMed: 25163664]

KEY POINTS

Question

What is the feasibility, safety, and clinical impact of molecular-testing strategies to guide discontinuation of respiratory isolation among hospitalized patients undergoing evaluation for active tuberculosis(TB)?

Results

In this prospective cohort study with a pragmatic, before-and-after implementation design, a molecular-testing strategy employing the GeneXpert MTB/RIF assay significantly reduced median time to isolation discontinuation(2.9 vs 2.5 days, p=0.001), and hospital discharge(6.0 vs 4.9 days, p=0.003), and saved approximately $13,347 per isolated non-TB patient.

Meaning

Xpert appears effective in facilitating faster, more patient-centered care for individuals placed in respiratory isolation while undergoing evaluation for active TB in U.S. hospitals.

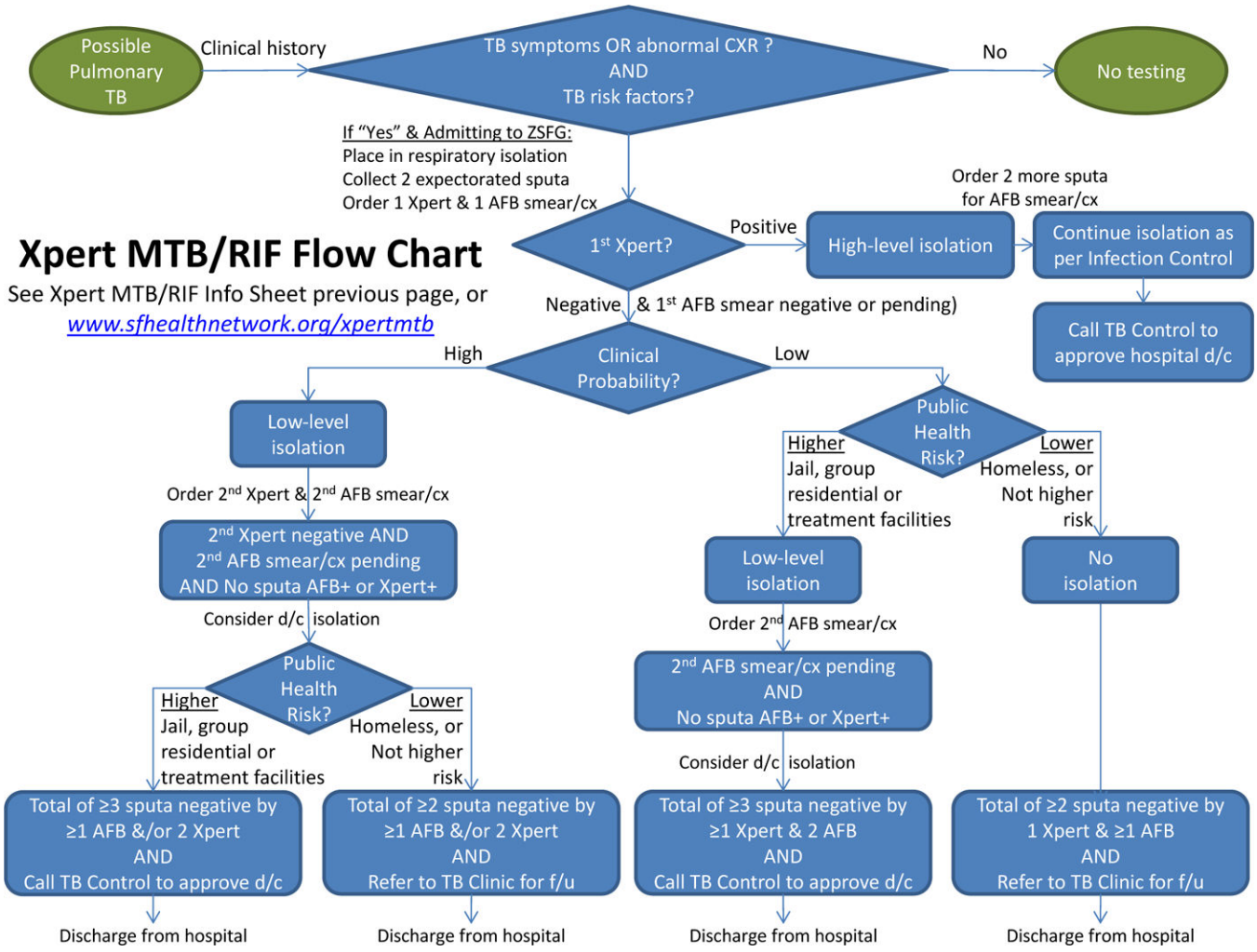

Figure 1. Algorithm incorporating GeneXpert MTB/RIF molecular testing to guide TB evaluation and discontinuation of respiratory isolation.

Legend: This algorithm was disseminated to clinicians and bedside nurses through information sessions, handouts, wall posters, and a website linked in all of these materials and in the electronic order entry system. The algorithm was designed by leaders from Clinical Microbiology, Hospital Infection Control, Nursing, Engineering, Emergency Medicine, HIV Medicine and Infectious Diseases, and Pulmonary Medicine at ZSFG, and the San Francisco Director of TB Control. The clinical probability of a patient having TB was assessed by bedside clinicians. "High-level" airborne infection isolation requires that a patient be placed in a room or tent with a negative-pressure ventilation system. "Low-level" respiratory isolation involves placing a patient in a conventional private room without a negative-pressure ventilation system when no high-level isolation rooms are available and the patient is considered to have a low clinical probability of having highly infectious TB. Homeless patients were deemed to have a lower public health risk based on San Francisco's robust system for and experience with registering, TB testing, and tracking homeless individuals in homeless shelters in the city. **Abbreviations:** AFB, acid-fast bacilli; CXR, chest x-ray; cx, mycobacterial culture; d/c, discharge; f/u, follow-up; ZSFG, Zuckerberg San

Francisco General Hospital; TB, tuberculosis; TB Control, TB Control Program at the San Francisco Department of Public Health. Xpert, Xpert MTB/RIF.

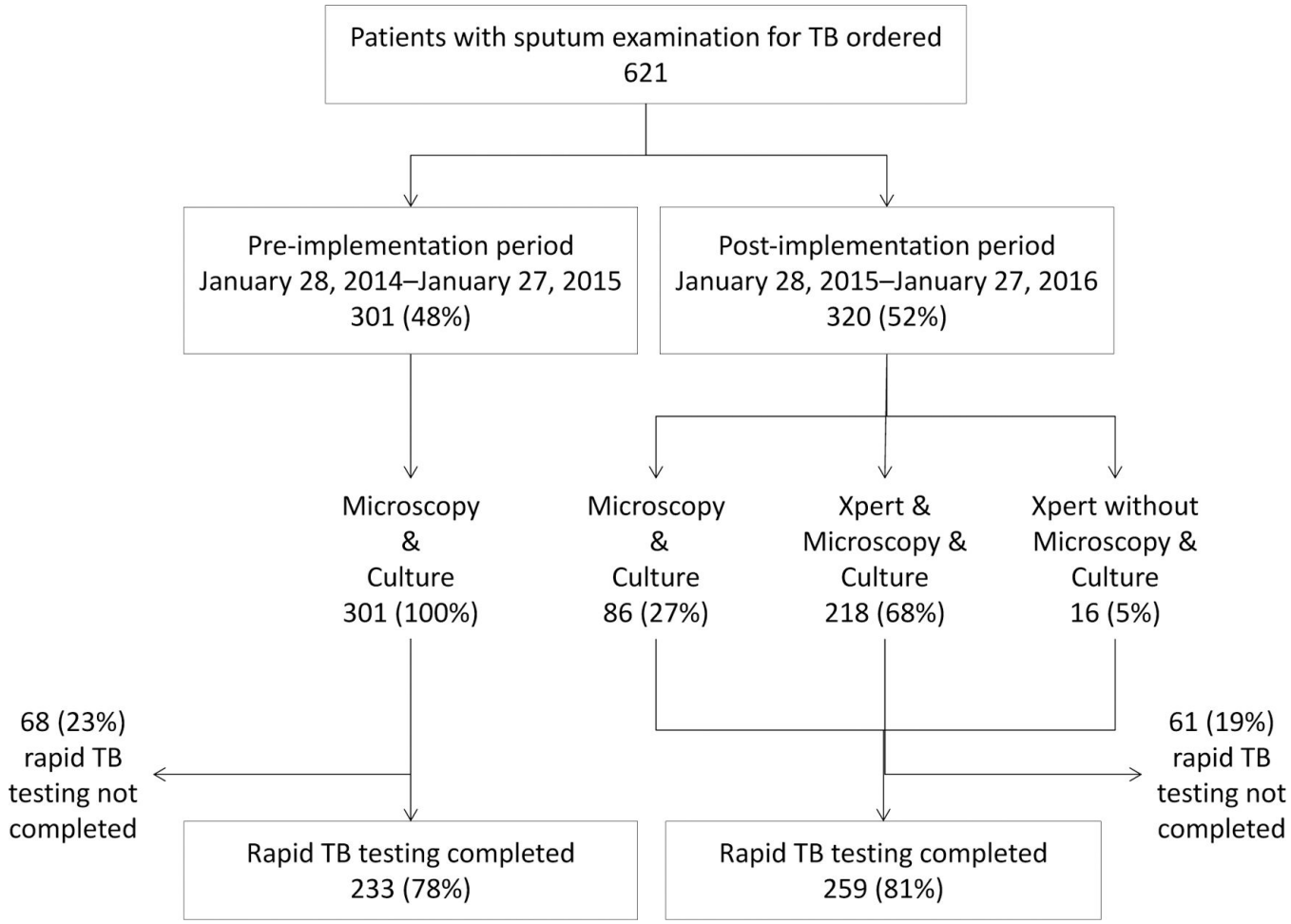

Figure 2. Flow diagram describing the TB evaluation process for all participants.

Abbreviations: TB, tuberculosis. **Legend:** We defined patients with ≤2 sputum smear microscopy results, if negative, as "Rapid TB testing not completed." In addition, we defined patients with only one Xpert performed, if negative, and no sputum smear microscopy results, as "Rapid TB testing not completed," in accordance with revised institutional guidelines for discontinuing respiratory isolation(Figure 1). Percentages may not add to 100% due to rounding.

Table 1.

Demographic and clinical characteristics of patients completing rapid TB evaluation.

Characteristic	Pre-implementation	Post-implementation	p-value[†]
n (%)[*]	n=233	n=259	
Age in years, median (IQR)	54 (45–62)	53 (44–64)	0.76
Female	62 (26.6%)	56 (21.6%)	0.20
Homeless	46 (19.7%)	64(24.7%)	0.19
Persons living with HIV	80 (34.3%)	85 (32.8%)	0.45
Rapid TB test-positive	10 (4.3%)	9 (2.7%)	0.64
AFB smear-positive	10 (4.3%)	8 (3.7%)	0.76
Xpert-positive	—	6 (2.3%)	—
Mtb culture-positive[¶]	8 (3.4%)	7 (2.7%)	0.64
NTM culture-positive[§]	43 (18.5%)	58 (22.4%)	0.28

Abbreviations: IQR, interquartile range; **AFB**, acid-fast bacilli; **TB**, tuberculosis; **Xpert**, Xpert MTB/RIF; ***Mtb***, *Mycobacterium tuberculosis*; **NTM,** non-tuberculous mycobacteria.

[*] **Legend**: Unless otherwise specified.

[†] Chi-squared test for binary outcomes; Wilcoxon rank-sum test for continuous outcomes.

[¶] 33 patients had missing or incomplete mycobacterial culture results in the pre-implementation period and 1 in the post-implementation period, either. Incomplete mycobacterial culture results occur when fewer than two samples are sent for culture, such as when an alternative diagnosis becomes apparent and the pre-test probability of TB is not high enough to warrant continuing testing.

[§] 2 NTM culture-positive patients were smear-positive in the pre-implementation period. 2 NTM culture-positive patients were smear-positive and 4 had incomplete smear examinations in the post-implementation period. No NTM culture-positive patients were Xpert-positive in the post-implementation period.

Table 2.

Length of hospital stay and time intervals in the diagnostic evaluation process for patients with negative results on rapid testing for pulmonary TB.

Time period, median (IQR)	Pre-implementation	Post-implementation	p-value
	n=223	n=250	
Hospital admission to hospital discharge, days *	6.0 (3.8–10.9)	4.9 (2.9–8.9)	0.003
Hospital admission to sputum collection, hours	19.1 (10.3–40.3)	18.0 (9.2–41.8)	0.62
Sputum collection to final negative result reporting, hours	39.1 (35.6–42.9)	22.4 (13.7–30.6)	<0.001
Sputum collection to first result reporting, hours	18.4 (15.5–23.6)	4.6 (3.4–6.9)	<0.001
Sputum collection to sputum receipt in lab, hours	1.5 (0.5–2.5)	1.1 (0.5–2.0)	0.02
Sputum receipt in lab to first result reporting, hours	16.0 (13.6–22.3)	2.9 (2.5–4.5)	<0.001
Final negative result reporting to hospital discharge, hours *	66.5 (26.6–160.3)	49.6 (21.5–139.8)	0.08

Abbreviations: IQR, interquartile range.

* **Legend**: One patient in the pre-implementation period and seven in the post-implementation period were missing the date and time of discharge from the hospital.

Table 3.

Length of stay in respiratory isolation and time intervals in the isolation process for patients with negative results on rapid testing for pulmonary TB.

Time period, median (IQR)	Pre-implementation*	Post-implementation*	p-value
	n=207	n=226	
Isolation admission to isolation discharge, days¶	2.9 (2.0–3.7)	2.5 (1.7–3.4)	0.001
Hospital admission to isolation admission, hours	2.4 (1.2–15.7)	1.8 (1.0–9.0)	0.06
Isolation admission to sputum collection, hours	12.9 (6.6–19.3)	13.5 (5.1–29.1)	0.50
Sputum collection to final negative result reporting, hours	39.3 (36.3–43.4)	21.9 (13.4–30.0)	<0.001
Final negative result reporting to isolation discharge, hours¶	13.9 (1.7–32.3)	15.9 (2.3–34.4)	0.52

Abbreviations: IQR, interquartile range.

*Legend: 16 patients in the pre-implementation period and 24 in the post-implementation period did not have isolation data available.

¶Two patients in the pre-implementation period and three in the post-implementation period were missing the date and time of discharge from isolation.