

Evaluation of Molecular Diagnostic Tests for TB (Option B Study)

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Request for Application: Performance Evaluation of Molecular Diagnostic Tests for Tuberculosis

Option B

Determining best practices for performing NAAT and the contribution of NAAT as it relates to the overall TB testing algorithm in the laboratory. Some examples include, number of diagnostic specimens receiving NAAT per patient (e.g., **incremental yield in smear negatives**), incremental yield of 1, 2, or 3 cultures inoculated per patient for diagnosis, or the need for confirmatory testing by another method when NAAT is positive.

SHL's Objectives

1. Determine the number of smear negative specimens from an individual patient on which NAAT should be performed in a low incidence population.
2. Determine how Rifampin resistance testing performs in a low prevalence setting.
3. Develop an algorithm indicating the number of NAATs to perform on smear negative specimens from patients based on suspicion for tuberculosis and risk factors.

Background

- Iowa has between 35 and 40 new TB cases per year
- Protocol at the time:
 - Perform naat on all new smear positive patients
 - Perform naat on smear negatives at the request of the TB controllers
 - We had been performing naat on up to three specimens per smear negative patient if the first naat was negative-what our controllers expected
- Wanted to move towards limiting that to two specimens per smear negative patient



- IRB Approval
- Purchase additional instrumentation and supplies
- Development of internal protocol
- Determination of enrollment criteria
- Development of enrollment process
- Maintenance of Data Collection Sheet
- Analyze data
- Determine algorithm

IRB Approval

IRB ID #: 201206743

To: Michael Pentella

From: IRB-01 DHHS Registration # IRB00000099,
Univ of Iowa, DHHS Federalwide Assurance # FWA00003007

Re: Iowa State Hygienic Laboratory Proposal for Evaluation of Molecular Diagnostic Tests for Tuberculosis (Study Option B)

Protocol Number:

Protocol Version:

Protocol Date:

Amendment Number/Date(s):

Approval Date: 07/03/12

Next IRB Approval Due Before: 07/03/13

Type of Application:

- New Project
- Continuing Review
- Modification

Type of Application Review:

- Full Board:
- Meeting Date:
- Expedited
- Exempt

Approved for Populations:

- Children
- Prisoners
- Pregnant Women, Fetuses, Neonates

Source of Support: Association of Public Health Laboratories

Investigational New Drug/Biologic Name:

Investigational New Drug/Biologic Number:

Name of Sponsor who holds IND:

Investigational Device Name:

Investigational Device Number:

Sponsor who holds IDE:

This approval has been electronically signed by IRB Chair:

J. Andrew Bertolatus, BA, MD

07/03/12 1404

Purchase Equipment and Supplies

Task/Supply Order List for Study B TB Project-Smear Negative Algorithm Design (red font indicates that that person completed the task)

Date Initiated	Assigned to:	Date Completed	Task
6/13/12	Mike/Univ	7/3/12	Apply for IRB
6/14/12	Yaz/Univ	6/28/12	Get MFK account (SHL) MFK:
6/19/12 (rec'd from CDC)	Yaz/Univ		Approval of Work Order sent by CDC
6/29/12	Beth	6/29/12	Order supplies (see supply list chart)
	Mike	NA	Order equipment
	Mary/Ryan	NA	Arrange for equipment installation
6/22/12	Mary	6/27/12	Write testing protocol for SHL staff (include algorithm that MO will use to submit)
6/29/12	Mary	6/29/12	Train SHL staff
6/14/12	Mary/Mike/Allan/Bridget	6/27/12	Complete/review spreadsheet for data collection (SHL and IDPH)
6/22/12	Mary	6/22/12	Start a log for recording successes and challenges encountered need date and outcome
6/20/12	Marv/lee Kester	NA (not feasible)	Data collection sheet posted on SHL site for SHL and IDPH shared access?



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www.instrumental.com

Study B Protocol/Checklist

- ✓ Place a green dot on the TRF, original specimen and processed specimen.
- ✓ Create a separate worksheet for Study B naats and place a green “B” sticker on the worksheet in the upper right-hand corner.
- ✓ Use grant specific MFK for MDDR Shipping.
- ✓ Make sure “not billed” QA event is added to each study patient’s “tbnaat1” test only, not the culture/smear, etc unless submitter has checked public health significance box.
- ✓ Ensure the QA event of “i-study b” is entered on each patient’s “tbnaat1”.
- ✓ Staff will track the number of initial diagnostic specimens submitted and limit to three of the same type within the first week to 10 days.

Please perform TB NAAT on the following patient with suspected TB disease

Enrollment Criteria-Patient Information Sheet

Please perform TB NAAT on the following patient with suspected TB disease

Name:	DOB: 1/1/1950	Name: Sample Patient	DOB: 1/1/1950
City/County:	Name:	City/County:	Name:
Plains, Iowa	1/1/1950	Plains, Iowa	Sample Patient
Submitter:	County Public Health		
City/County:	Plains, Iowa		
Submitter to County Public Health			

Submitter of TB NAAT must have signs/symptoms consistent with pulmonary TB.
In order to conduct TB NAAT, the patient must have signs/symptoms consistent with pulmonary TB.

- CXR or CT report that is consistent with pulmonary TB disease
- Abnormal CXR or CT report etiology unknown
- CXR site of plain weight consistent with pulmonary TB disease
- CXR site of plain weight consistent with pulmonary TB disease
- Coughing > three weeks consistent with pulmonary TB disease
- Abnormal CXR or CT report etiology unknown
- Hemoptysis
- Unexplained weight loss with breathing or coughing
- Coughing > three weeks
- Hemoptysis
- Chest pain or pain with breathing or coughing
- Other (List):

Additional Risk Factors:
 Close contacts of a person with infectious TB disease

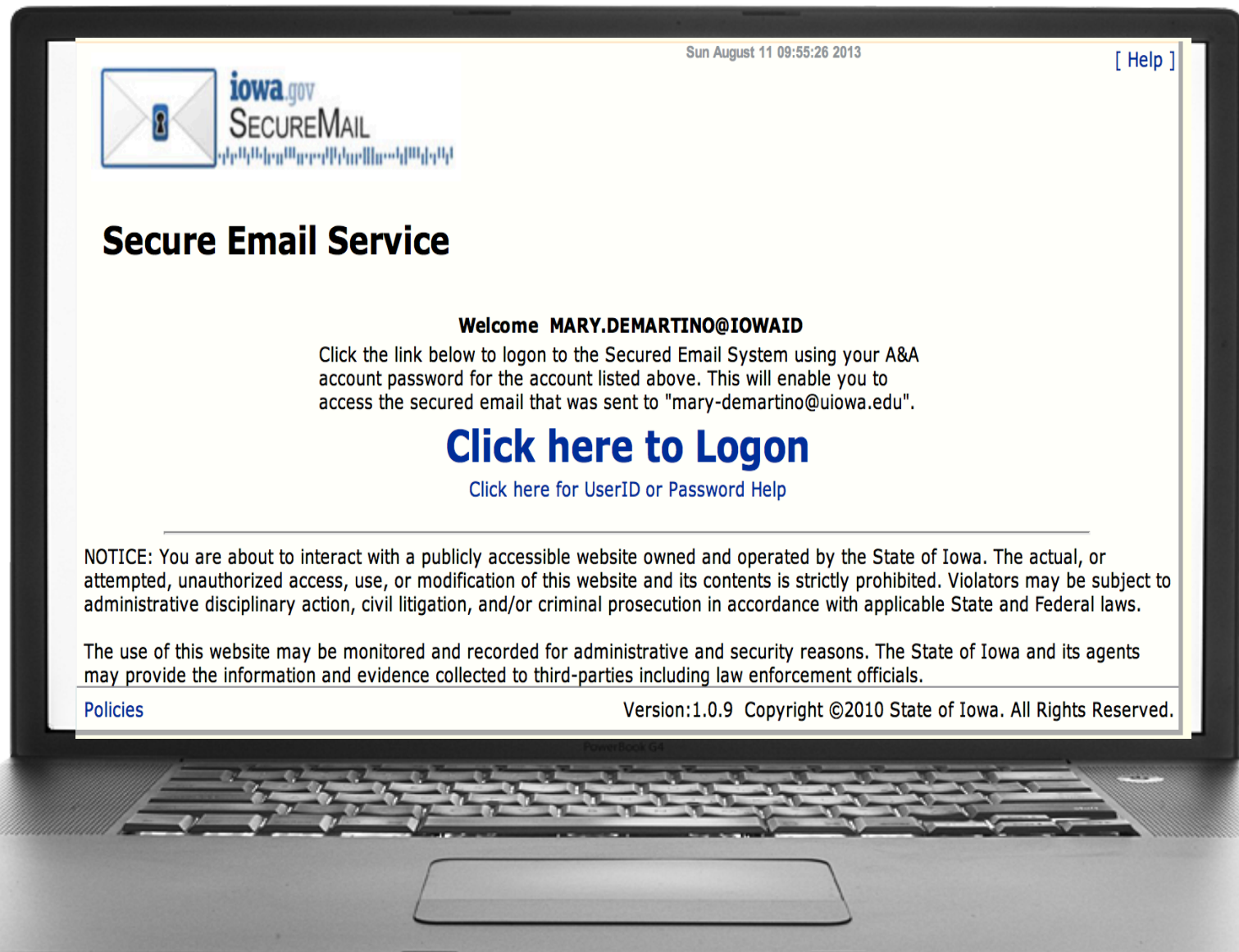
- Persons at risk for exposure to persons with TB disease include:
 - Close contacts of a person with infectious TB disease
 - Close contacts of a person with infectious TB disease
 - Close contacts of a person with infectious TB disease
 - Close contacts of a person with infectious TB disease
- Persons more likely to progress from LTBI to TB disease include:
 - Recent untreated persons (within 6 weeks) with a positive TST result
 - Recent untreated persons with a positive TST result
 - Recent untreated persons with a positive TST result
 - Recent untreated persons with a positive TST result
 - Recent untreated persons with a positive TST result
 - Recent untreated persons with a positive TST result
 - Recent untreated persons with a positive TST result
 - Recent untreated persons with a positive TST result

Clinical conditions increase the risk of progression from TB infection to TB disease:

- HIV infection
- Diabetes mellitus
- Chronic renal failure or being on hemodialysis
- Silicosis
- Gastric surgery
- Being on hemodialysis
- Being on hemodialysis
- Being on hemodialysis
- Head and neck cancer
- Head and neck cancer
- Head and neck cancer
- Head and neck cancer



Enrollment Process



Sun August 11 09:55:26 2013

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Maintenance of Data Collection- Specimen Information

DATA COLLECTION FOR APHL/CDC GRANT STUDY B-DEVELOPMENT OF A SMEAR NEGATIVE/NAAT ALGORITHM

Pt # for study	Specimen Information								GeneXpert			CDC
	PHIMS #	Spec Type	DOC	Rec'd	Smear	Culture Result (P orN)	Date +	Final ID	Mtbc	rpoB Mutation	Reported	CDC Rif Result
1	2012069142	sputum	7/13/12	7/16/12	neg	N			not det	NA	7/16/12	NA
	2012069143	sputum	7/14/12	7/16/12	neg	N			not det	NA	7/16/12	NA
	2012069146	sputum	7/13/12	7/16/12	neg	N			not det	NA	7/16/12	NA
34	2012114503	sputum	11/16/12	11/16/12	2+	P	11/26/12	Mtbc	Detected	not det	11/16/12	NA
	first specimen is smear positive and naat positive- no additional specimens tested											

Maintenance of Data Collection- Patient Information

Patient Information									
Last Name	First Name	DOB	Gender	S/S of TB	↑clinical suspicion	physician-high likelihood	travel hx/foreign born/high risk setting	ordering physician	Comments
R	O	2/2/30	m	X		X		Davidson/Allan Lynch	contact with known case; comorbidities
R	O	2/2/30	m	X		X		Davidson/Allan Lynch	
R	O	2/2/30	m	X		X		Davidson/Allan Lynch	
M	C	2/28/84	m	X			X	Pope/Konz	

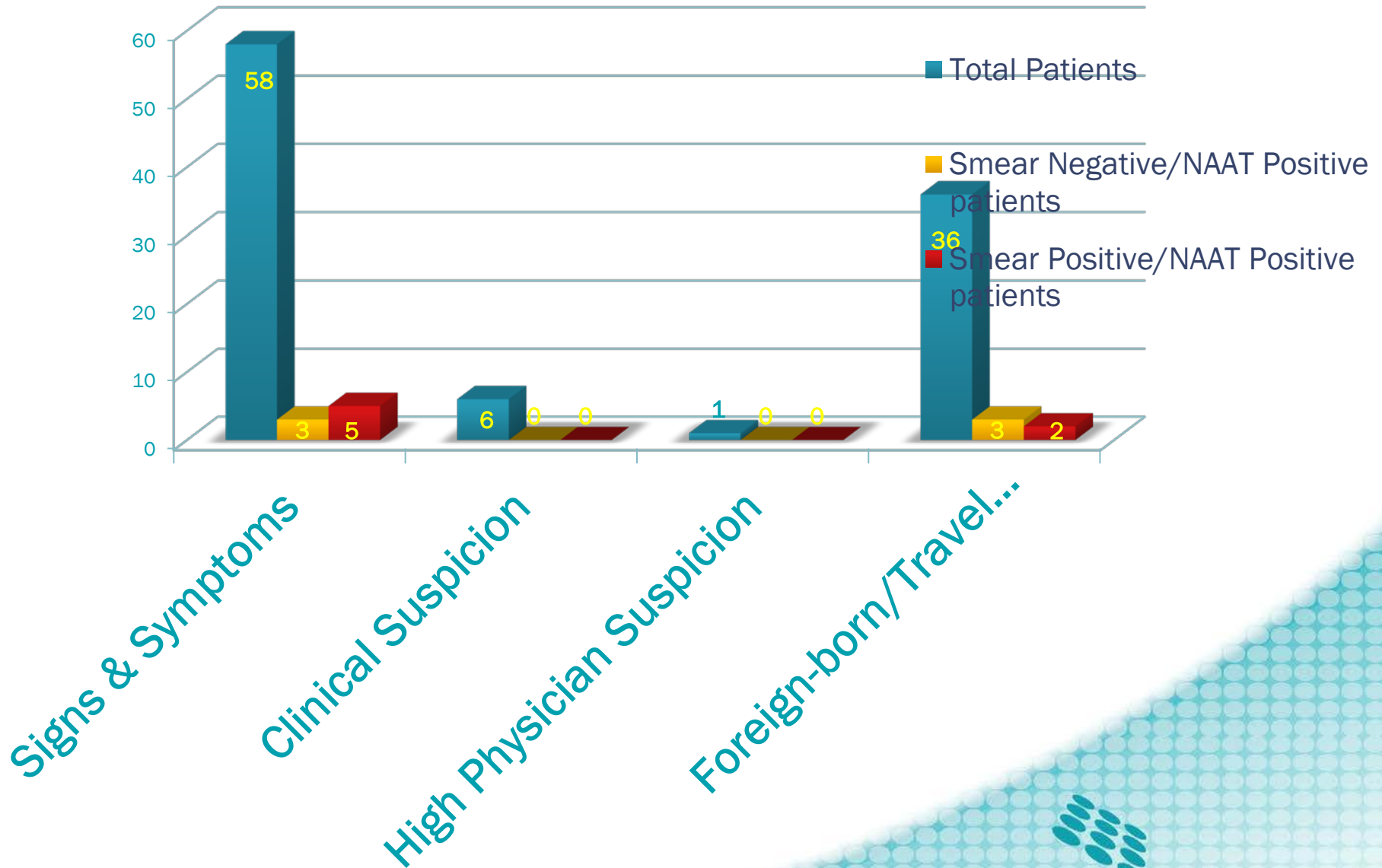
Data-Patients Enrolled-Specimens Tested

Total # of Specimens Tested	154
# of Patients for Whom IDPH Requested Enrollment	64
# of Enrolled Patients with specimens submitted	59
# of Patients with three specimens submitted	45 (76%)
# of Patients Enrolled with less than three specimens	14 (24%)
# of Patients with one specimen submitted	9 (15.3%)
# of Patients with two specimens submitted	5 (8.5%)

Data-Based on Enrollment Criteria

Criteria	Signs and Symptoms	Clinical Suspicion	High Physician Suspicion	Foreign-born/Travel Hx/High risk setting
Total Patients	58	6	1	36
Smear Negative/naat positive patients	3	0	0	3 (all immigrants from high risk countries)
Smear positive/naat positive patients	5	0	0	2 (all immigrants from high risk countries)

Data-Based on Enrollment Criteria



Data For Smear Negative Patients

# of Smear Negative Patients with three specimens submitted	41
# of Smear Negative Patients with three specimens submitted that were naat positive	3 (7%)
- naat positive on 1 st specimen	2 (67%)
-naat positive on 2 nd specimen	1 (33%)
-naat positive on 3 rd specimen	0

Data For Smear Positive Patients

# of Smear Positive Patients	10
# of patients with culture positive for Mtbc	6
# with naat positive on 1 st specimen	5
# with naat negative on 1 st specimen/+ on 2 nd specimen*	1

*naat positive on 2nd specimen but 2nd specimen was smear negative

Data-Other Findings

# of smear negative patients with negative naat and culture positive for Mtbc	1
# of smear negative patients with positive naat and culture negative for Mtbc	1
# of naat positive patients with naat results indicating that the organism would be rifampin resistant	0
# of patients with Mtbc where conventional susceptibility testing demonstrated rifampin resistance	0

Objective 1-Mostly Met

- Regardless of smear results patients who grew *Mycobacterium tuberculosis* complex (mostly) did not require more than two specimens to achieve a positive naat.

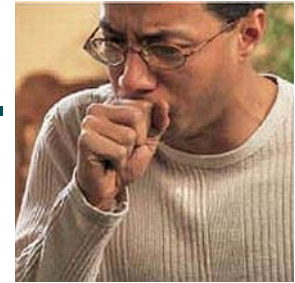


Objective 2-Not Met

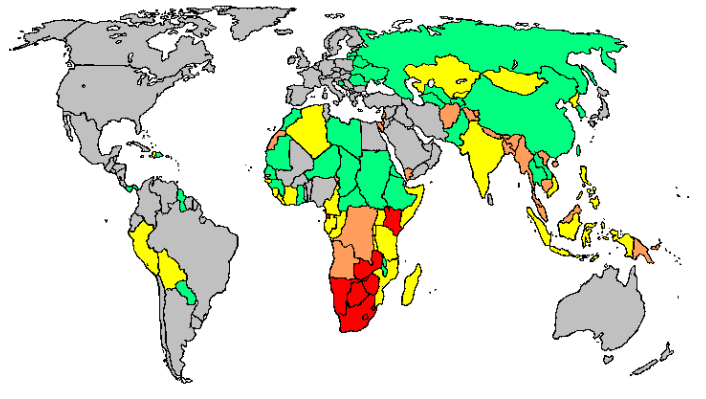
- We had no specimens that were Rifampin resistant by the GeneXpert and no patients whose conventional susceptibility testing indicated rifampin resistance.

Conclusions on Risk Factors

➤ 58 (98%) of the 59 patients tested were noted to have signs and symptoms of TB.



➤ 37 (63%) of the 59 patients tested were noted as meeting the criteria of being foreign-born or having a history of travel to a high risk country or living in a high-risk setting.



Objective 3-Met

- 100% of the naat positive specimens, regardless of smear results, were noted to have signs and symptoms of TB and immigrated from a high risk country.
- This indicates that presenting with signs and symptoms of TB is the most important indicator when deciding if a patient should have a naat performed.



Naat identified 7% (3 out of 41) of smear negative patients who were

M. tuberculosis complex positive within 24 hours of receipt of specimen.



Ensuring that the requested number of specimens recommended for initial diagnosis of tuberculosis were submitted.



Patients with inconsistent smear results and naat results for the three initial diagnostic specimens.

- There were two patients who had specimens that were smear negative, naat negative and culture positive for *Mycobacterium tuberculosis* complex.



There was one patient whose first specimen was smear positive, naat negative and culture positive. Their second specimen was smear negative, naat positive and culture positive and their third specimen was smear negative, naat negative and the culture negative.



There was one patient with three specimens submitted. All three were smear negative and culture negative but the first specimen received was naat positive. The naat on each of the other two specimens was negative. TB Controllers indicate that this patient was reported as a verified case.



Michael Pentella-CLIA Director

SHL Staff

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IDPH TB Controllers

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