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 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

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

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

Name: Sample Patient
City/County: Plains, Iowa
DOB: 1/1/1990
City/County: Plains, Iowa
Submitter: County Public Health

Submitters on County Public Health: The patient must have signs/symptoms consistent with pulmonary TB.

In order to consider the TB NAAT specimen, the patient must have signs/symptoms consistent with pulmonary TB.

Specimens/Specimen Information:

- CXR or CT report that is consistent with pulmonary TB disease
- CXR or CT report that is consistent with pulmonary TB disease
- CXR or CT report that is consistent with pulmonary TB disease
- Abnormal CXR or CT report etiology unknown
- Coughing < three weeks
- Hemoptysis
- Coughing > three weeks
- Hemoptysis
- Other (List):
  - __________
  - __________
  - __________
  - __________
  - __________

Additional Risk Factor: Exposure to persons with TB disease includes:

- Close contacts of a person with infectious TB disease

Additional Risk Factor: Persons at risk for exposure to persons with TB disease include:

- Close contacts of a person with infectious TB disease
- Persons who reside in the United States who have been exposed to persons with TB disease
- Persons who reside outside the United States who have been exposed to persons with TB disease
- Persons who reside in the United States who have been exposed to persons with TB disease
- Persons who reside outside the United States who have been exposed to persons with TB disease
- Persons who reside in the United States who have been exposed to persons with TB disease
- Persons who reside outside the United States who have been exposed to persons with TB disease

Persons at risk for exposure to persons with TB disease include:

- Persons with a history of pharyngeal TB or TB disease
- Persons with a history of pharyngeal TB or TB disease
- Persons with a history of pharyngeal TB or TB disease
- Persons with a history of pharyngeal TB or TB disease
- Persons with a history of pharyngeal TB or TB disease
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- Persons with a history of pharyngeal TB or TB disease

Clinical condition to increase the risk of progression from LTBI to TB disease:

- Clinical condition: weight 10% below ideal
- Clinical condition: weight 10% below ideal
- Clinical condition: weight 10% below ideal
- Clinical condition: weight 10% below ideal
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- Clinical condition: weight 10% below ideal
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Clinical condition to increase the risk of progression from LTBI to TB disease:

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Clinical condition to increase the risk of progression from LTBI to TB disease:

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- Clinical condition: weight 10% below ideal
- Clinical condition: weight 10% below ideal
- Clinical condition: weight 10% below ideal
- Clinical condition: weight 10% below ideal
- Clinical condition: weight 10% below ideal
- Clinical condition: weight 10% below ideal

Other (List):

- __________
- __________
- __________
- __________
- __________
- __________
- __________
- __________

APHL ASSOCIATION OF PUBLIC HEALTH LABORATORIES
Enrollment Process

Secure Email Service

Welcome MARY.DEMARTINO@IOWAID
Click the link below to logon to the Secured Email System using your A&A account password for the account listed above. This will enable you to access the secured email that was sent to "mary-demartino@uiowa.edu".

Click here to Logon

Click here for UserID or Password Help

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Policies

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## Maintenance of Data Collection - Specimen Information

<table>
<thead>
<tr>
<th>Pt # for study</th>
<th>PHIMS #</th>
<th>Spec Type</th>
<th>DOC</th>
<th>Rec'd</th>
<th>Smear</th>
<th>Culture Result (P or N)</th>
<th>Date +</th>
<th>Final ID</th>
<th>Mtbc</th>
<th>rpoB Mutation</th>
<th>CDC Rif Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2012069142</td>
<td>sputum</td>
<td>7/13</td>
<td>7/16</td>
<td>neg</td>
<td>N</td>
<td>NA</td>
<td>not det</td>
<td>NA</td>
<td>7/16/12</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>2012069143</td>
<td>sputum</td>
<td>7/14</td>
<td>7/16</td>
<td>neg</td>
<td>N</td>
<td>NA</td>
<td>not det</td>
<td>NA</td>
<td>7/16/12</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>2012069146</td>
<td>sputum</td>
<td>7/13</td>
<td>7/16</td>
<td>neg</td>
<td>N</td>
<td>NA</td>
<td>not det</td>
<td>NA</td>
<td>7/16/12</td>
<td>NA</td>
</tr>
<tr>
<td>34</td>
<td>2012114503</td>
<td>sputum</td>
<td>11/16</td>
<td>11/16</td>
<td>2+</td>
<td>P</td>
<td>11/26</td>
<td>Mtbc</td>
<td>Detected</td>
<td>not det</td>
<td>11/16/12</td>
</tr>
</tbody>
</table>

First specimen is smear positive and naat positive - no additional specimens tested.
## Maintenance of Data Collection - Patient Information

<table>
<thead>
<tr>
<th>Last Name</th>
<th>First Name</th>
<th>DOB</th>
<th>Gender</th>
<th>S/S of TB</th>
<th>*clinical suspicion</th>
<th>physician-high likelihood</th>
<th>travel hx/foreign born/high risk setting</th>
<th>ordering physician</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>O</td>
<td>2/2/30 m</td>
<td>M</td>
<td>X</td>
<td>X</td>
<td></td>
<td>Davidson/Allan Lynch</td>
<td></td>
<td>contact with known case; comorbidities</td>
</tr>
<tr>
<td>R</td>
<td>O</td>
<td>2/2/30 m</td>
<td>M</td>
<td>X</td>
<td>X</td>
<td></td>
<td>Davidson/Allan Lynch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>O</td>
<td>2/2/30 m</td>
<td>M</td>
<td>X</td>
<td>X</td>
<td></td>
<td>Davidson/Allan Lynch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>C</td>
<td>2/28/84 m</td>
<td>M</td>
<td>X</td>
<td></td>
<td></td>
<td>Pope/Konz</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Data-Patients Enrolled-Specimens Tested

<table>
<thead>
<tr>
<th>Total # of Specimens Tested</th>
<th>154</th>
</tr>
</thead>
<tbody>
<tr>
<td># of Patients for Whom IDPH Requested Enrollment</td>
<td>64</td>
</tr>
<tr>
<td># of Enrolled Patients with specimens submitted</td>
<td>59</td>
</tr>
<tr>
<td># of Patients with three specimens submitted</td>
<td>45 (76%)</td>
</tr>
<tr>
<td># of Patients Enrolled with less than three specimens</td>
<td>14 (24%)</td>
</tr>
<tr>
<td># of Patients with one specimen submitted</td>
<td>9 (15.3%)</td>
</tr>
<tr>
<td># of Patients with two specimens submitted</td>
<td>5 (8.5%)</td>
</tr>
</tbody>
</table>
## Data-Based on Enrollment Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Signs and Symptoms</th>
<th>Clinical Suspicion</th>
<th>High Physician Suspicion</th>
<th>Foreign-born/Travel Hx/High risk setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Patients</td>
<td>58</td>
<td>6</td>
<td>1</td>
<td>36</td>
</tr>
<tr>
<td>Smear Negative/naat positive patients</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3 (all immigrants from high risk countries)</td>
</tr>
<tr>
<td>Smear positive/naat positive patients</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>2 (all immigrants from high risk countries)</td>
</tr>
</tbody>
</table>
Data-Based on Enrollment Criteria

- **Total Patients**: 58
- **Smear Negative/NAAT Positive patients**: 3
- **Smear Positive/NAAT Positive patients**: 6

**Categories**:
- Signs & Symptoms
- Clinical Suspicion
- High Physician Suspicion
- Foreign-born/Travel...

*Data Based on Enrollment Criteria*
# Data For Smear Negative Patients

<table>
<thead>
<tr>
<th># of Smear Negative Patients with three specimens submitted</th>
<th>41</th>
</tr>
</thead>
<tbody>
<tr>
<td># of Smear Negative Patients with three specimens submitted that were naat positive</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>- naat positive on 1\textsuperscript{st} specimen</td>
<td>2 (67%)</td>
</tr>
<tr>
<td>- naat positive on 2\textsuperscript{nd} specimen</td>
<td>1 (33%)</td>
</tr>
<tr>
<td>- naat positive on 3\textsuperscript{rd} specimen</td>
<td>0</td>
</tr>
</tbody>
</table>
## Data For Smear Positive Patients

<table>
<thead>
<tr>
<th># of Smear Positive Patients</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td># of patients with culture positive for Mtbc</td>
<td>6</td>
</tr>
<tr>
<td># with naat positive on 1\textsuperscript{st} specimen</td>
<td>5</td>
</tr>
<tr>
<td># with naat negative on 1\textsuperscript{st} specimen/+ on 2\textsuperscript{nd} specimen*</td>
<td>1</td>
</tr>
</tbody>
</table>

*naat positive on 2\textsuperscript{nd} specimen but 2\textsuperscript{nd} specimen was smear negative*
# Data-Other Findings

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td># of smear negative patients with negative naat and culture positive for Mtbc</td>
<td>1</td>
</tr>
<tr>
<td># of smear negative patients with positive naat and culture negative for Mtbc</td>
<td>1</td>
</tr>
<tr>
<td># of naat positive patients with naat results indicating that the organism would be rifampin resistant</td>
<td>0</td>
</tr>
<tr>
<td># of patients with Mtbc where conventional susceptibility testing demonstrated rifampin resistance</td>
<td>0</td>
</tr>
</tbody>
</table>
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
Ryan Jepson
Beth Albaugh
Jolynn Koehler
Jennifer Elwood
Bob Rotzoll
Erin Nelson

IDPH TB Controllers
Bridget Konz
Allan Lynch