Performance Evaluation and Clinical Application of MTB NAAT in Orange County, CA

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Orange County Public Health Laboratory
TB Case Count and Rate:
Orange County, CA and the United States, 2012

**Orange County**
- 192 cases
- TB rate = 6.3 per 100,000 population

**California**
- 2,185 cases
- TB rate=5.8 per 100,000 population

**United States**
- 9,951 cases
- TB rate=3.2 per 100,000 population
Characteristics of Active TB Cases
Orange County and the United States, 2012

Orange County
- U.S. born: 10%
- Foreign-born: 90%

United States
- U.S. born: 37%
- Foreign-born: 63%
Tuberculosis Cases by Race/Ethnicity
Orange County and the United States, 2012

### Orange County
- **Asian**: 69.8%
- **Hispanic**: 24.5%
- **Other**: 0.5%
- **White**: 4.2%
- **Black**: 1.0%

### United States
- **Asian**: 30.8%
- **Hispanic**: 28.3%
- **White**: 15.9%
- **Black**: 22.5%
- **Other**: 2.4%
OCPHL TB Services Provided

Provide testing services for a suburban population of over 3 million residents

- Direct detection of MTB
- Culture and identification of mycobacteria
  - AccuProbe (GenProbe)
  - HPLC
  - 16S DNA Sequencing
  - Conventional Biochemical Testing
- DST for MTB using first and second-line drugs (MGIT 960)
OCPHL’s Experience with NAAT

- OCPHL has been involved in NAAT testing and research since 1993.
- Our data was referenced in the 2009 CDC guidelines for NAAT testing (MMWR, 2009).
- Publications include:
Study A

- Collaborate with TB Control Program
- Expand current NAAT algorithm to follow CDC recommendations (MMWR 2009)
- Analyze performance of GeneXpert in comparison to culture results, patient diagnostic and treatment information

Study C

- Evaluate GeneXpert for its ability to detect mutations often associated with Rifampin-resistance
- OC is a low prevalence (2.2%) jurisdiction for Rifampin-resistance
Routine Algorithm for NAAT Testing and Current Grant (highlighted)

Processed Respiratory Specimens (N=550)

Culture (LJ, MGIT)
  - MTB by Culture
    - DST MGIT 960
  - Culture Negative for MTB
  - Smear Positive (N=62)
    - NAAT
  - Smear Negative (N=488)
    - For this study: NAAT

AFB Smear
Objective 1:

• Collaborate with the TB Control Program to assess the clinical impact of positive and negative NAAT results
Study A

- TB Case?
- Did NAAT result affect decision to treat? How?
- Did NAAT result initiate a contact investigation?
- Did NAAT result affect isolation of patient?
### Study A

**Summary of the clinical impact of NAAT in conjunction with smear results**

<table>
<thead>
<tr>
<th></th>
<th>TB Case?</th>
<th>Contact Investigation</th>
<th>NAAT initiated Contact Investigation?</th>
<th>Pt Isolated</th>
<th>NAAT affect isolation?</th>
<th>Avg Days Isolated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>Yes</td>
<td>No</td>
<td>NA*</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Smear-Pos/NAAT-Pos</td>
<td>28 (5.4)</td>
<td>28</td>
<td>0</td>
<td>0</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>Smear-Neg/NAAT-Pos</td>
<td>18 (3.5)</td>
<td>14</td>
<td>4</td>
<td>0</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Smear-Pos/NAAT-Neg</td>
<td>9 (1.7)</td>
<td>0</td>
<td>9</td>
<td>0</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Smear-Neg/NAAT-Neg</td>
<td>465 (89.4)</td>
<td>56</td>
<td>400</td>
<td>9</td>
<td>27</td>
<td>431</td>
</tr>
<tr>
<td>Total No.</td>
<td>520 (100)</td>
<td>98</td>
<td>413</td>
<td>9</td>
<td>60</td>
<td>452</td>
</tr>
</tbody>
</table>

*NA = Result not available
Objective 2:

- Provide evidence to develop an effective validated laboratory algorithm that directs use of NAAT at a TB Programmatic level by identifying patient populations on whom NAAT testing should be performed to maximize efficiency of NAAT for appropriate TB suspects.
Distribution of Variables in the study population
(N=520 patients)
Study A

Objective 3:

- To determine the effectiveness of performing NAAT on patients that have a negative AFB smear

N=550 specimens

<table>
<thead>
<tr>
<th>Cepheid GeneXpert</th>
<th>MTB Detection</th>
<th>MTB Detected in Any Culture</th>
<th>Smear Positive</th>
<th>Smear Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>83.7%</td>
<td>86.2%</td>
<td>96.9%</td>
<td>58.8%</td>
</tr>
<tr>
<td>Specificity</td>
<td>98.0%</td>
<td>99.8%</td>
<td>96.7%</td>
<td>98.1%</td>
</tr>
<tr>
<td>PPV</td>
<td>80.4%</td>
<td>98.0%</td>
<td>96.9%</td>
<td>52.6%</td>
</tr>
<tr>
<td>NPV</td>
<td>98.4%</td>
<td>98.4%</td>
<td>96.7%</td>
<td>98.5%</td>
</tr>
</tbody>
</table>
Study A

Objective 4:

• To determine usefulness of AFB smear microscopy in an era of NAAT by comparing NAAT to AFB smear results
### Study A

Parameters of AFB Microscopy compared to GeneXpert for Identification of MTB

<table>
<thead>
<tr>
<th></th>
<th>AFB Microscopy</th>
<th>GeneXpert</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>65.3%</td>
<td>83.7%</td>
</tr>
<tr>
<td>Specificity</td>
<td>94.0%</td>
<td>98.0%</td>
</tr>
<tr>
<td>PPV</td>
<td>51.6%</td>
<td>80.4%</td>
</tr>
<tr>
<td>NPV</td>
<td>96.5%</td>
<td>98.4%</td>
</tr>
</tbody>
</table>

### Distribution of AFB Smear Results

<table>
<thead>
<tr>
<th>Smear</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neg</td>
<td>488</td>
<td>88.7%</td>
</tr>
<tr>
<td>1+</td>
<td>29</td>
<td>5.3%</td>
</tr>
<tr>
<td>2+</td>
<td>15</td>
<td>2.7%</td>
</tr>
<tr>
<td>3+</td>
<td>13</td>
<td>2.4%</td>
</tr>
<tr>
<td>4+</td>
<td>5</td>
<td>0.9%</td>
</tr>
</tbody>
</table>
GeneXpert Results Compared to Smear
(N=51 specimens that were detected by NAAT)

<table>
<thead>
<tr>
<th>AFB Smear Result</th>
<th>High</th>
<th>Med</th>
<th>Low</th>
<th>V Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>10%</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>20%</td>
<td>0</td>
<td>1</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>30%</td>
<td>0</td>
<td>6</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>40%</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>50%</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>60%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>70%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>80%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>90%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>100%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Objective 5:

• To evaluate the overall performance of NAAT for the population of Orange County, and to explore the best approach to using NAAT, including the use of detection of possible Rifampin-resistance
Overall Performance of the GeneXpert for Detection of MTB and Rifampin-resistance

<table>
<thead>
<tr>
<th>Cepheid GeneXpert</th>
<th>MTB Detection</th>
<th>MTB Detected in Any Culture</th>
<th>RIF-R Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>83.7%</td>
<td><strong>86.2%</strong></td>
<td>100.0%</td>
</tr>
<tr>
<td>Specificity</td>
<td>98.0%</td>
<td><strong>99.8%</strong></td>
<td>100.0%</td>
</tr>
<tr>
<td>PPV</td>
<td>80.4%</td>
<td>98.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>NPV</td>
<td>98.4%</td>
<td><strong>98.4%</strong></td>
<td>100.0%</td>
</tr>
</tbody>
</table>
550 SPECIMENS

49 MTB+

32 SMEAR +
- 31 NAAT+
- 1 NAAT-

17 SMEAR -
- 10 NAAT+
- 7 NAAT-

501 MTB-

30 SMEAR +
- 1 NAAT+
- 29 NAAT-

471 SMEAR -
- 9 NAAT+
- 462 NAAT-

MTB CX + ON OTHER SPECIMEN

4 MTB CX + ON OTHER SPECIMENS

4 MTB CX + ON OTHER SPECIMENS

5 HISTORY OF TB TREATMENT

36 MTB CX + ON OTHER SPECIMENS
Study C

Objective 1
• To assess the PPV of the GeneXpert for detecting mutations associated with Rifampin-resistance

Objective 2
• To compare the turnaround time of the GeneXpert with culture DST for Rifampin resistance

Objective 3
• To determine the overall performance of GeneXpert in detecting Rifampin resistance
Study C

Objective 1

- To assess the PPV of the GeneXpert for detecting mutations associated with Rifampin-resistance

<table>
<thead>
<tr>
<th>Cepheid GeneXpert</th>
<th>RIF-R Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPV</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
Objective 2

- To compare the turnaround time of the GeneXpert with culture DST for detection of Rifampin resistance
- NAAT result was reported within an average of 2.4 days from the date received, whereas the culture DST result was reported within average of 30.8 days from the date received
Objective 3

- To determine the overall performance of GeneXpert in detecting Rifampin resistance

<table>
<thead>
<tr>
<th>Cepheid GeneXpert</th>
<th>RIF-R Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>100.0%</td>
</tr>
<tr>
<td>Specificity</td>
<td>100.0%</td>
</tr>
<tr>
<td>PPV</td>
<td>100.0%</td>
</tr>
<tr>
<td>NPV</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
### Results of the GeneXpert in Detecting Rifampin Resistance

<table>
<thead>
<tr>
<th></th>
<th>MTB RIF-R</th>
<th>MTB RIF-S</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>GeneXpert RIF-R</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>GeneXpert RIF-S</td>
<td>0</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>GeneXpert MTB Not Detected*</td>
<td>0</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>47</td>
<td>49</td>
</tr>
</tbody>
</table>
Conclusions

• The GeneXpert NAAT is a useful test that provides rapid results for early detection of MTB.

• When positive for MTB detection, it can accurately detect mutations associated with Rifampin-resistance.

• The GeneXpert turnaround time for detection of possible Rifampin resistance was much faster than culture DST.
Conclusions

- Sensitivity of NAAT in smear-negative specimens was 58.8%, however NAAT accurately detected MTB on 10 specimens that were smear-negative.

- Eight TB cultures were reported as “MTB Not-Detected” by GeneXpert.
Recommendations

• Continue NAAT on smear-positives
• Continue NAAT on smear-negatives per client request based on clinical suspicion of MTB
• We are still continuing data collection for additional specimens (total of 670)
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• Dr. Christopher Ried
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