NAAT in the Clinical Laboratory and Impact on Infection Control
9th National Conference on Laboratory Aspects of Tuberculosis
APHL

Susan Novak-Weekley, S(M), ASCP, Ph.D., D(ABMM)
Director of Microbiology, Molecular Infectious Disease, Serology
SCPMG Regional Reference Laboratories, North Hollywood CA
Research Studies

- Roche Molecular
- Pocared
- Nanosphere
- Bruker

- No personal disclosures
The only comprehensive online resource for clinical microbiologists.

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- **ASM Programs** can be found on one site that houses all of ASM's clinical content.
- **Lab Management** links users to a variety of tools that help facilitate and optimize the work of the laboratory manager.
Agenda

- Introduction to Kaiser Permanente
- Background *M. tuberculosis*
- AFB Testing at KP / GeneXpert Assay
- Future Opportunities – Infection Control
Our Strategy

INTEGRATED DELIVERY SYSTEM

HEALTH PLAN
The Kaiser Permanente Model
A Prepaid Integrated Healthcare Delivery System

- America’s largest not-for-profit health plan
- Prepaid Service (Capitation, Not Fee for Service)
  - Prevention = Success
- Integration
  - Health Plan, Hospitals, Physician Group
Kaiser Permanente

- Kaiser Southern California
  - >4 Million Members So Cal
  - 14 Hospitals
    - Each with Medical Center Lab
  - ~200 Medical Office Buildings
  - ~6000 physicians
  - ~200,000 Admissions Per Year
  - 1 Centralized Regional Reference Laboratory (soon to be 2)
    - Microbiology (full service lab)
      - ~18,000 AFB Cultures annually
    - 4 Million tests annually
Global TB Burden

• Global burden of TB in 2013\(^1\)
  – 9.0 million new cases
  – 1.5 million deaths
  – 480,000 people developed **MDR-TB** worldwide

• US TB incidence in 2013\(^2\)
  – 9,582 new cases reported
  – 65\% of cases occurred in foreign-born person
  – Primary MDR TB (Multi-drug Resistant TB) rate at 1.0\% 

• Rapid access to test results is critical
  – Accurate diagnosis
  – Appropriate treatment
  – Limit the spread of infection

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2. Reported Tuberculosis in The United States 2013, Centers for Disease control and Prevention
US TB Burden

Growing concerns about TB & MDR-TB

- An estimated 10 to 15 million US citizens have latent TB infection, and about ten percent of these individuals will develop TB at some point in their lives.\(^1\)

- Costly TB outbreaks still occur, multi-drug resistant TB (MDR-TB) continues to spread, and extensively-drug resistant TB (XDR-TB) is now present, as well. Altogether, TB-related costs approach $1 billion each year in the US.\(^2\)

Tuberculosis cases among US born and foreign-born

* Per 100,000 population.
† Data are updated as of February 24, 2014. Data for 2013 are provisional.

Source: MMWR March 21, 2014 vol. 63 / No. 11
Rate of tuberculosis (TB) cases, by state/area --- United States, 2013

Source: MMWR March 21, 2014 vol. 63 / No. 11
TB Cases CA

- 2008: 2600
- 2009: 2400
- 2010: 2300
- 2011: 2200
- 2012: 2100
- 2013: 2000
- 2014: 1900
Figure 13. Tuberculosis Cases with Multidrug Resistance (MDR) on Initial or Final Drug Susceptibility Testing*: California, 2002-2011

*Cases with resistance to at least isoniazid and rifampin reported on the Initial Drug Susceptibility Report (Follow-up 1) or on the Case Completion Report (Follow-up 2)

California Department of Public Health, Tuberculosis Control Branch
## KP STATS

<table>
<thead>
<tr>
<th></th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong># AFB CULTURES</strong></td>
<td>17943</td>
<td>15807</td>
<td>14933</td>
<td>14867</td>
<td>15772</td>
<td>17210</td>
<td>17483</td>
<td>17879</td>
</tr>
<tr>
<td><strong># AFB POS CXS</strong></td>
<td>1651</td>
<td>1474</td>
<td>1432</td>
<td>1529</td>
<td>1569</td>
<td>1929</td>
<td>1777</td>
<td>2058</td>
</tr>
<tr>
<td>(9.2%)</td>
<td>(9.3%)</td>
<td>(9.6%)</td>
<td>(10.2%)</td>
<td>(9.9%)</td>
<td>(11.2%)</td>
<td>(10.16%)</td>
<td>(11.5%)</td>
<td></td>
</tr>
<tr>
<td>AFB POS Cx</td>
<td>1651</td>
<td>1474</td>
<td>1432</td>
<td>1529</td>
<td>1569</td>
<td>1929</td>
<td>1777</td>
<td>2058</td>
</tr>
<tr>
<td><strong># MTBC Cx POS</strong></td>
<td>407</td>
<td>341</td>
<td>341</td>
<td>362</td>
<td>416</td>
<td>426</td>
<td>404</td>
<td>367</td>
</tr>
<tr>
<td>(24.6%)</td>
<td>(23.1%)</td>
<td>(23.8%)</td>
<td>(25.7%)</td>
<td>(26.5%)</td>
<td>(22.8%)</td>
<td>(22.7%)</td>
<td>(17.8%)</td>
<td></td>
</tr>
</tbody>
</table>
AFB Ordering/Algorithms – Kaiser

- **Orderable - Culture**
  - Includes smear
  - Reflexive testing on AFB smear positives ONLY
    - MTB PCR **not orderable** within our EMR – lab orderable only
    - CDC Recommendations – Challenges with who gets culture orders

- **Orderable - AFB Smear only**

- **Susceptibility testing**
  - Send out to reference laboratory
  - One of the most challenging areas in the lab to deal with
    - Physicians are not happy with TAT
    - Want testing internalized
    - Sessions at this meeting highlight challenges clinical labs face
## AFB Smear Only – In Line Physician Decision Support

<table>
<thead>
<tr>
<th>Name</th>
<th>Code</th>
<th>Formulary</th>
<th>Sig/Dose</th>
<th>Type</th>
<th>Pref List</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFB CULTURE</td>
<td>87116E</td>
<td></td>
<td></td>
<td>Lab</td>
<td>SCAL FACILITY RV f</td>
<td></td>
</tr>
<tr>
<td>AFB CULTURE, BLOOD</td>
<td>87116H</td>
<td></td>
<td></td>
<td>Lab</td>
<td>SCAL FACILITY RV f</td>
<td></td>
</tr>
<tr>
<td>AFB SMEAR, KNOWN TB PATIENT</td>
<td>87206AE</td>
<td></td>
<td></td>
<td>Lab</td>
<td>SCAL FACILITY RV f</td>
<td></td>
</tr>
</tbody>
</table>

3 loaded. No more to load.
AFB Ordering – Kaiser Challenges

- **AFB Culture – known positive patients**
  - Multiple cultures were being ordered on the same known TB positive patient to remove patient from isolation
    - Unchecked this created increased *workload, waste and cost* for the department
    - Some patients >30 cultures within a month

- **Created orderable AFB Smear Only**
  - Concern – physicians don’t order culture and would use for primary diagnosis
  - Tracked by department that patient is a known TB positive patient
    - Manual tracking inherently difficult
  - Continued education on usefulness of this order
Updated Guidelines for the use of NAAT in the Diagnosis of TB

- CDC recommends that **NAA testing be performed on at least one respiratory specimen from each patient** with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test result would alter case management or TB control activities, such as contact investigations. These guidelines update the previously published guidelines (1,2).
History of Molecular Testing TB within Kaiser

- Roche TB PCR - 1998 - 2011
- Gen-probe MTD - March 2011 to June 2014
- GeneXpert MTB/RIF - June 2014 to present

Roche Gen Probe Cepheid
Hologic Amplified MTD Test
Hologic MTD

- The Hologic Amplified Mycobacterium Tuberculosis Direct (MTD) Test is a target-amplified nucleic acid probe test for the in vitro diagnostic detection of Mycobacterium tuberculosis complex ribosomal ribonucleic acid (rRNA) in acid-fast bacilli (AFB) smear positive and negative concentrated sediments prepared from sputum (induced or expectorated), bronchial specimens (e.g., bronchoalveolar lavages or bronchial aspirates) or tracheal aspirates.

- FDA approved smear neg and smear pos sediments

- The MTD test utilizes Transcription-Mediated Amplification (TMA) and HPA to qualitatively detect M. tuberculosis complex rRNA.
MTD

- Am J Respir Crit Care Med – 2008, 178:300
- Single first sputum tested by NAA can rapidly detect patient that are in need of respiratory isolation, better than 3 consecutive smears
- NAA potential to shorten respiratory isolation time

Feasibility of Shortening Respiratory Isolation with a Single Sputum Nucleic Acid Amplification Test

Michael Campos¹, Andrew Quartin¹, Eliana Mendes¹, Alexandre Abreu¹, Samuel Gurevich¹, Luis Echarte¹, Tanira Ferreira², Timothy Cleary¹, Elena Hollender¹,², and David Ashkin¹,²
### Table A.2-a: MTD Performance Using Patient Diagnosis as the Endpoint

#### 1st Specimen
**N=206**

<table>
<thead>
<tr>
<th></th>
<th>Smear Positive Patient</th>
<th>Smear Negative Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>87.5% (28/32)</td>
<td>64.0% (16/25)</td>
</tr>
<tr>
<td></td>
<td>[71.0%-96.5%]</td>
<td>[42.5%-82.0%]</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>100% (7/7)</td>
<td>100% (142/142)</td>
</tr>
<tr>
<td></td>
<td>[59.0%-100%]</td>
<td>[97.4%-100%]</td>
</tr>
<tr>
<td><strong>PPV</strong></td>
<td>100% (28/28)</td>
<td>100% (16/16)</td>
</tr>
<tr>
<td></td>
<td>[87.7%-100%]</td>
<td>[79.4%-100%]</td>
</tr>
<tr>
<td><strong>NPV</strong></td>
<td>63.6% (7/11)</td>
<td>94.0% (142/149)</td>
</tr>
<tr>
<td></td>
<td>[30.8%-89.1%]</td>
<td>[90.6%-98.1%]</td>
</tr>
</tbody>
</table>

### Table A.2-b: MTD Performance Using Patient Diagnosis as the Endpoint

#### 1st and 2nd Specimen
**N=165**

<table>
<thead>
<tr>
<th></th>
<th>Smear Positive Patient</th>
<th>Smear Negative Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>100% (24/24)</td>
<td>71.4% (15/21)</td>
</tr>
<tr>
<td></td>
<td>[85.8%-100%]</td>
<td>[47.8%-88.7%]</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>100% (6/6)</td>
<td>99.1% (113/114)</td>
</tr>
<tr>
<td></td>
<td>[54.1%-100%]</td>
<td>[95.2%-100%]</td>
</tr>
<tr>
<td><strong>PPV</strong></td>
<td>100% (24/24)</td>
<td>93.8% (15/16)</td>
</tr>
<tr>
<td></td>
<td>[85.8%-100%]</td>
<td>[69.8%-99.8%]</td>
</tr>
<tr>
<td><strong>NPV</strong></td>
<td>100% (6/6)</td>
<td>95.0% (113/119)</td>
</tr>
<tr>
<td></td>
<td>[54.1%-100%]</td>
<td>[89.3%-98.1%]</td>
</tr>
</tbody>
</table>
GeneXpert Dx System Platforms

Smear neg/pos
Direct specimen or sediment
Workflow - Xpert MTB-RIF

1. Sputum liquefaction and inactivation with 2:1 sample reagent
2. Transfer of 2 ml material into test cartridge
3. Cartridge inserted into MTB-RIF test platform (end of hands-on work)
4. Sample automatically filtered and washed
5. Ultrasonic lysis of filter-captured organisms to release DNA
6. DNA molecules mixed with dry PCR reagents
7. Seminested real-time amplification and detection in integrated reaction tube
8. Printable test result

Source: Boehme et al., NEJM 2010
The Xpert® MTB/RIF Assay is a qualitative, nested real-time polymerase chain reaction (PCR) in vitro diagnostic test for:

- Detection of MTB complex DNA
- Detection of rifampin-resistance associated mutations of the \(rpoB\) gene
Kaiser Beta Study – GeneXpert MTB

Evaluation of the Cepheid Xpert MTB/RIF Assay for Direct Detection of *Mycobacterium tuberculosis* Complex in Respiratory Specimens

Elizabeth M. Marlowe,1* Susan M. Novak-Weekley,1 Joven Cumpio,1 Susan E. Sharp,2 Michelle A. Momeny,2 Anna Babst,3 Jonathan S. Carlson,3 Masae Kawamura,3 and Mark Pandori3

TABLE 1. Comparison of GeneXpert MTB/RIF-positive, MTB culture-positive results with smear results

<table>
<thead>
<tr>
<th>Smear result (n = 216)</th>
<th>No. of assay results:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MTB culture+, GeneXpert+</td>
</tr>
<tr>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Numerous (score, 4+)</td>
<td>21</td>
</tr>
<tr>
<td>Moderate (score, 3+)</td>
<td>12</td>
</tr>
<tr>
<td>Rare/few (score, 1+/2+)</td>
<td>52</td>
</tr>
<tr>
<td>Negative (no acid-fast bacilli seen)</td>
<td>31</td>
</tr>
<tr>
<td>Total</td>
<td>116</td>
</tr>
</tbody>
</table>

* Smear results represent sputum and bronchial specimens combined. Note that one bronchial specimen is not included in the table. This specimen was GeneXpert MTB/RIF assay inhibitory, smear negative, culture negative, PCR inhibitory, and MTD negative.

JCM, 2011, 49:1621

98% smear positive
72% smear negative
Internal GeneXpert Data

<table>
<thead>
<tr>
<th>Smear -/Culture+</th>
<th>N</th>
<th>Xpert +</th>
<th>% agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum</td>
<td>6</td>
<td>4</td>
<td>67</td>
</tr>
<tr>
<td>Alt Respiratory*</td>
<td>8</td>
<td>6</td>
<td>75</td>
</tr>
<tr>
<td>Bone</td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Tissue</td>
<td>4</td>
<td>3</td>
<td>75</td>
</tr>
<tr>
<td>Abscess</td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Urine</td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>16</td>
<td>76.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Smear+/TMA+/Culture+</th>
<th>N</th>
<th>Xpert Positive</th>
<th>% Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum</td>
<td>30</td>
<td>30</td>
<td>100</td>
</tr>
<tr>
<td>Aspirate</td>
<td>2</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td>32</td>
<td>100</td>
</tr>
</tbody>
</table>
Kaiser Experience

- Implementation of GeneXpert
  - Improved TAT for result
  - Cost savings due to labor
  - Moderately complex test
    - Less experienced molecular techs
  - Fewer indeterminate results
  - Platform used for other testing
The Future
Infection Control

- County/State Public Health Departments demand 3 consecutive negative smears on patients before removal from isolation
  - AFB smear only
    - Educational issues
- Newer options for removing patients from isolation
POLICY FOR HOUSING PATIENTS WITH CONFIRMED OR SUSPECTED TUBERCULOSIS WHO ARE CONSIDERED INFECTIOUS

The following policy must be followed when using California Department of Public Health, Tuberculosis Control Branch local assistance funding allocated for housing acid fast bacillus (AFB) sputum smear positive patients and patients with confirmed or suspected pulmonary MDR-TB, regardless of sputum smear status.\(^1\),\(^4\),\(^5\)

1) AFB sputum smear positive patients must be singly housed in self-contained housing units that do not share air\(^3\) with other units until:

   a) Three (3) consecutive negative AFB sputum smears from respiratory specimens have been collected, at least 8 hours apart, in which at least one was an early AM or induced sputum, or BAL; and

   b) They have completed at least 14 daily doses of multi-drug, anti-TB therapy, taken and tolerated; and

   c) They exhibit clinical improvement.\(^4\)

   (If such housing is not available, AFB isolation in a health care facility should be used.)

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1 Compliance with this policy will reduce the risk of transmission to a minimum when homeless TB patients must be housed outside the hospital setting; however, smear positive patients optimally should be placed in AFB isolation.

2 A self-contained housing unit provides all facilities required for activities of daily living (i.e., sleeping, eating, and personal hygiene), to help ensure that contact with others does not occur.

3 A housing unit that does not share air with other units has no ventilation system in common with other occupied units, nor any other means for air to move from one unit to another (e.g., under a door adjoining two units). If an exhaust air vent (any vent from which air is not supplied) is present, other than in the bathroom, it must be assumed that air is shared with other units.

4 “Guidelines for the Assessment of Tuberculosis Patient Infectiousness and Placement into High and Lower Risk Settings,” CDPH/CTCA Joint Guidelines, 5/1/2009
**Xpert MTB/RIF Expanded Claims**

*Intended Use*

- The Xpert® MTB/RIF Assay is a qualitative, nested real-time polymerase chain reaction (PCR) *in vitro* diagnostic test for:
  - Detection of MTB complex DNA
  - Detection of rifampin-resistance associated mutations of the *rpoB* gene
  - An aid in the decision of whether continued airborne infection isolation (AII) is warranted

- Decisions regarding the removal of patients from AII need not wait for culture results
### Test Performance Comparison

**Culture as Gold Standard**

- Single Xpert is ~25% more sensitive compared to three AFB smears
- Two Xpert is ~30% more sensitive compared to three AFB smears

<table>
<thead>
<tr>
<th></th>
<th>Overall Sensitivity vs. Culture</th>
<th>Probability of Culture Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two AFB Smears</td>
<td>69.2%</td>
<td>94.9%</td>
</tr>
<tr>
<td>Three AFB Smears</td>
<td>60.4%</td>
<td>93.7%</td>
</tr>
<tr>
<td>One Xpert</td>
<td>85.2%</td>
<td>97.6%</td>
</tr>
<tr>
<td>Two Xperts</td>
<td>91.2%</td>
<td>98.5%</td>
</tr>
</tbody>
</table>

Because the MTB/RIF test can detect TB better than the smear, results from one or two MTB/RIF tests can be used in the decision to remove patients from isolation.

FDA Press Release, Feb 12, 2015

Source: Xpert MTB/RIF Package Insert, 301-1404 Rev B, Table 17
Negative Predictive Value

Xpert MTB/RIF Neg vs. AFB Smear Pos, Culture Pos

- Xpert MTB/RIF strongly predicts the results from AFB Smear and thus suitable to substitute for AFB Smear

<table>
<thead>
<tr>
<th>Xpert Test</th>
<th>Xpert Negative, Smear Positive, Culture positive</th>
<th>Total Negatives</th>
<th>Probability of Culture Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>One Xpert</td>
<td>2</td>
<td>775</td>
<td>99.7% (773/775)</td>
</tr>
<tr>
<td>Two Xperts</td>
<td>0</td>
<td>772</td>
<td>100% (772/772)</td>
</tr>
</tbody>
</table>

Source: Xpert MTB/RIF Package Insert, 301-1404 Rev B, Tables 13, 15
Considerations – Next steps

- Guidelines established with Infection Control and ID
- Smear negative NAAT
  - Look at ordering patterns
- Cost implications
  - Increased PCR testing will impact laboratory budget
  - Difficult to assess hospital impact
- NAAT for removal of isolates could potentially replace “AFB smear only” in our system
  - Important to control utilization
  - Large system – would need decision support for ordering
- Discussions regarding 1 or 2 PCR needed?
Thank You... Questions

susan.m.novak@kp.org