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

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Agenda

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

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Our Strategy

INTEGRATED
DELIVERY SYSTEM

HEALTH PLAN

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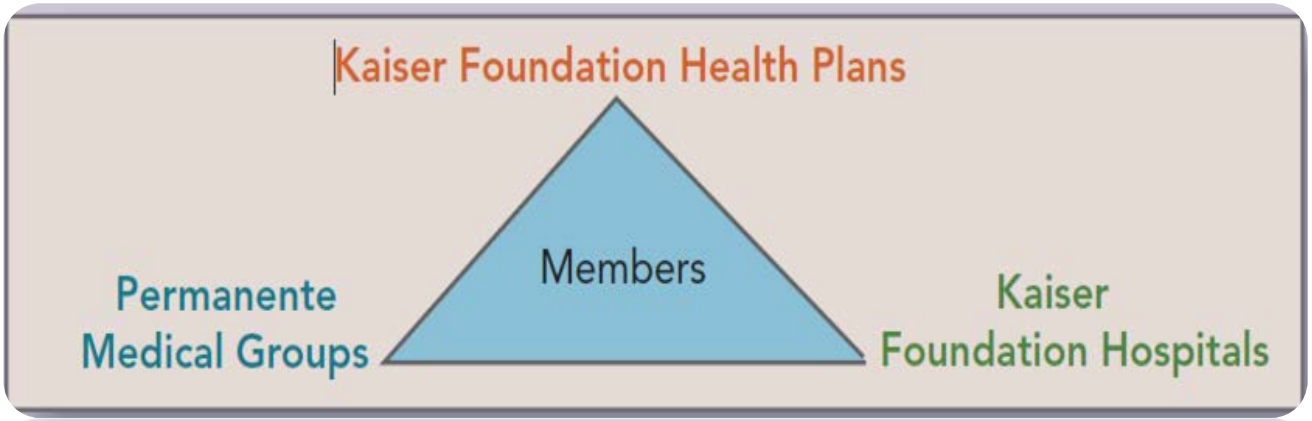
The Kaiser Permanente Model
A Prepaid Integrated Healthcare Delivery System

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



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Kaiser Permanente

- Kaiser Southern California
  - >4Million 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

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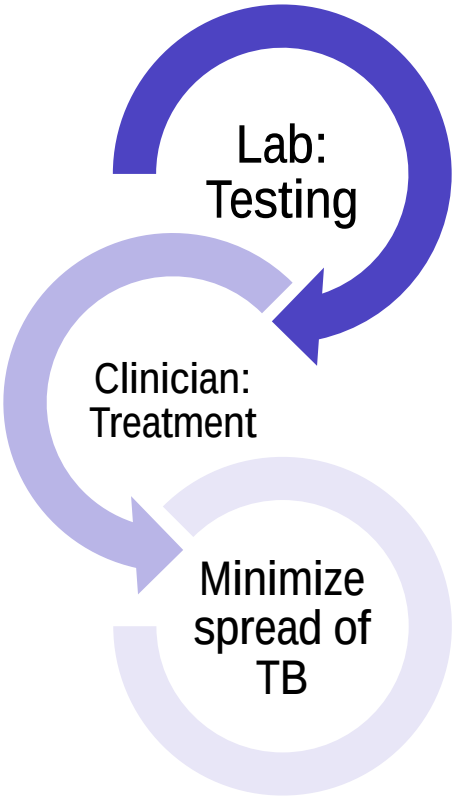
Global TB Burden



- 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

1. Global Tuberculosis Report 2014, World Health Organization, ISBN 978 92 4 156480 9
2. Reported Tuberculosis in The United States 2013, Centers for Disease control and Prevention

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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].

Credit John Froschauer / AP
In this 2003 file photo, Dr. Masa Narita, TB Control Officer for Public Health - Seattle & King County, looks at x-rays of tuberculosis patient lungs. There were 116 cases of TB in King County in 2010.

1. Bennett DE, Courval JM, Onorato IM, et al. Prevalence of TB infection in the US population, 1999–2000 [Abstract 67921]. In: Program and abstracts, 131st annual meeting of the American Public Health Association; San Francisco, California, November 15–19, 2003.
2. Tuberculosis: A Serious Re-Emerging Threat. Silver Spring, MD: Association of Public Health Laboratories; 2009; Available at http://www.aphl.org/policy/priorities/Documents/TuberculosisFactSheet2009.pdf .

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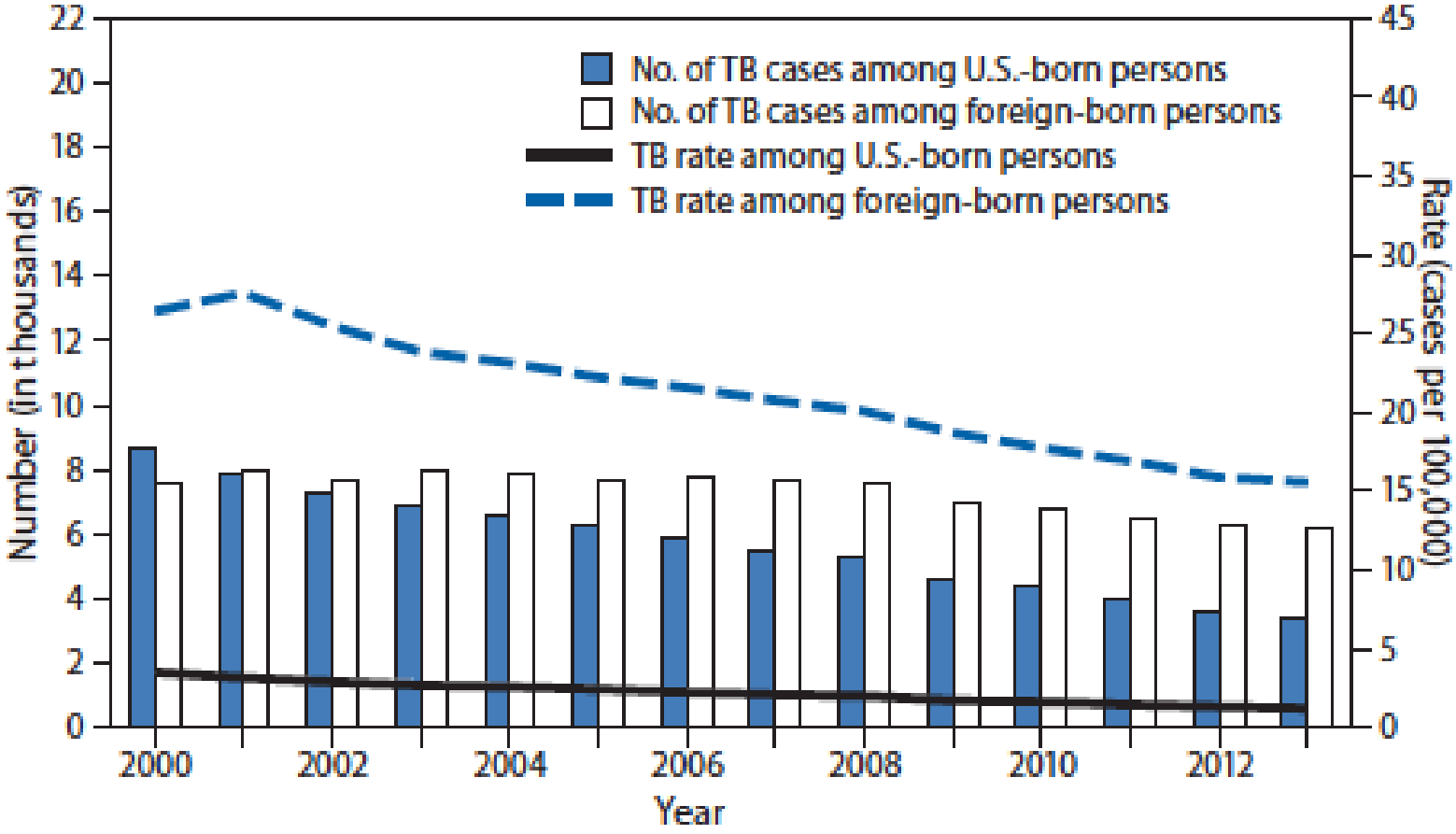
Tuberculosis cases among US born and foreign-born



* 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

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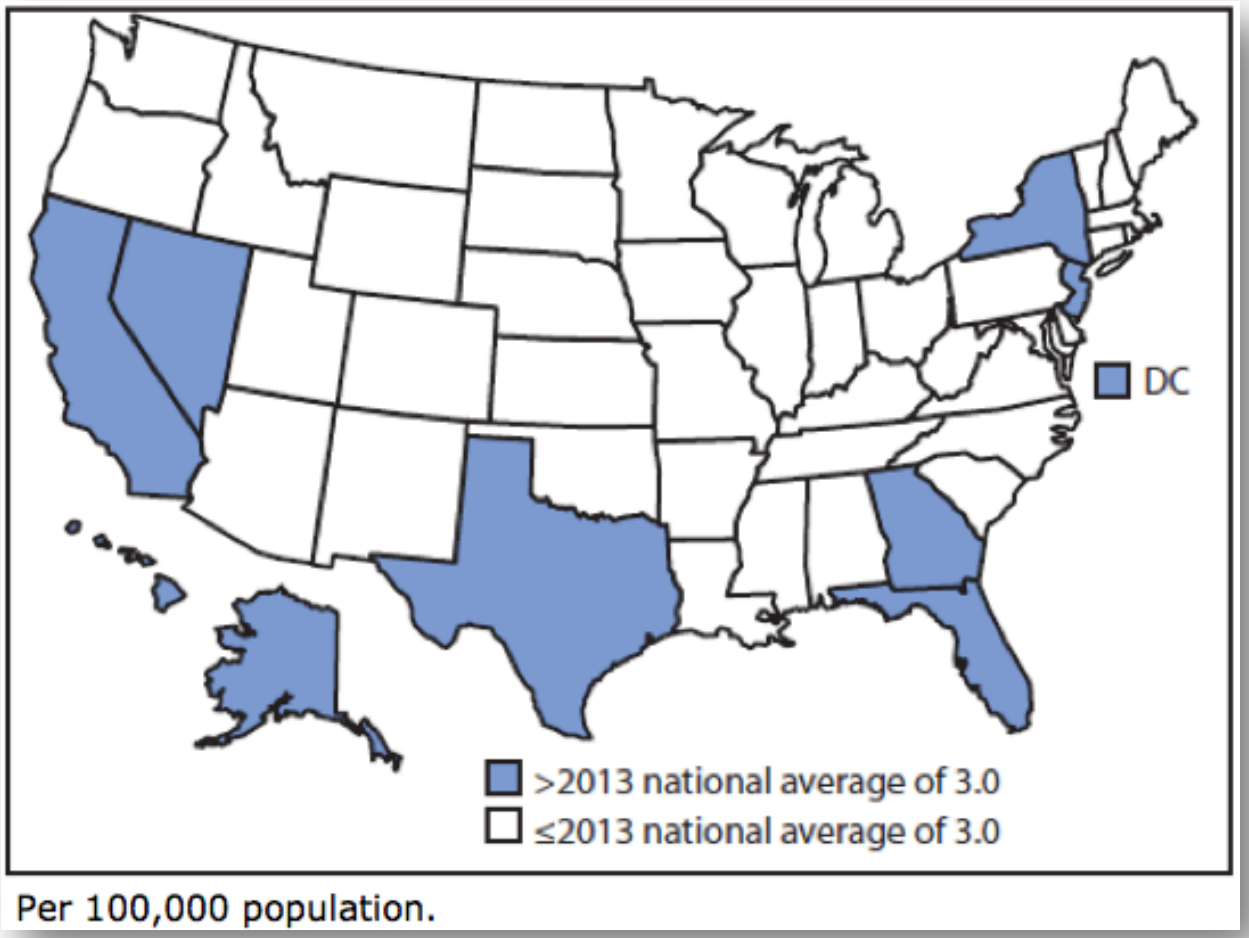
Rate of tuberculosis (TB) cases, by state/area --- United States, 2013



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

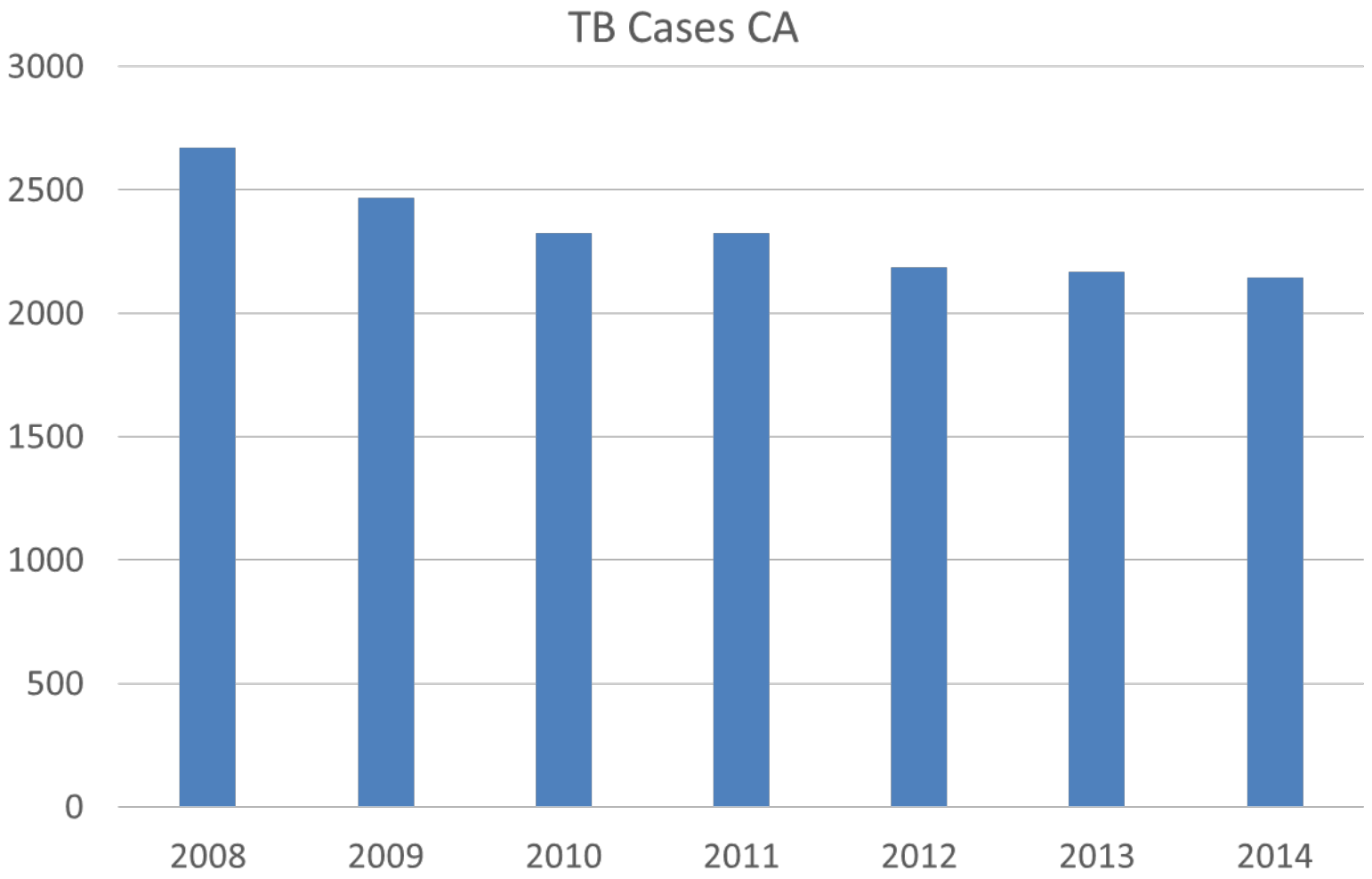


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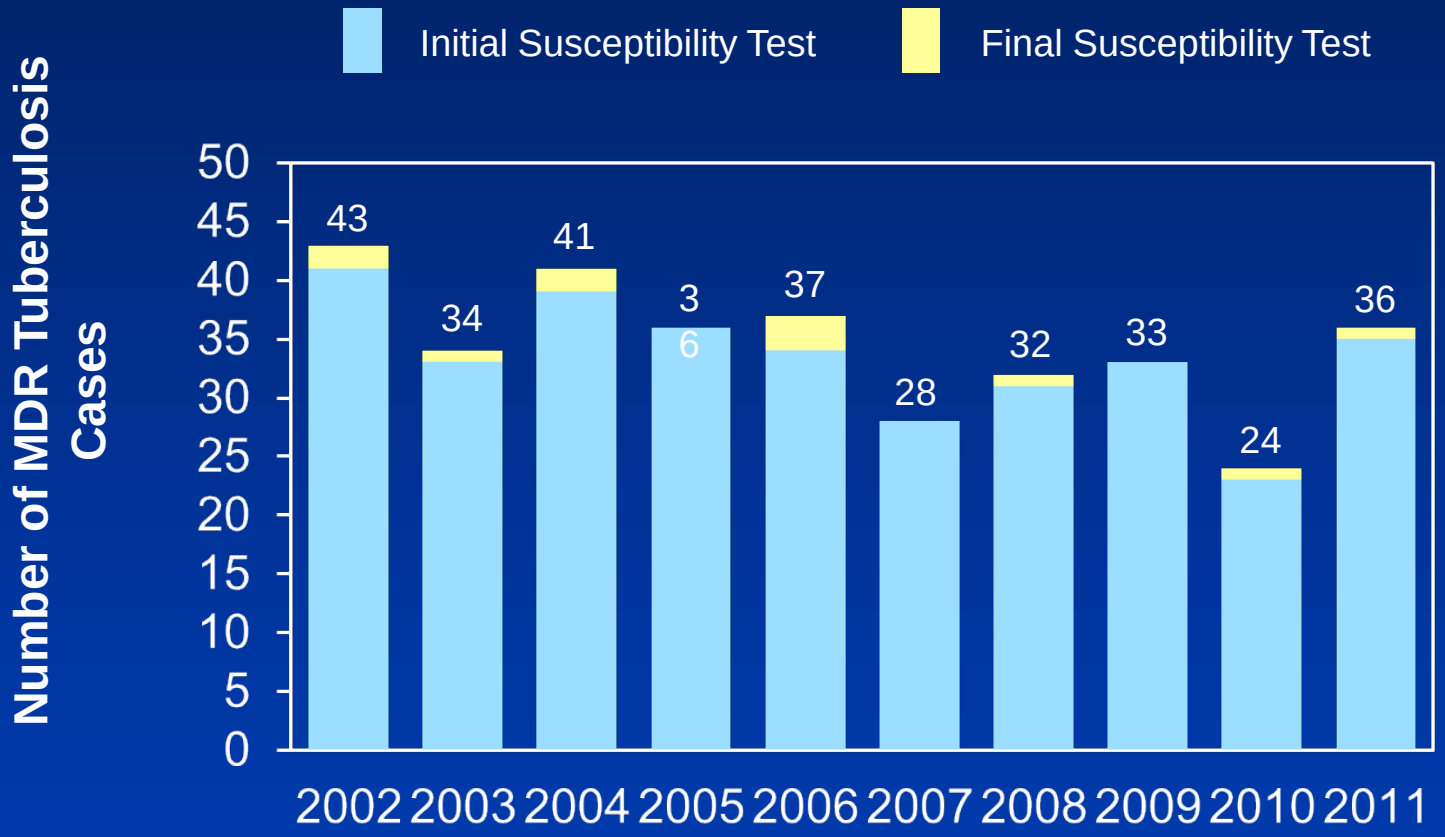
Figure 13. Tuberculosis Cases with Multidrug Resistance (MDR) on Initial or Final Drug Susceptibility Testing*: California, 2002-2011



*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

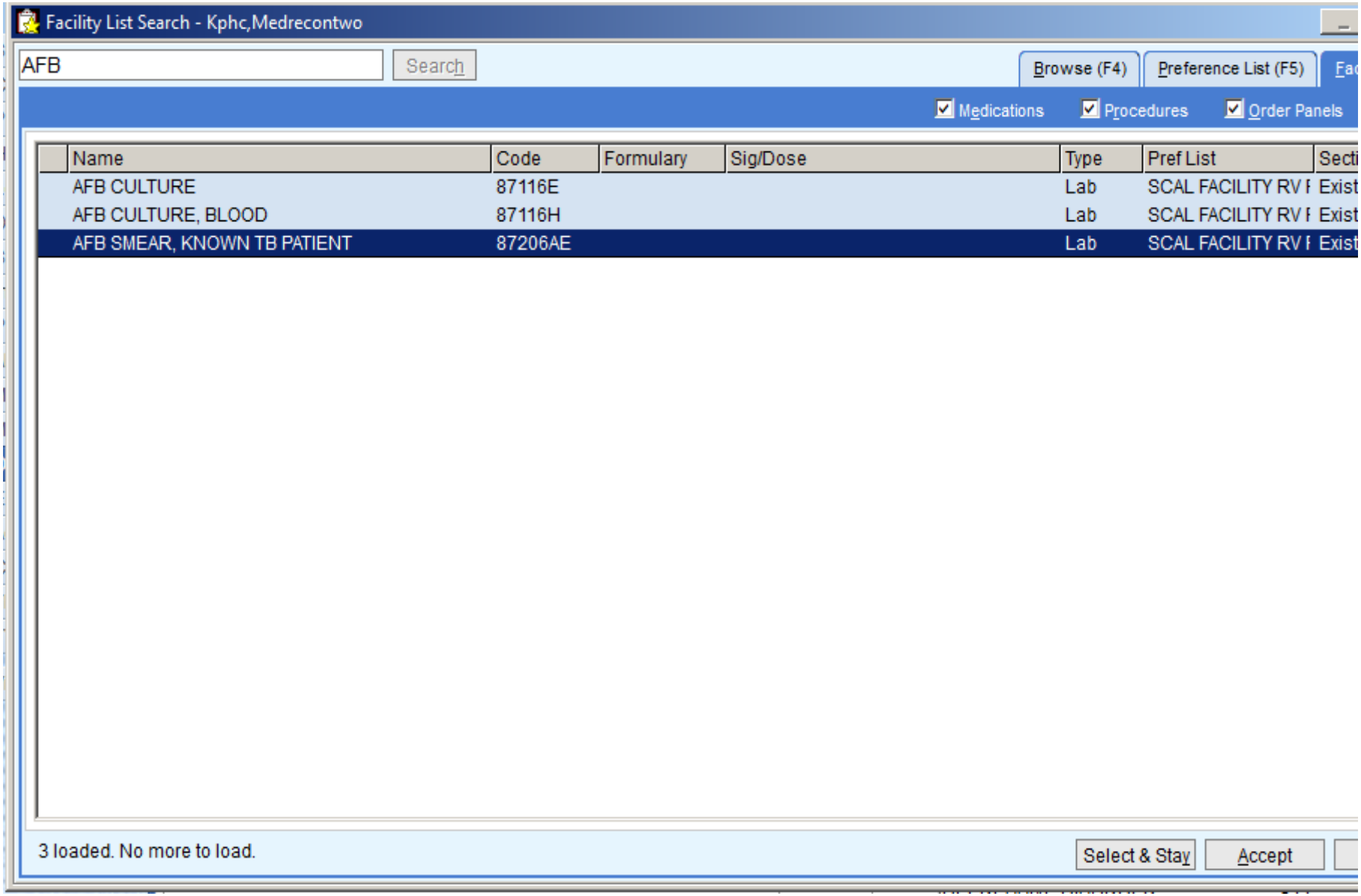
KP STATS

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

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



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*).

January 16, 2009 / 58(01);7-10 MMWR

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

Hologic Amplified MTD Test

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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 Campos[1], Andrew Quartin[1], Eliana Mendes[1], Alexandre Abreu[1], Samuel Gurevich[1], Luis Echarte[1], Tanira Ferreira[2], Timothy Cleary[1], Elena Hollender[1,2], and David Ashkin[1,2]

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

1st Specimen
N=206

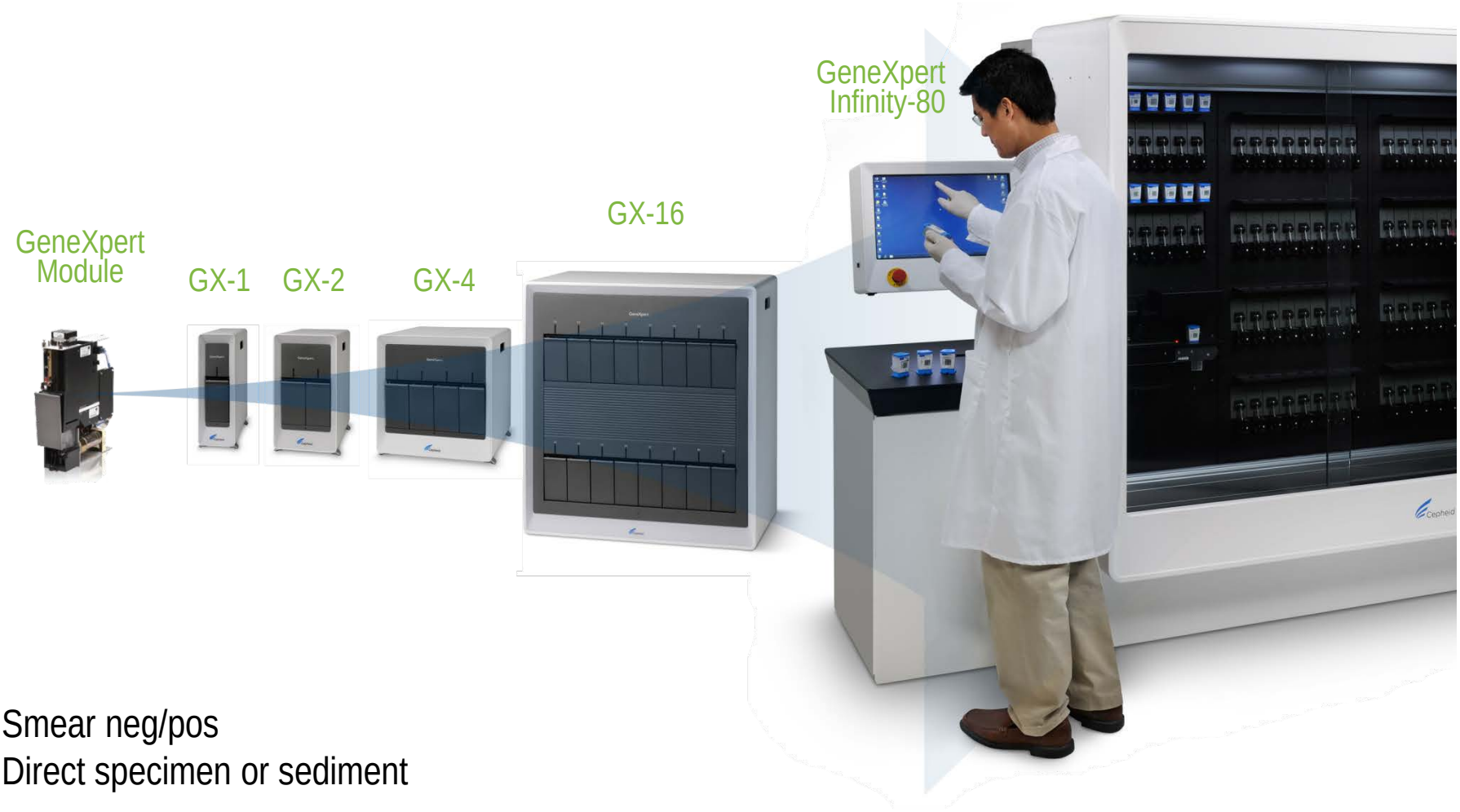
	Smear Positive Patient	Smear Negative Patient
Sensitivity	87.5% (28/32) [71.0%-96.5%]	64.0% (16/25) [42.5%-82.0%]
Specificity	100% (7/7) [59.0%-100%]	100% (142/142) [97.4%-100%]
PPV	100% (28/28) [87.7%-100%]	100% (16/16) [79.4%-100%]
NPV	63.6% (7/11) [30.8%-89.1%]	94.0% (142/149) [90.6%-98.1%]

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

1st and 2nd Specimen
N=165

	Smear Positive Patient	Smear Negative Patient
Sensitivity	100% (24/24) [85.8%-100%]	71.4% (15/21) [47.8%-88.7%]
Specificity	100% (6/6) [54.1%-100%]	99.1% (113/114) [95.2%-100%]
PPV	100% (24/24) [85.8%-100%]	93.8% (15/16) [69.8%-99.8%]
NPV	100% (6/6) [54.1%-100%]	95.0% (113/119) [89.3%-98.1%]

GeneXpert Dx System Platforms



Smear neg/pos
Direct specimen or sediment

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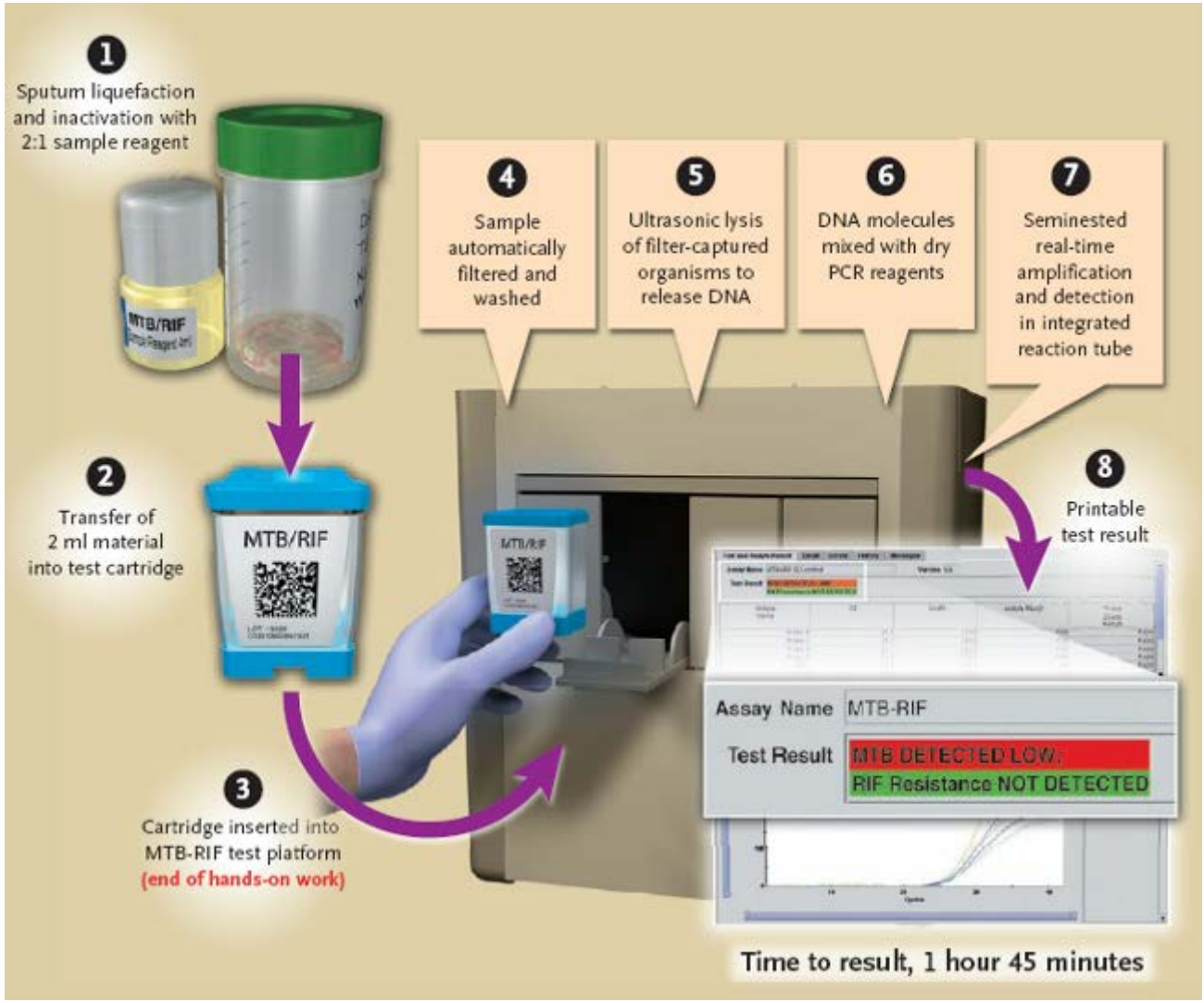
Workflow - Xpert MTB-RIF



Source: Boehme et al., NEJM 2010

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Xpert MTB/RIF

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

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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 Pandori[3]

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

Smear result (n = 216)	No. of assay results:				
	MTB culture$^+$, GeneXpert$^+$	MTB culture$^+$, GeneXpert$^-$	MTB culture$^-$, GeneXpert$^+$	MTB culture$^-$, GeneXpert$^-$	Total
Positive					
Numerous (score, 4+)	21	0	1	13	35
Moderate (score, 3+)	12	0	0	2	14
Rare/few (score, 1+/2+)	52	2	3	20	77
Negative (no acid-fast bacilli seen)	31	12	0	47	90
Total	116	14	4	82	216

[a] 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

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Internal GeneXpert Data

Smear -/Culture+	N	Xpert +	% agreement
Sputum	6	4	67
Alt Respiratory*	8	6	75
Bone	1	1	100
Tissue	4	3	75
Abscess	1	1	100
Urine	1	1	100
Total	21	16	76.2

Smear+/TMA+/Culture+	**N**	**Xpert Positive**	**% Agreement**
Sputum	30	30	100
Aspirate	2	2	100
Total	**32**	**32**	**100**

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

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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

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State of CA Department of Public Health

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[2] 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

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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

	Overall Sensitivity vs. Culture	Probability of Culture Negative
Two AFB Smears	69.2%	94.9%
Three AFB Smears	60.4%	93.7%
One Xpert	85.2%	97.6%
Two Xperts	91.2%	98.5%

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

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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

Xpert Test	Xpert Negative, Smear Positive, Culture positive	Total Negatives	Probability of Culture Negative
One Xpert	2	775	99.7% (773/775)
Two Xperts	0	772	100% (772/772)

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

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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

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