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

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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

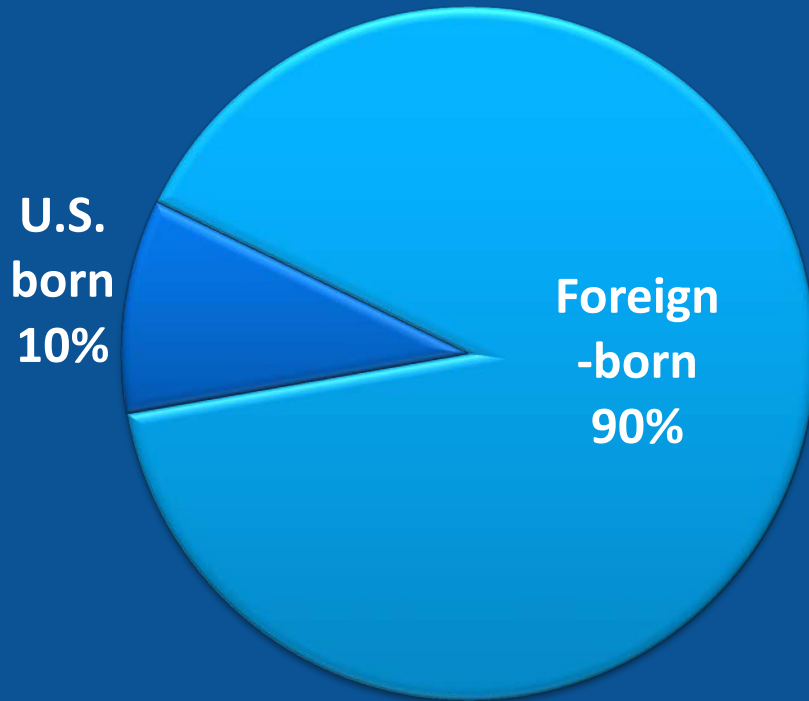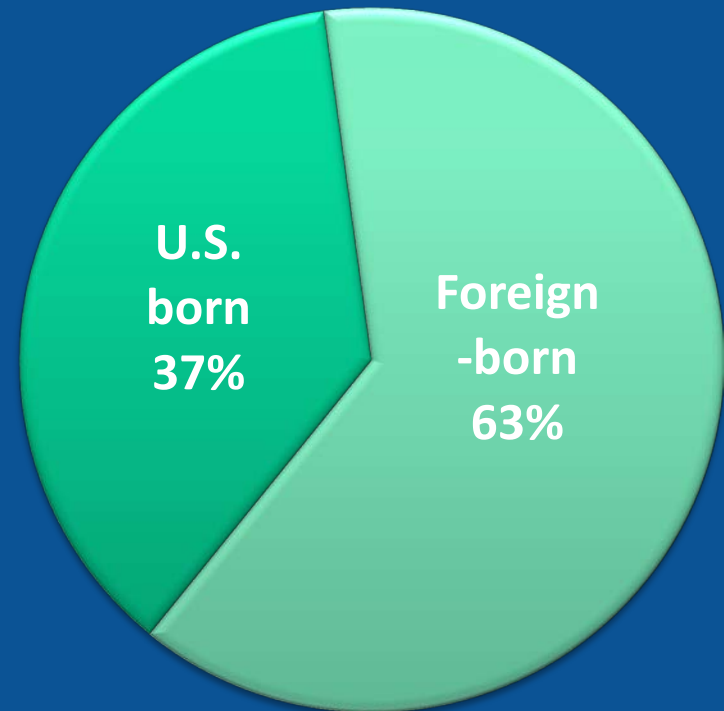**United States**
- 9,951 cases
- TB rate=3.2 per 100,000 population

Characteristics of Active TB Cases
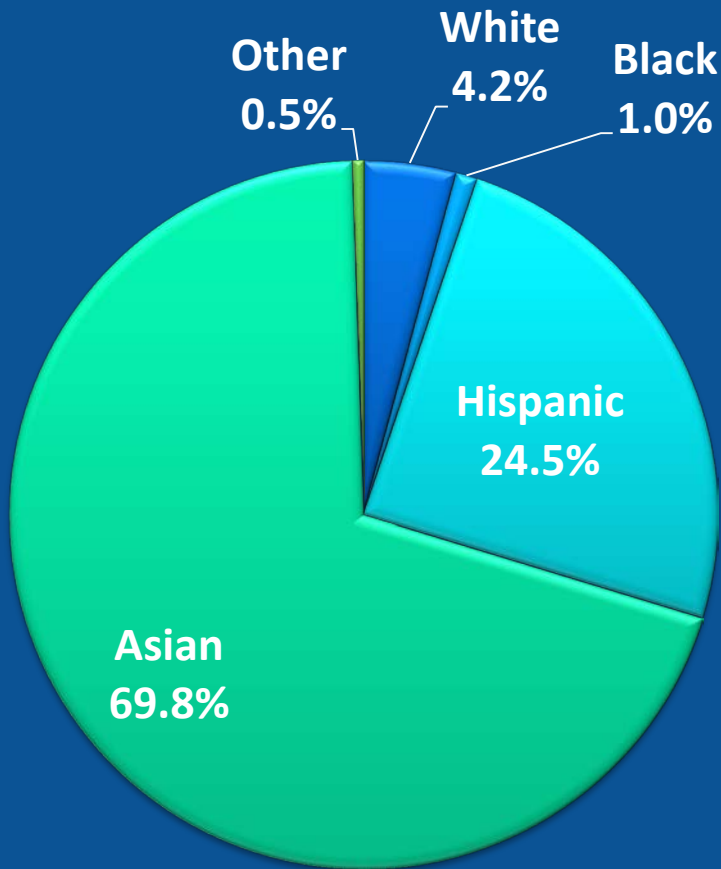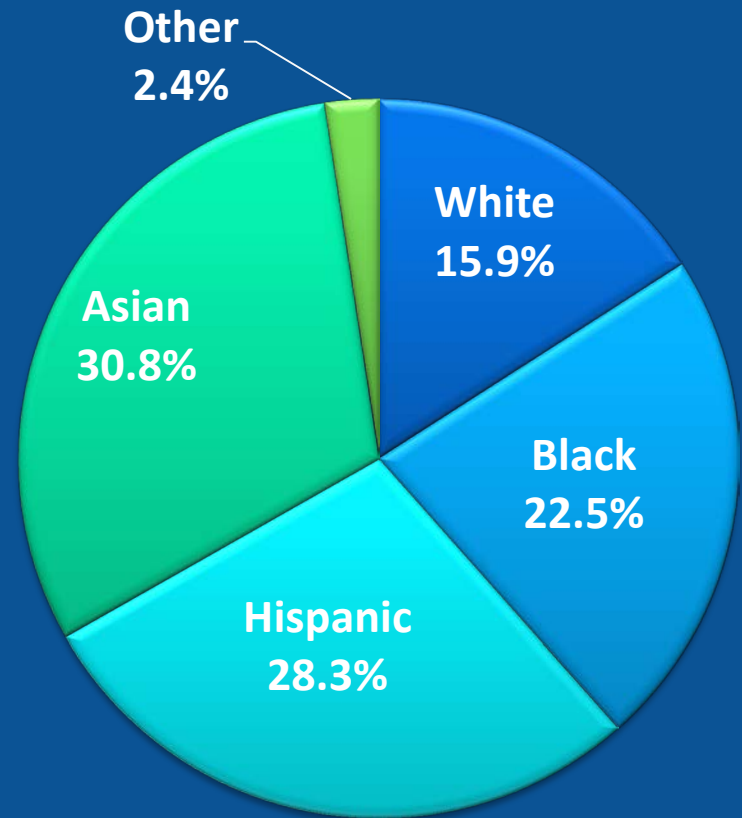# Orange County and the United States, 2012

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

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:

  - Moore et al. (2005) Reduction in turnaround time for laboratory diagnosis of pulmonary tuberculosis by routine use of a nucleic acid amplification test. Diagnostic Microbiology and Infectious Disease 52: 247-254.

  - Moore and Curry (1998) Detection and identification of Mycobacterium tuberculosis directly from sputum sediments by ligase chain reaction. J Clin Microbiol 36:1028–1031.

  - Moore et al. (1996) Amplification of rRNA for assessment of treatment response of pulmonary tuberculosis patients during antimicrobial therapy. J Clin Microbiol 34:1745–1749.

  - Moore and Curry (1995) Detection and identification of Mycobacterium tuberculosis directly from sputum sediments by Amplicor PCR. J Clin Microbiol 33:2686– 2691.

  - Jonas et al. (1993) Detection and identification of Mycobacterium tuberculosis directly from sputum sediments by amplification of rRNA. Journal Clin Microbiol 31:2410-2416.

Grant Proposal

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)
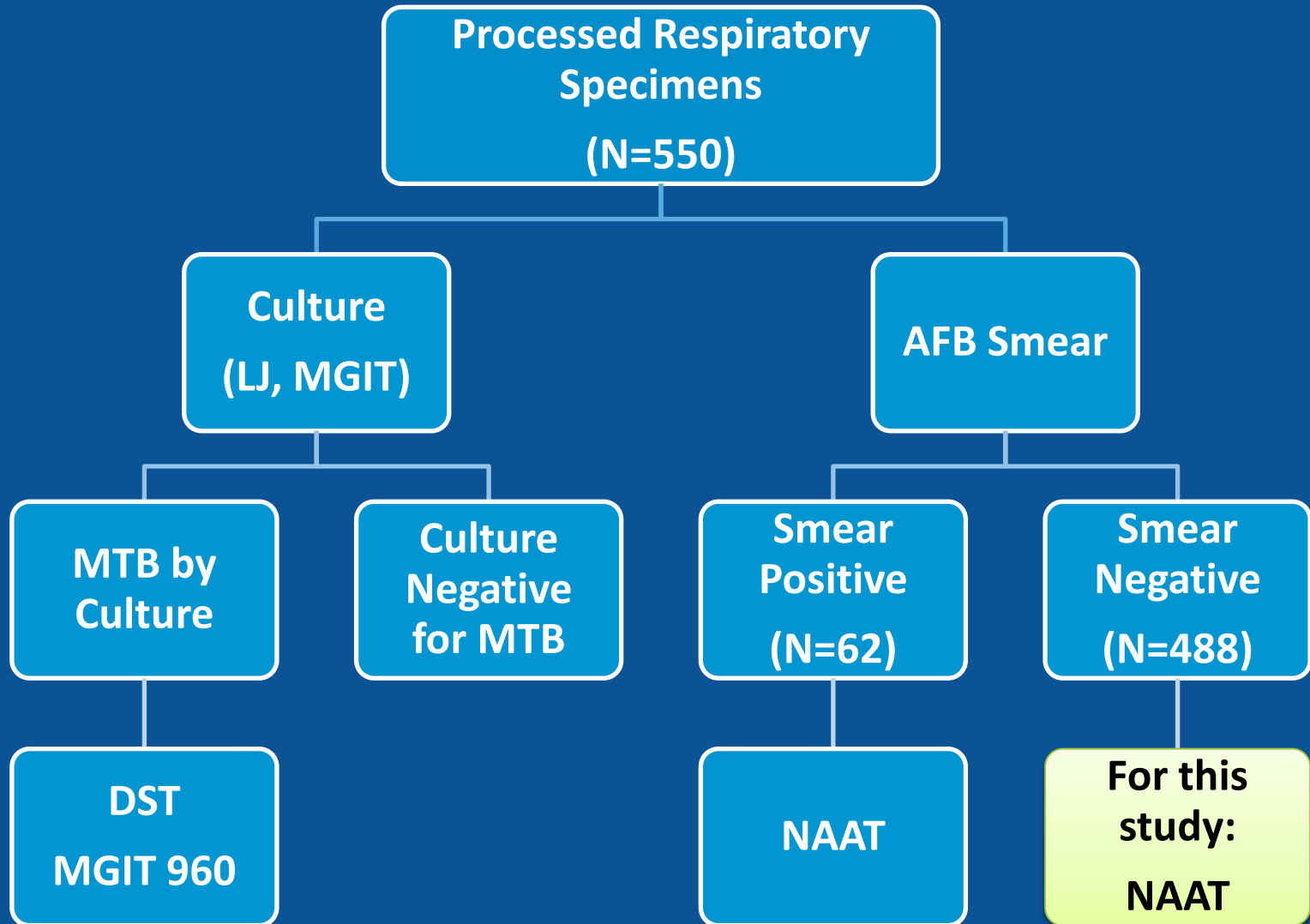
Study A

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

|	No. (%)	TB Case?			Contact Investigation			NAAT initiated Contact Investigation?			Pt Isolated		NAAT affect isolation?			Avg Days Isolated
		Yes	No	NA*	Yes	No	NA*	Yes	No	NA*	Yes	No	Yes	No	NA*	
Smear-Pos/ NAAT-Pos	28 (5.4)	28	0	0	19	8	1	12	16	0	28	0	13	14	1	68
Smear-Neg/ NAAT-Pos	18 (3.5)	14	4	0	12	6	0	7	11	0	15	3	7	11	0	26.2
Smear-Pos/ NAAT-Neg	9 (1.7)	0	9	0	2	7	0	0	9	0	4	5	4	5	0	13
Smear-Neg/ NAAT-Neg	465 (89.4)	56	400	9	27	431	7	3	445	17	70	395	11	433	21	14.4
Total No.	520 (100)	98	413	9	60	452	8	22	481	17	117	403	35	463	22	

*NA = Result not available

Study A

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)
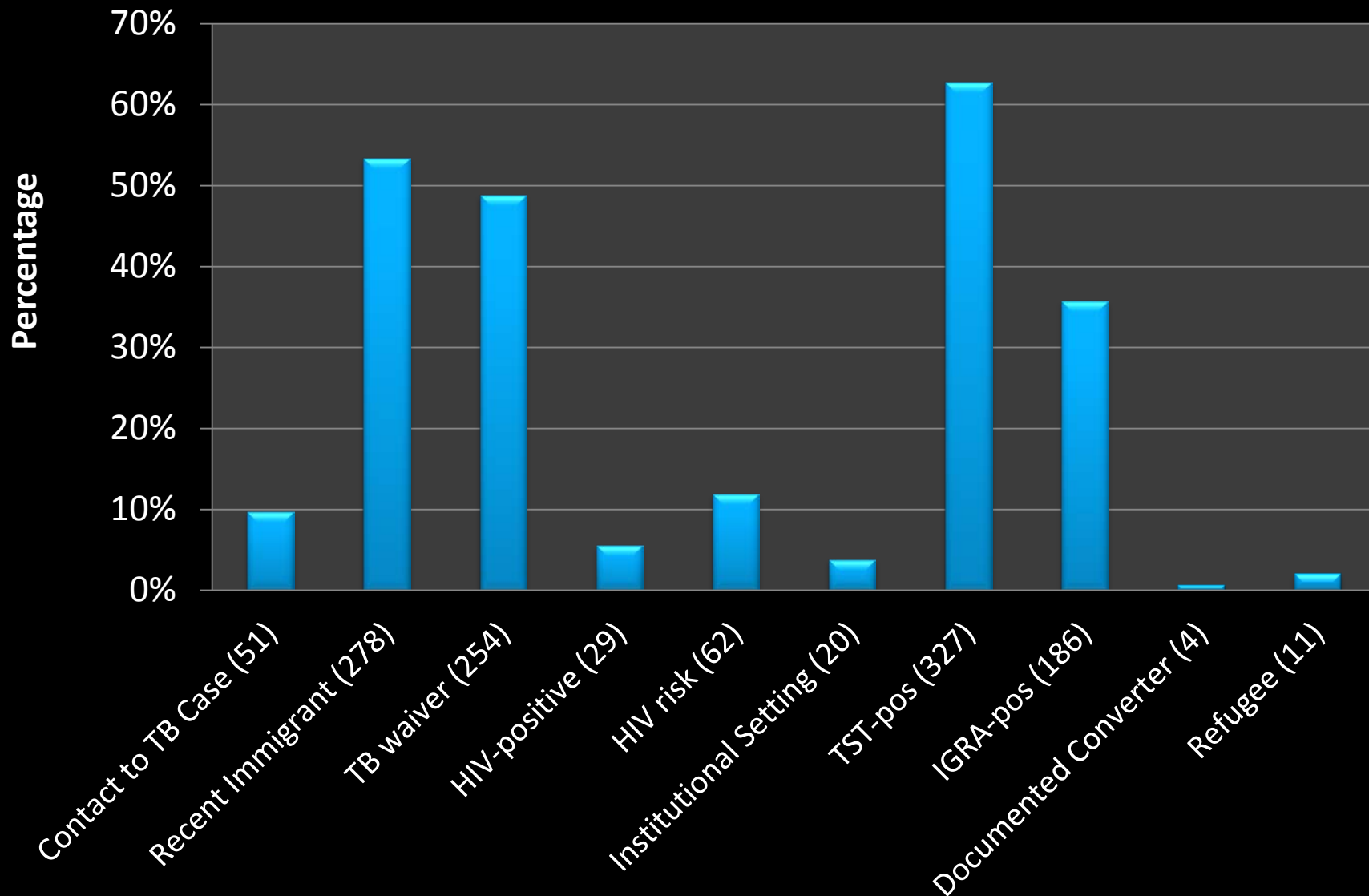
Study A

Objective 3:

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

N=550 specimens

Cepheid GeneXpert	MTB Detection	MTB Detected in Any Culture	Smear Positive	Smear Negative
Sensitivity	83.7%	86.2%	96.9%	58.8%
Specificity	98.0%	99.8%	96.7%	98.1%
PPV	80.4%	98.0%	96.9%	52.6%
NPV	98.4%	98.4%	96.7%	98.5%

Study A

Objective 4:

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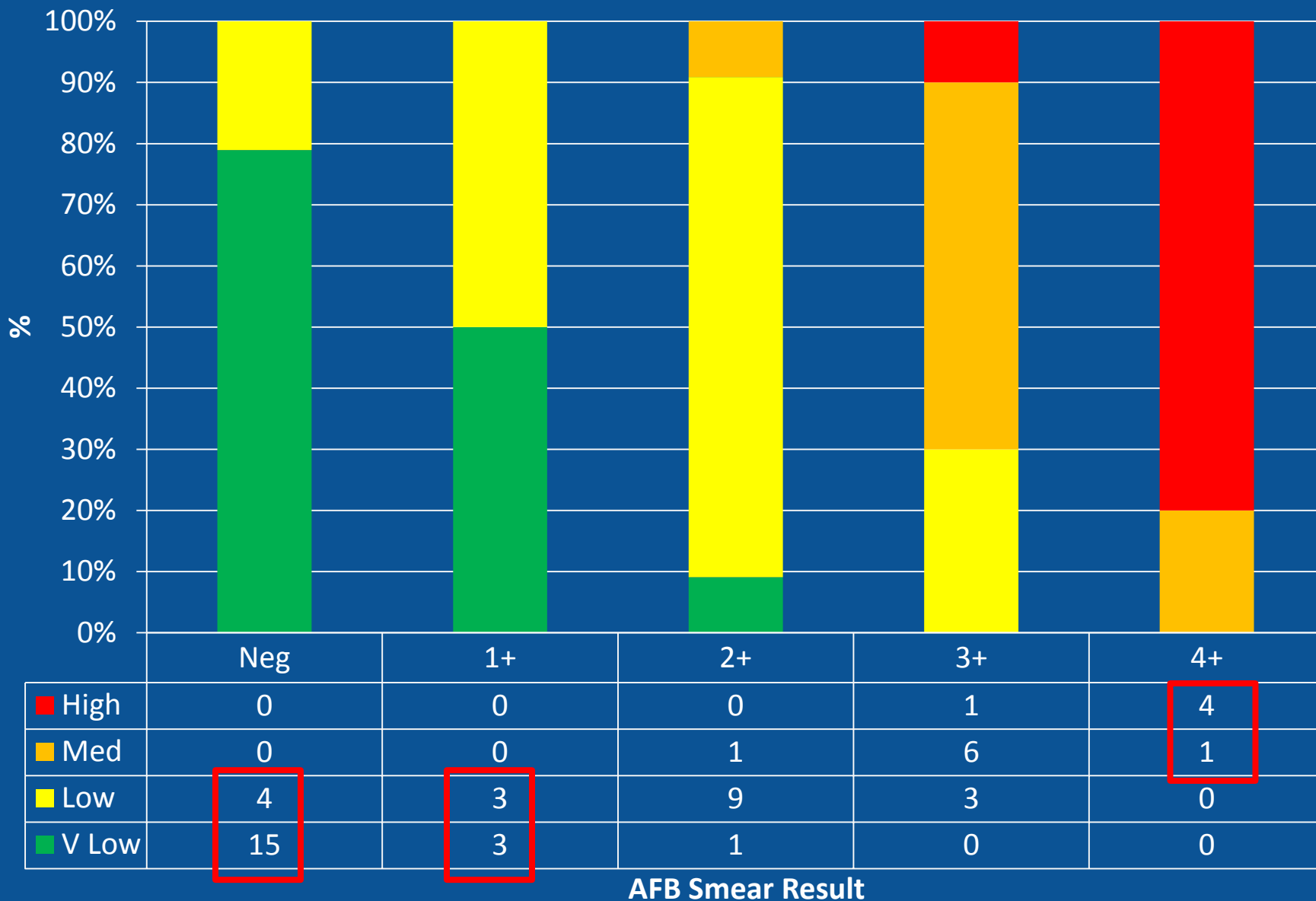
Study A

Parameters of AFB Microscopy compared to GeneXpert for Identification of MTB

	AFB Microscopy	GeneXpert
Sensitivity	65.3%	83.7%
Specificity	94.0%	98.0%
PPV	51.6%	80.4%
NPV	96.5%	98.4%

Distribution of AFB Smear Results

Smear	No.	%
Neg	488	88.7%
1+	29	5.3%
2+	15	2.7%
3+	13	2.4%
4+	5	0.9%

GeneXpert Results Compared to Smear
(N=51 specimens that were detected by NAAT)

|	Neg	1+	2+	3+	4+
High	0	0	0	1	4
Med	0	0	1	6	1
Low	4	3	9	3	0
V Low	15	3	1	0	0

AFB Smear Result

Study A

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

Cepheid GeneXpert	MTB Detection	MTB Detected in Any Culture	RIF-R Detection
Sensitivity	83.7%	86.2%	100.0%
Specificity	98.0%	99.8%	100.0%
PPV	80.4%	98.0%	100.0%
NPV	98.4%	98.4%	100.0%
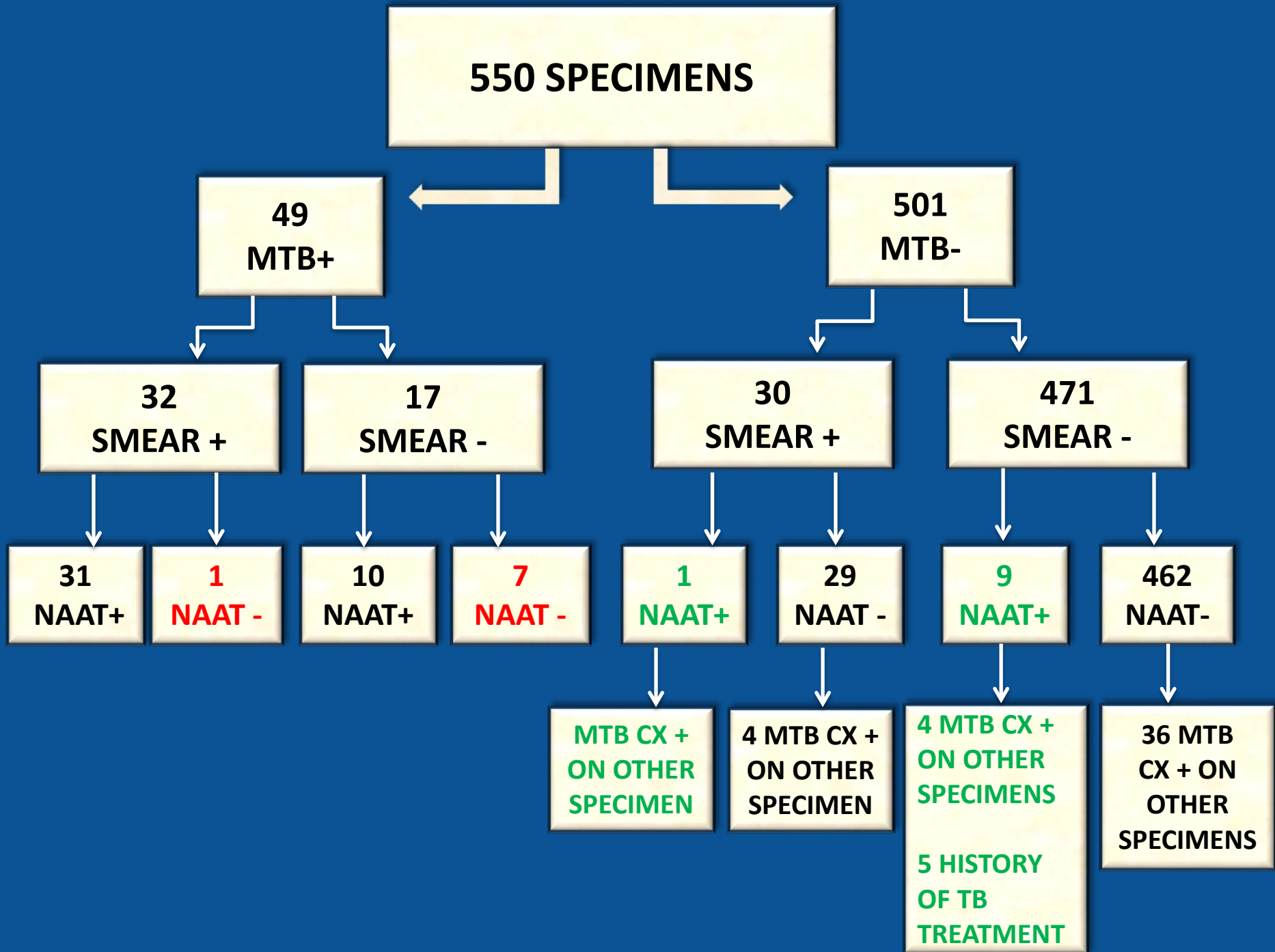
Study C

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

Cepheid GeneXpert	RIF-R Detection
PPV	100.0%

Study C

- 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

Study C

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

Cepheid GeneXpert	RIF-R Detection
Sensitivity	100.0%
Specificity	100.0%
PPV	100.0%
NPV	100.0%

Results of the GeneXpert in Detecting Rifampin Resistance

	MTB RIF-R	MTB RIF-S	TOTAL
GeneXpert RIF-R	2	0	2
GeneXpert RIF-S	0	39	39
GeneXpert MTB Not Detected*	0	8	8
Total	2	47	49

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)

Acknowledgements

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Thank You!