Potential impact of Xpert-based triage of TB suspects in a low burden setting

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NAATs are highly accurate

Test	NAA method	AFB+ Sensitivity	Specificity
Amplicor	PCR	0.96 (0.94 to 0.97)	0.83 (0.8 to 0.86)
Cobas Amplicor	PCR	0.96 (0.95 to 0.97)	0.74 (0.68 to 0.8)
BDP	SDA	0.98 (0.96 to 0.99)	0.89 (0.84 to 0.93)
E-MTD	TMA	0.97 (0.95 to 0.98)	0.96 (0.93 to 0.97)
LCx	LCR	0.96 (0.94 to 0.98)	0.71 (0.64 to 0.78)

Test	NAA method	AFB− Sensitivity	Specificity
Amplicor	PCR	0.61 (0.57 to 0.65)	0.97 (0.968 to 0.974)
Cobas Amplicor	PCR	0.64 (0.59 to 0.69)	0.993 (0.992 to 0,994)
BDP	SDA	0.71 (0.66 to 0.76)	0.97 (0.964 to 0.974)
E-MTD	TMA	0.76 (0.7 to 0.8)	0.97 (0.966 to 0.974)
LCx	LCR	0.57 (0.5 to 0.64)	0.98 (0.978 to 0.985)

Greco S et al Thorax. 2006

NAATs have been recommended for a long time

November 01, 1996 / 45(43);950-952

Notices to Readers Nucleic Acid Amplification Tests for Tuberculosis

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

Updated Guidelines for the Use of Nucleic Acid Amplification Tests in the Diagnosis of Tuberculosis

NAATs are uncommonly used in routine practice

Coming-of-Age of Nucleic Acid Amplification Tests for the Diagnosis of Tuberculosis

Susan E. Dorman
Johns Hopkins University School of Medicine, Center for Tuberculosis Research, Baltimore, Maryland

Despite the encouraging study results and their commercial availability, these NAA tests for the diagnosis of TB have not been implemented widely in the United States.

A national audit of the laboratory diagnosis of tuberculosis and other mycobacterial diseases within the United Kingdom

F A Drobniewski, B Watt, E G Smith, J G Magee, R Williams, J Holder, J Ostrowski

- < ¼ of laboratories performing mycobacterial tests in the UK offered molecular testing

Barriers to NAAT use

- Concerns about workload
- High training/personnel costs

CHEST Original Research
RESPIRATORY INFECTIONS

Use of the Amplified *Mycobacterium tuberculosis* Direct Test in a Public Health Laboratory*

Test Performance and Impact on Clinical Care

Renata L. Guerra, MD; Nancy M. Hooper, BA; James F. Baker, BS; Roya Alborz, MS; Derek T. Armstrong, MHS; Gina Maltas, BSN; Julia A. Kiehlbauch, PhD; and Susan E. Dorman, MD

Conclusion: **In this public health setting, MTD was accurate and rapidly detected more than half of the smear-negative PTB cases. For smear-positive PTB suspects, MTD had excellent concordance with definitive diagnosis, but clinicians often inappropriately initiated TB therapy despite a negative MTD result.** *(CHEST 2007; 132:946–951)*

Diagnostic Accuracy → Impact

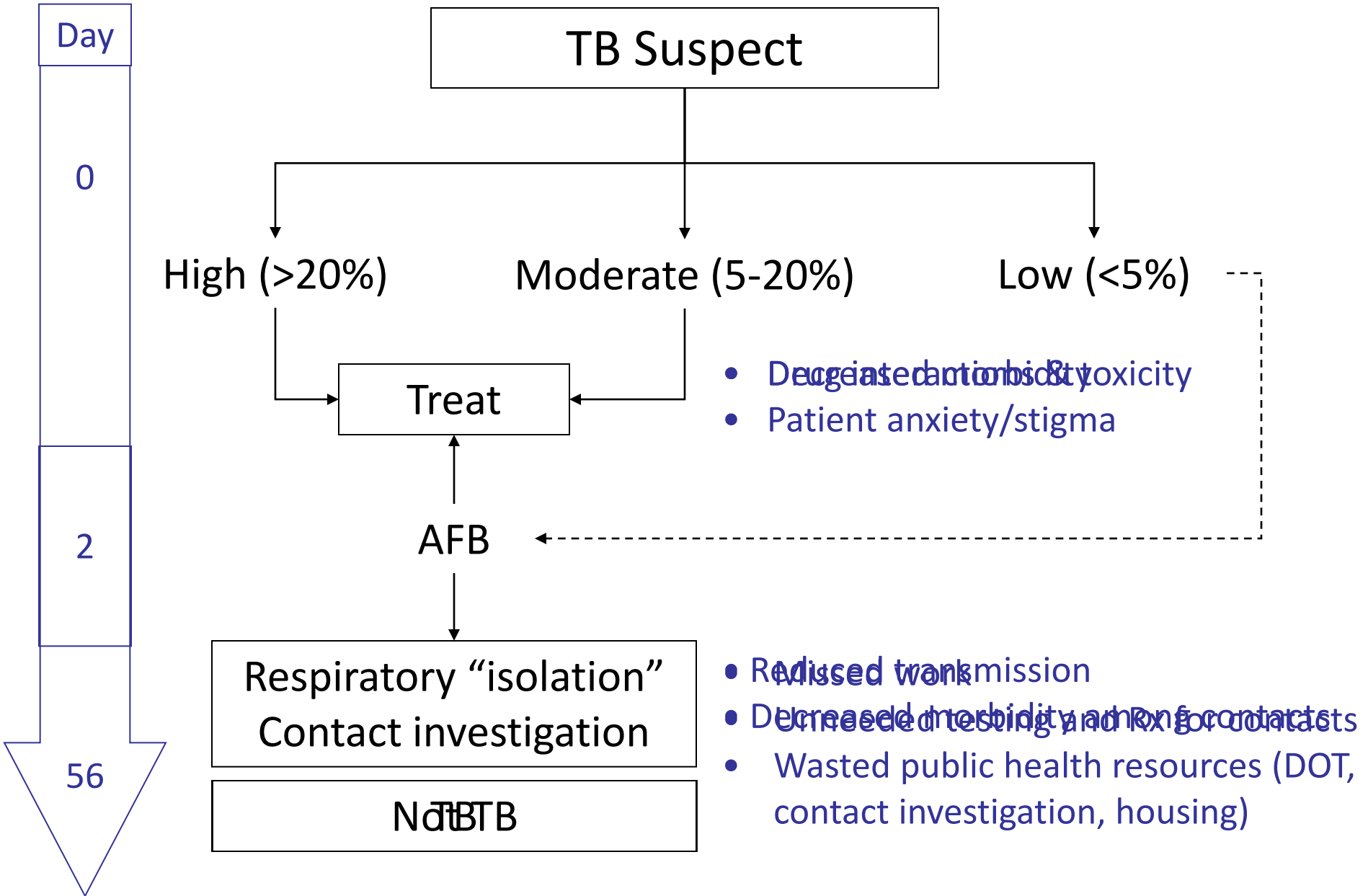
- How does testing change clinical decisions?

- How do those decisions affect clinical and public health outcomes?

"< 1% of all publications have evaluated the clinical impact of diagnostic tests."

-- Madhu Pai (ATS 2010)

Patient- and public health-important outcomes

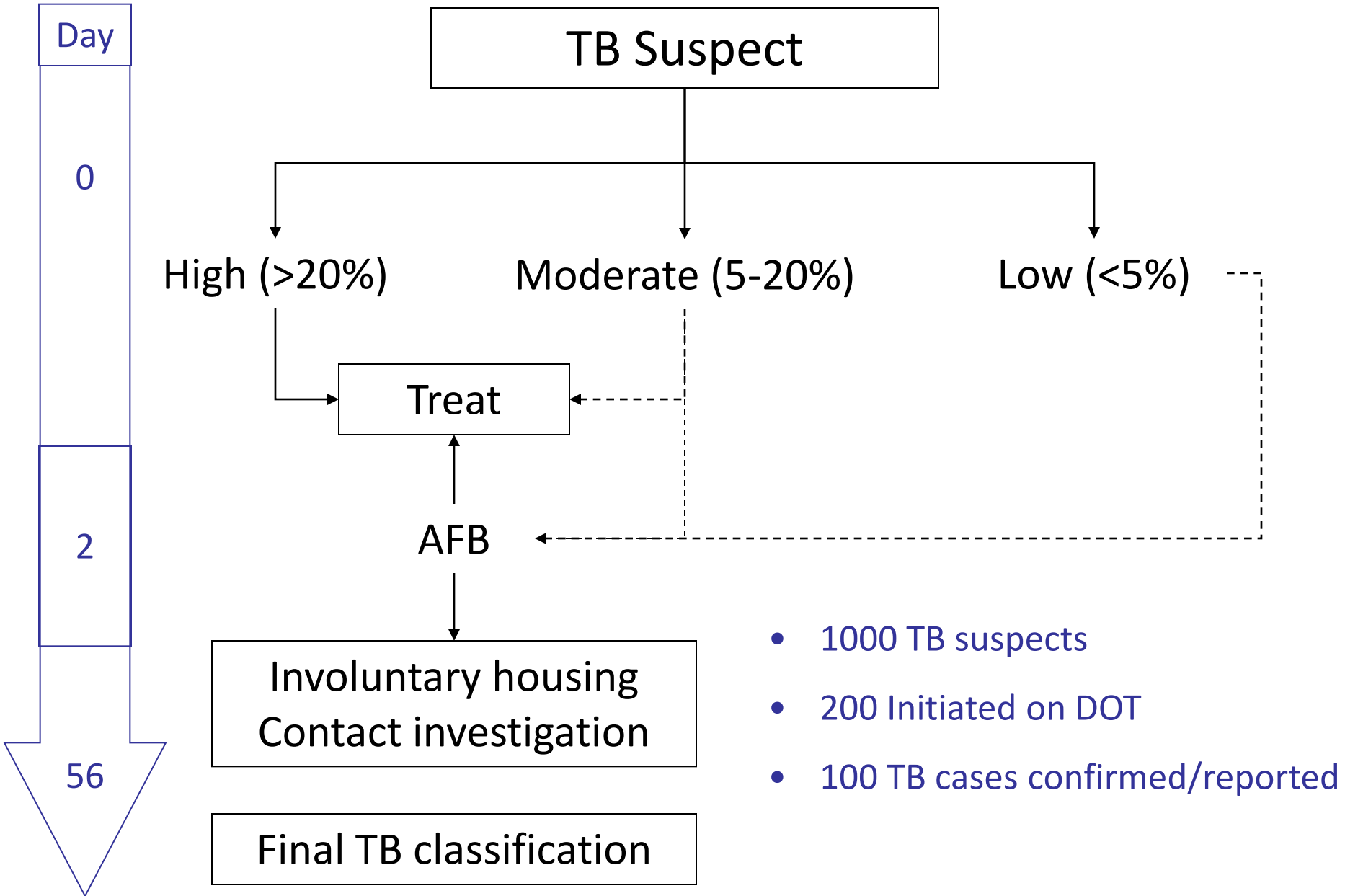


Study objectives

- Compare the accuracy of clinician- vs. Xpert-driven treatment decisions

- Measure potential impact of Xpert-driven changes to decisions that impact on patient- and public health-important outcomes
  - Treatment
  - Contact investigation

Study setting: San Francisco DPH TB Clinic

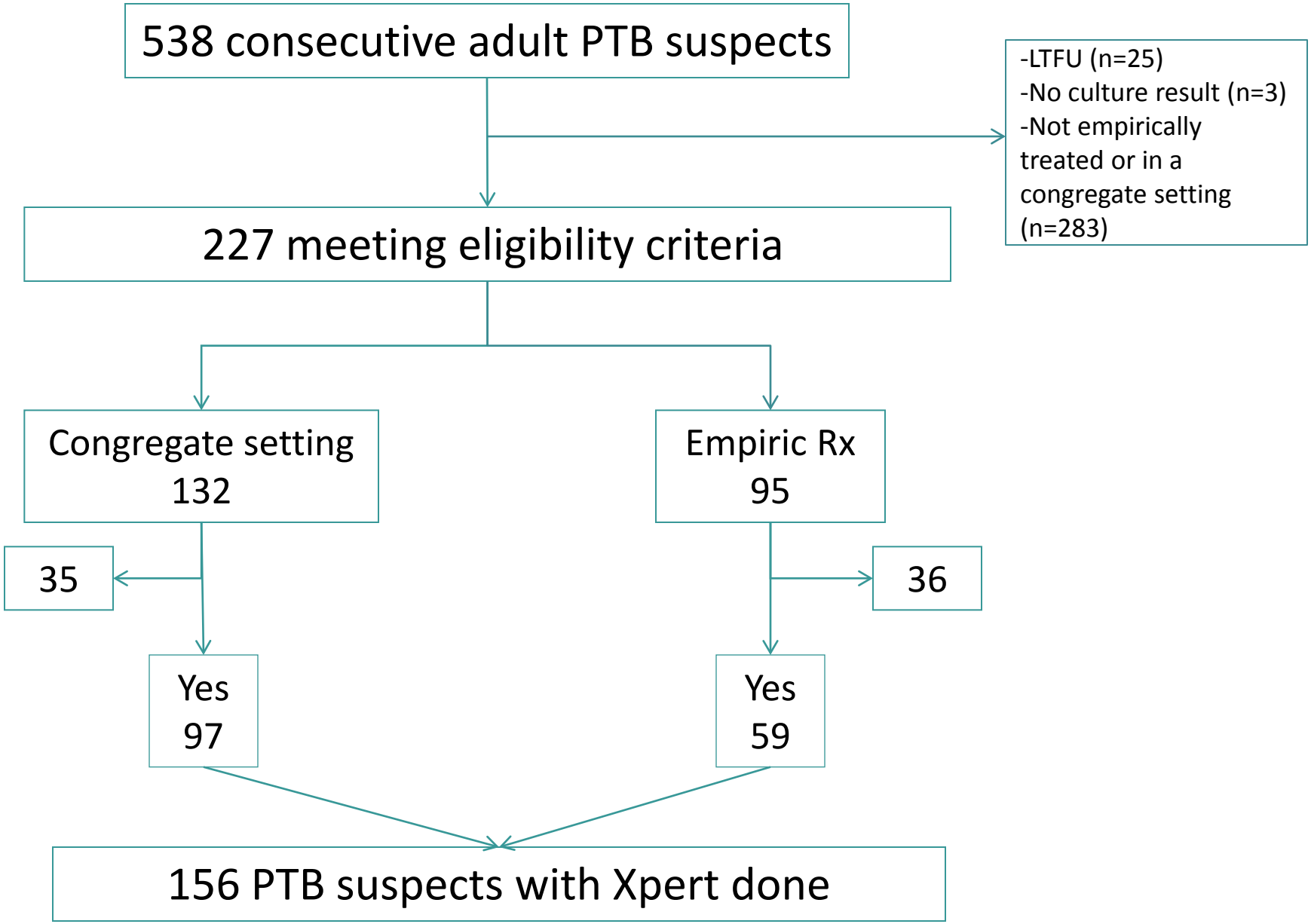


- 1000 TB suspects
- 200 Initiated on DOT
- 100 TB cases confirmed/reported

Study Protocol

- Time period: April 2010 – June 2011
- Adult PTB suspects referred for Xpert testing if:
  - Empiric TB treatment prescribed
  - Living in congregate settings
- Diagnostic accuracy
  - Index test: Sputum Xpert MTB/RIF
  - Reference standard: Mycobacterial culture
- Hypothetical impact of Xpert-directed clinical/public health decisions
  - Number of treatment decisions / contact investigations changed
  - Total treatment days gained/lost

Study Population: April 2010 – June 2011



Demographic and clinical characteristics

Characteristic, N (%)	**N=156**
Female sex	102 (65)
Median age (IQR)	52 (39-60)
Foreign born	117 (75)
Homeless*	20 (13)
History of viral hepatitis, chronic liver disease, alcohol use	38 (24)
Possible interactions with TB medications**	11 (7)
Clinician's level of suspicion for TB	
Low	79 (51)
Medium	44 (28)
High	33 (21)
AFB smear-positive	22 (14)
Culture-confirmed TB	13 (8)

Abbreviations: IQR = inter quartile range; ART = antiretroviral therapy; TB = tuberculosis

*6 missing observations

**Anti-seizure medication, ART, birth control, floroquinolones, immunosuppressive therapy, methadone, other; 30 missing observations

Diagnostic Accuracy

Culture Gold Standard

	TB (13)	Not TB (143)
Xpert + (12)	12 TP	3 FP
Xpert - (144)	1 FN	140 TN

Sensitivity = 92% (64, 100)

Specificity = 98% (94, 100)

PPV = 80% (52, 96)

NPV = 99% (96, 100)

Accuracy to Impact Schema

	TB	Not TB
Test+ **Empiric TB Rx +**	True Positive **Early rule-in**	False Positive **Over-treatment**
Test- **Empiric TB Rx -**	False Negative **Under-treatment**	True Negative **Early rule-out**

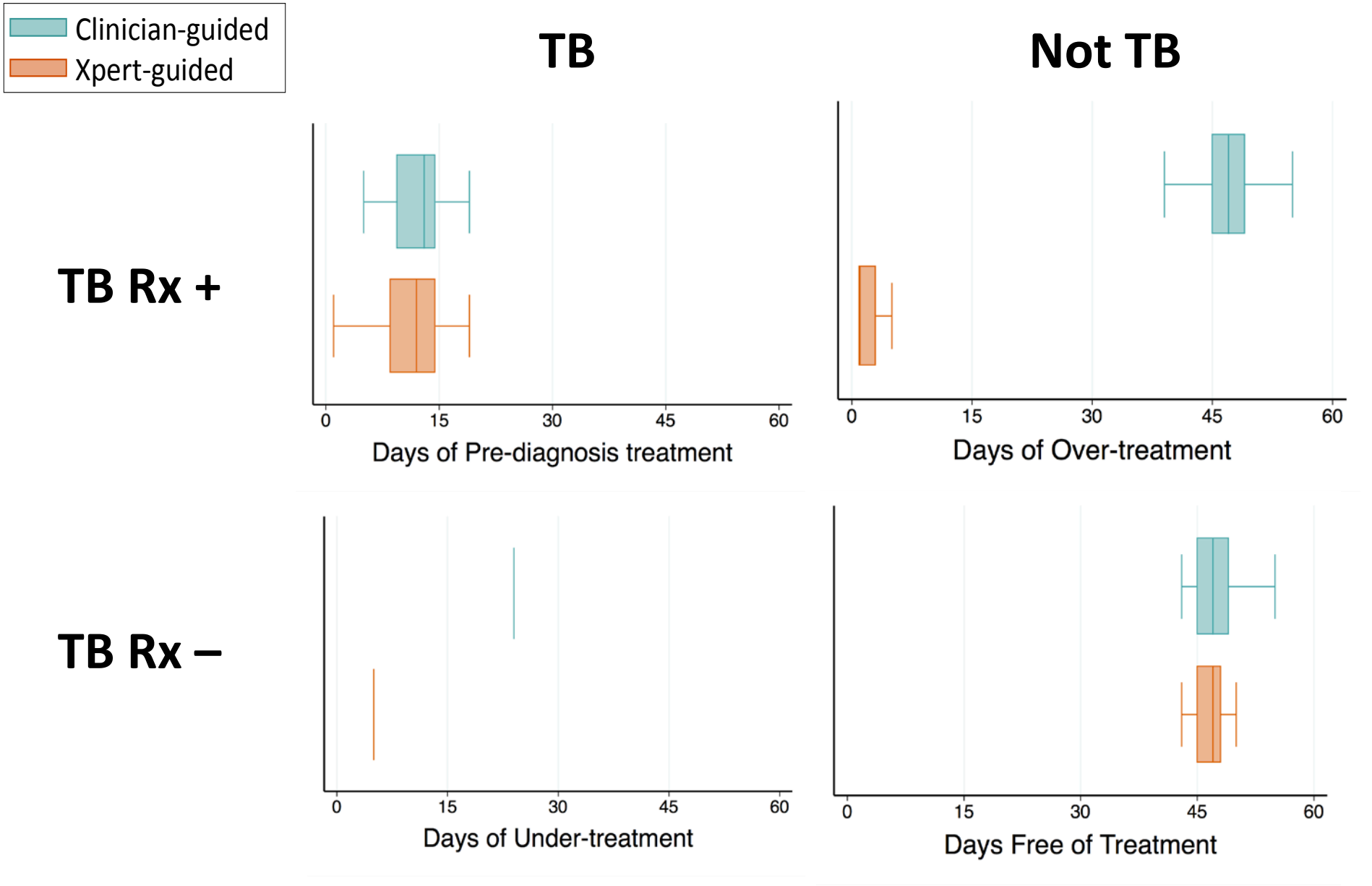
Re-classifying treatment decisions using Xpert results

Clinician-guided vs. Xpert	**TB**	**Not TB**
Empiric TB Rx +	**Early rule-in** **Xpert+** **Xpert-**	**Over-treatment** **Xpert+** **Xpert-**
Empiric TB Rx –	**Under-treatment**	**Early rule-out**

Potential incremental clinical impact of Xpert

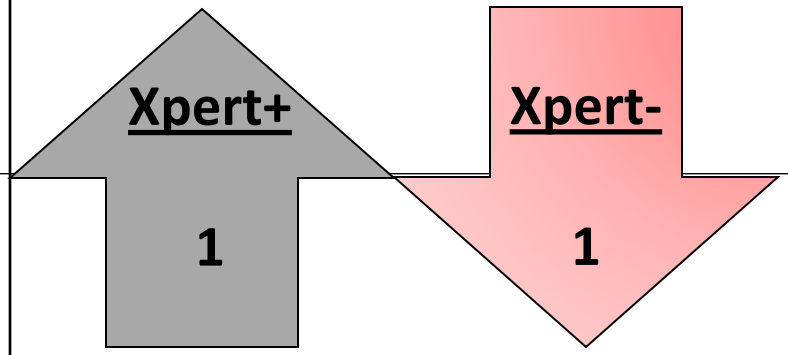
Clinician-guided ***vs. Xpert***	**TB** (n=13)	**Not TB** (n=143)
Empiric TB Rx + (n=59)	Added Sensitivity = 0% 12→12 Early deaths 1→2 Early losses Xpert+ 1 / Xpert- 1	Over Rx Days: 2200→111 47→40 Over-Treats 3→3 Over-Treats Xpert+ 1 / Xpert- 45
Empiric TB Rx – (n=97)	1→1 Under-Treats 1→1 Under-Treats Under Rx Days: 24→5	96→96 Early deaths 3→3 Early losses Added Specificity = +30%

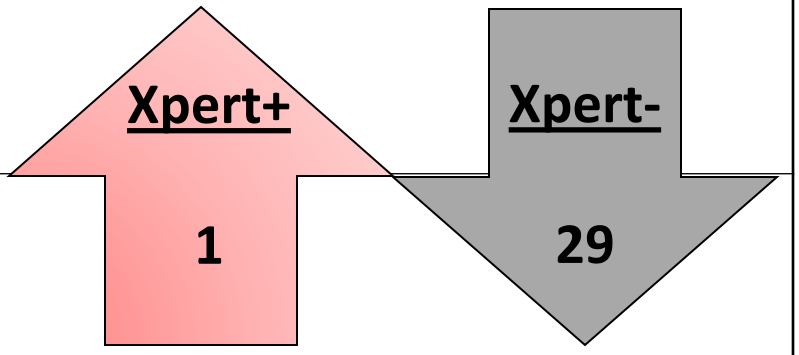
Clinical Impact of Xpert MTB/RIF



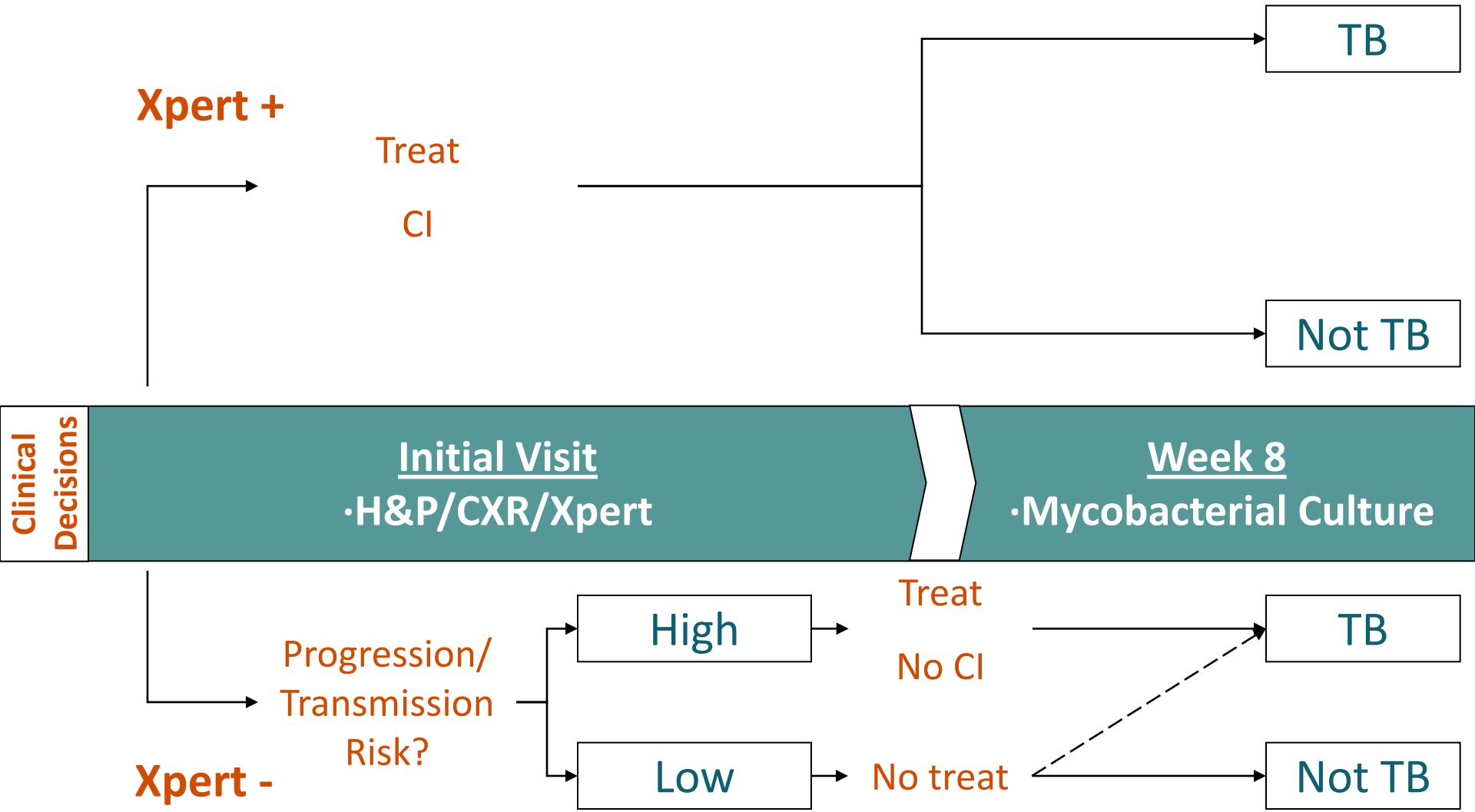
Contact Investigations

	TB (n=13)	**Not TB** (n=143)
Yes (n=41)	12 → 12 Early Investigations	29 → 29 Excess Investigations
	Xpert+ 1	**Xpert-** 1
	Xpert+ 1	**Xpert-** 29
No (n=115)	1 → 1 Missed Investigation	114 → 114 Non-investigations





Future diagnostic algorithm?



Limitations

- Non-consecutive patient selection
- Low number of TB cases (particularly smear-negatives)
- Data reflect hypothetical rather than actual decisions
- Did not model economic costs

Conclusions

- Xpert-directed modification of initial clinical and public health decisions could lead to substantial decreases in:
  - Unnecessary treatment
  - Contact investigation

- An Xpert-directed algorithm had minimal impact on missed treatment days among TB cases

- Moving from accuracy to impact could help the adoption of Xpert into routine algorithms for clinical and public health decisions in low burden countries

Alternatives to RCTs

- RCTs provide high quality evidence but
  - Expensive
  - Require large numbers of patients or clusters
  - Emphasize internal over external validity
  - May not be acceptable to patients or communities

- Evidence of impact can be obtained through non-randomized studies
  - Stepped-wedge designs
  - Interrupted time series

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