Evolution of New TB Diagnostics for Detection and Resistance

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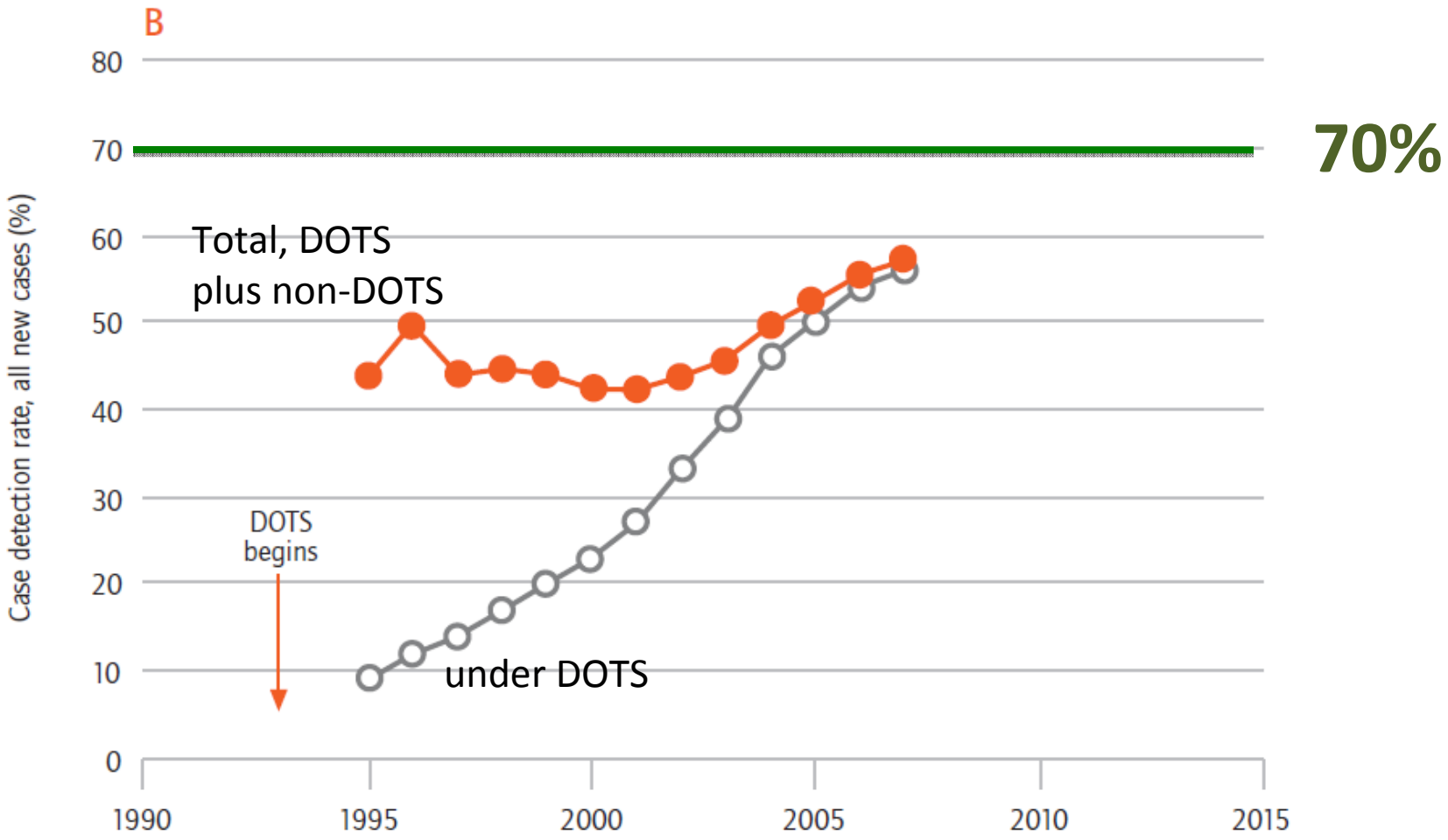
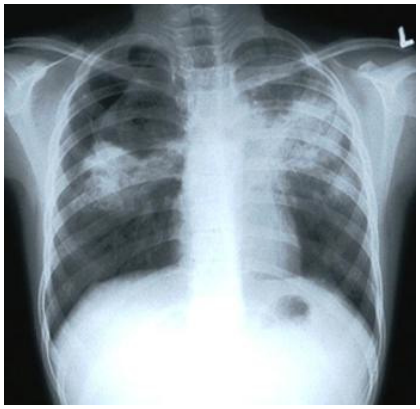
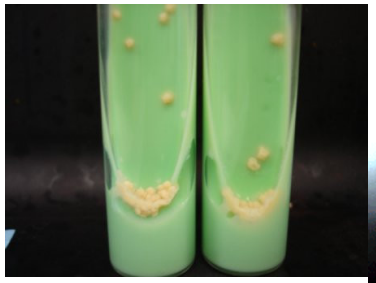
The target TB case detection rate of 70% has not been reached

WHO, Global Tuberculosis Control 2009



Commonly used TB diagnostic modalities





Overview

- New technologies
  - Xpert MTB/RIF
  - Urine lipoarabinomannan tests
  - Other TB diagnostics on the horizon

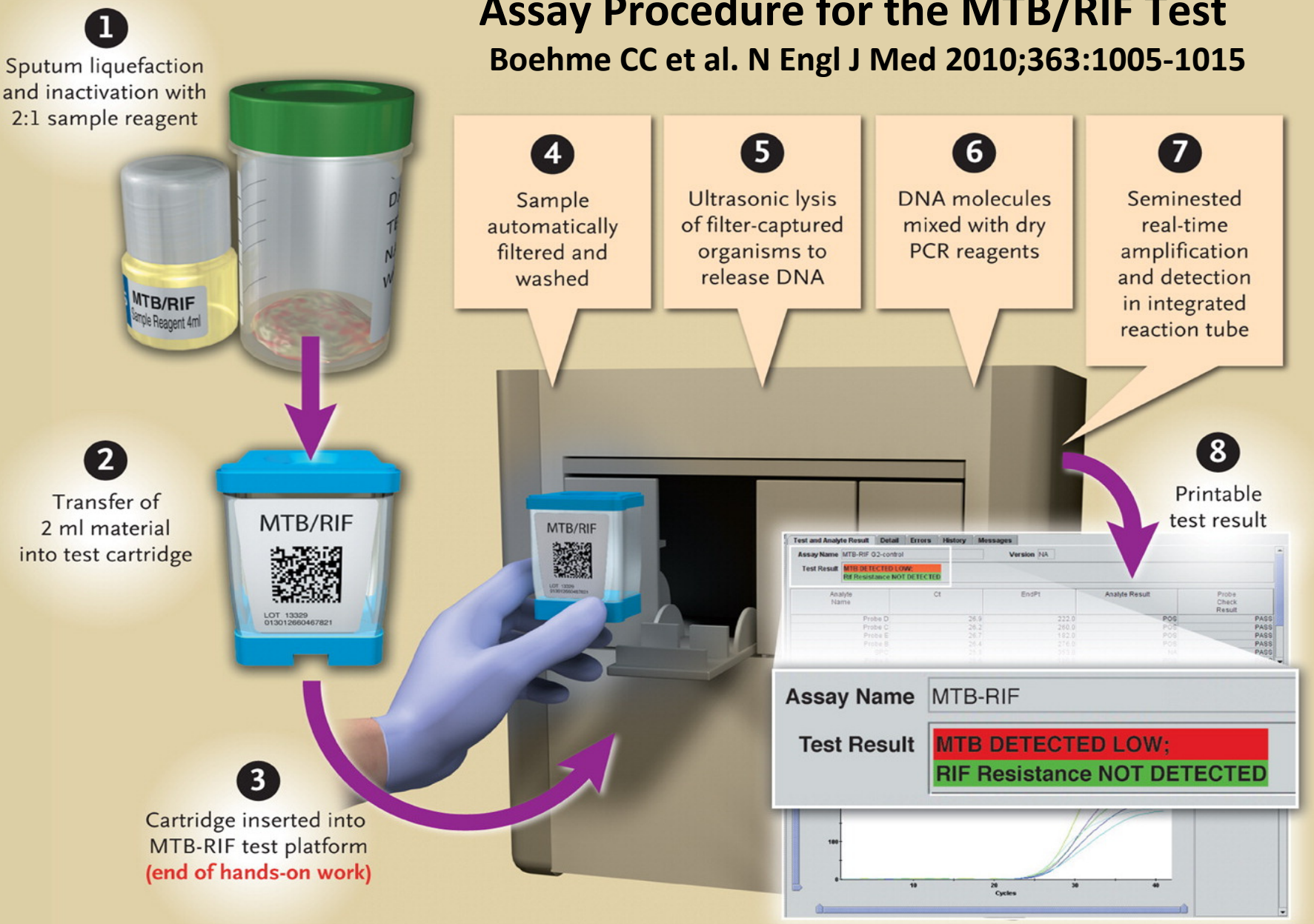
- Beyond “accuracy”

Xpert MTB/RIF

- For detection of *M. tuberculosis* and common mutations that confer resistance to rifampin (from respiratory specimens)
- Molecular test: hemi-nested real-time PCR of MTB-specific region of *rpoB* gene, which is then probed with molecular beacons for mutations
- Fully automated; uses GeneXpert platform (Cepheid, Sunnyvale, CA)
- Integrated sample processing and PCR; disposable plastic cartridge contains all reagents
- 2 manual steps: addition of bactericidal buffer to sputum then transfer of defined volume to cartridge

Assay Procedure for the MTB/RIF Test

Boehme CC et al. N Engl J Med 2010;363:1005-1015



Time to result, 1 hour 45 minutes

The NEW ENGLAND JOURNAL of MEDICINE

Xpert MTB/RIF

- High **analytical specificity** for *M. tuberculosis* conferred through careful selection of amplification target

- **Analytical sensitivity**: LOD 131 cfu/ml (D Helb et al JCM 2010;48:229)
  - Smear microscopy LOD ≈ 10,000 cfu/ml

Evaluation Study of Xpert MTB/RIF

C. Boehme et al. NEJM 2010;363:1005

- Cross-sectional study of diagnostic test accuracy in intended target population using best available reference standard (FIND)
- Population and Procedures
  - Peru, Azerbaijan, South Africa x 2, India
  - Adults with pulmonary TB symptoms
  - 3 sputa obtained (2 spot, 1 morning)
- Lab Methods for each participant
  - 2 of 3 sputa: decontamination then ZN smear microscopy, solid & liquid culture, Xpert MTB/RIF
  - 1 of 3 sputa: direct ZN smear microscopy, Xpert MTB/RIF (no decontamination)

Evaluation Study of Xpert MTB/RIF

C. Boehme et al. NEJM 2010;363:1005

- Results
  - 1730 eligible participants
    - 976 with HIV status known; 40.2% HIV-positive
  - Final diagnostic category
    - Smear positive, culture positive TB: 32.8%
    - Smear negative, culture positive TB: 10.1%
    - Rifampin-resistant TB: 12.2%

Evaluation Study of Xpert MTB/RIF

C. Boehme et al. NEJM 2010;363:1005

# Xpert tests per participant	**Sensitivity**			**Specificity**
	All CX POS	SM POS, CX POS	SM NEG, CX POS	
1 sputum	**675/732 92.2%**	551/561 98.2%	124/171 72.5%	**604/609 99.2%**
3 sputa	**723/741 97.6%**	566/567 99.8%	157/174 90.2%	**604/616 98.1%**

HIV POS: 93.9%, HIV NEG: 98.4%

Evaluation Study of Xpert MTB/RIF

C. Boehme et al. NEJM 2010;363:1005

	Xpert SENSITIVITY for Rifampin Resistance # correct/# total %	Xpert SPECIFICITY for Rifampin Resistance # correct/# total %
Phenotypic DST	200/205 97.6%	505/515 98.1%
Phenotypic DST and Discrepant Resolution by Sequencing	209/211 99.1%	506/506 100.0%

Xpert MTB/RIF

- Attributes & Advantages
  - Simple to perform, minimal training required
  - Not prone to cross-contamination
  - Requires minimal biosafety facilities (Banada JCM 2010)
  - “Near-care” (? POC)
- Shortcomings & Disadvantages
  - Complex instrument (calibration, electrical supply)
  - Platform well-suited to detecting limited # of mutations
  - Cost for instrument and cartridges

Xpert MTB/RIF

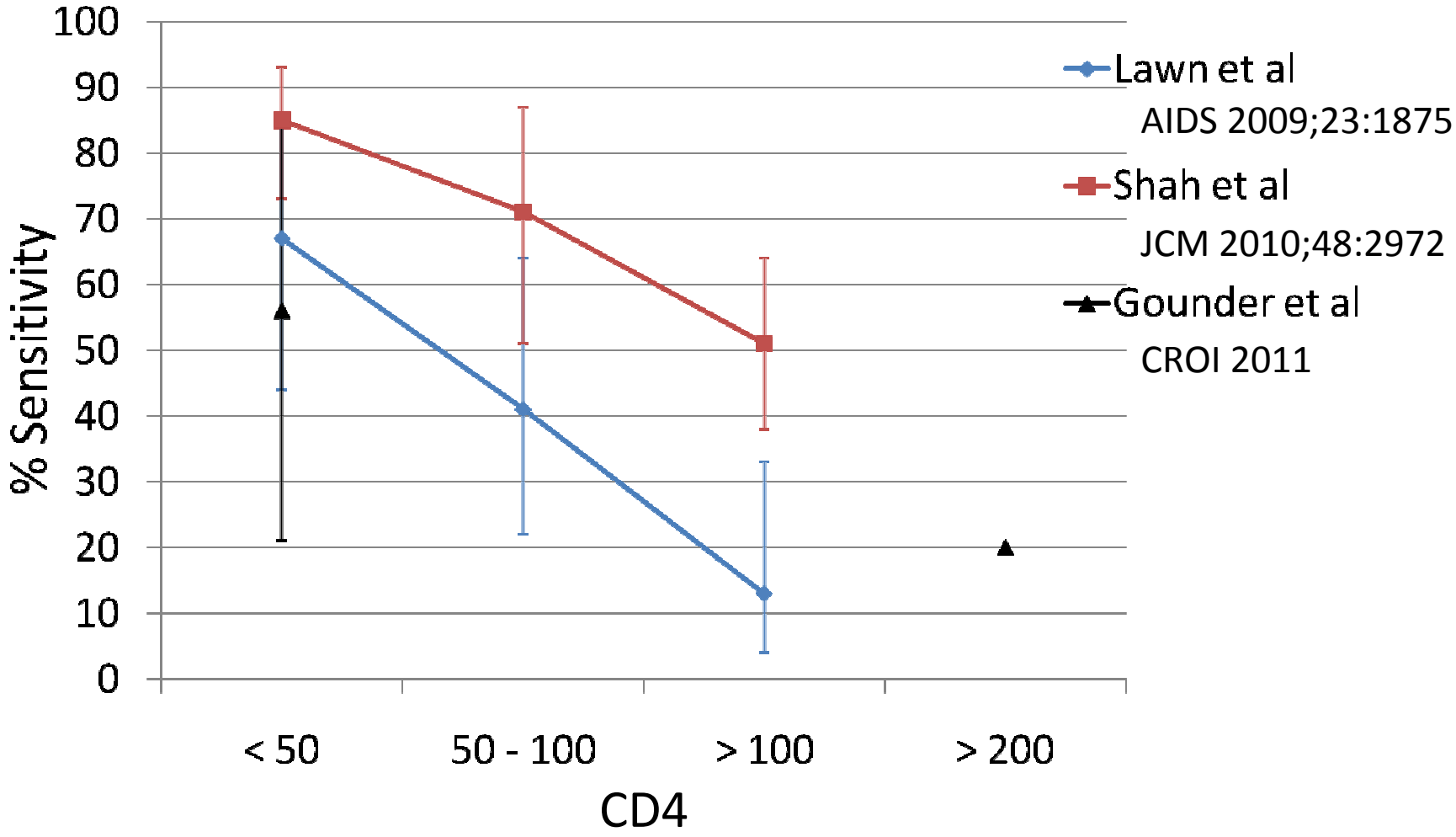
- WHO evidence review to policy announcement, Sept to Dec 2010
- WHO expert group recommendations:
  - ***"Xpert should be used as the initial diagnostic test in individuals suspected of having MDR-TB or HIV-associated TB"*** (strong recommendation)
  - ***"Xpert may be used as a follow-on test to microscopy where MDR and/or HIV is of lesser concern, especially in smear-negative specimens"*** (conditional recommendation, recognizing resource implications)

Courtesy of Dr. K. Weyer

Urine Assays for Mycobacterial Lipoarabinomannan (LAM)

- Background
  - LAM
    - 17.5 kd lipopolysaccharide component of MTB cell wall; heat stable
    - Released from metabolically active or degraded MTB
    - Prelim data animal models & some humans: in urine
  - Urine-based test
    - Urine easy to obtain
    - Lacks infection control issues of blood, sputum
    - Inverness: ELISA format; lateral flow under development

Sensitivity of Inverness LAM ELISA, by CD4 Count in HIV/TB Patients



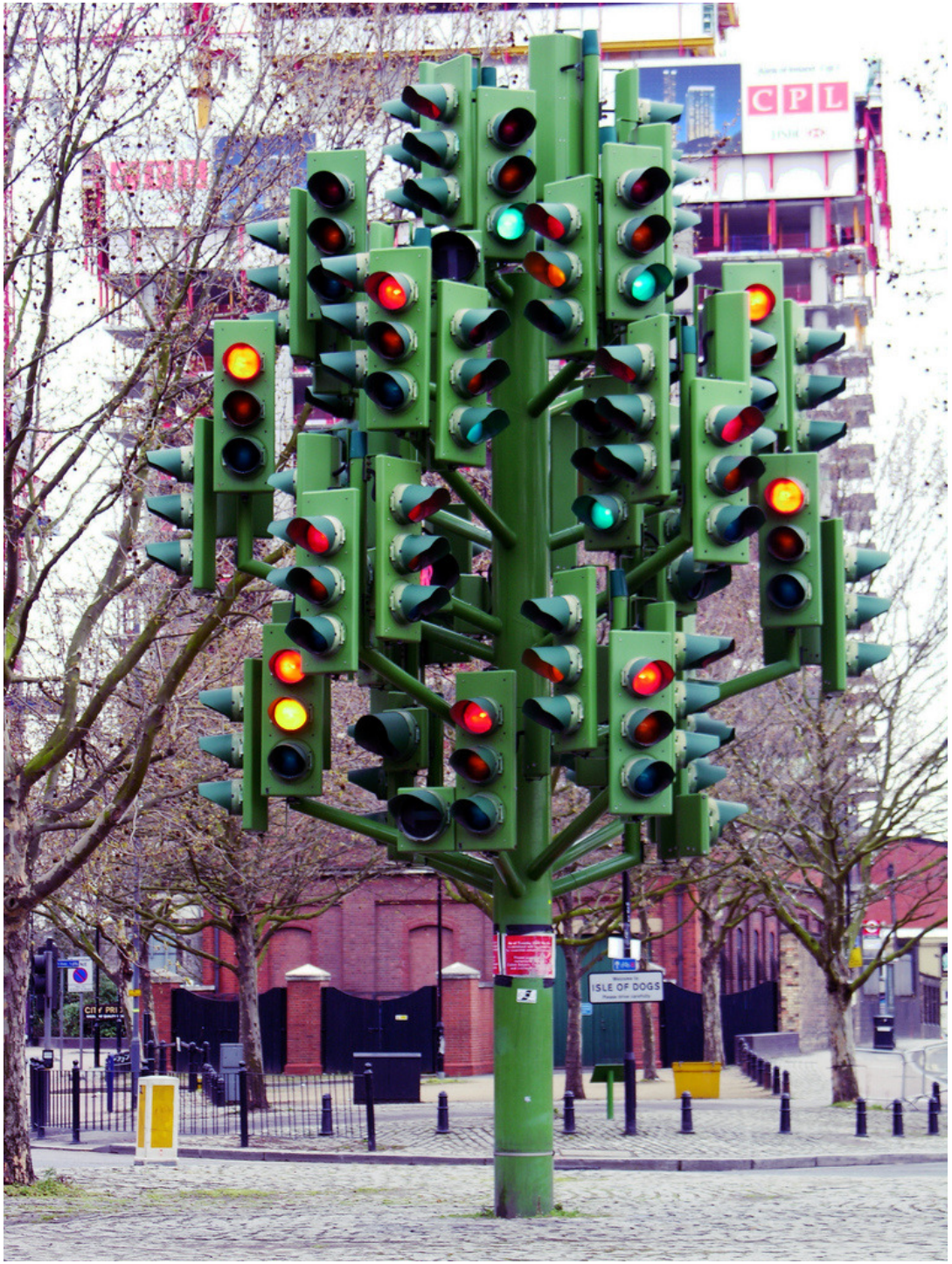
Beyond the current LAM ELISA…

- Lateral flow format
  - Dheda et al, 301 HIV+ hospitalized adults
  - Sensitivity LF 71% (61, 79) vs ELISA 61% (52, 70)
  - LF sensitivity if CD4<100: 86% (77, 93)

- This test performs best in those patients (advanced HIV) in whom conventional TB tests perform least well
- Expanding interest in the biology of mycobacterial products in clinical specimens
- Bringing new detection platforms, experts into TB field
- Prompting discussion of/strategies for integrating non-sputum tests into TB dx algorithms

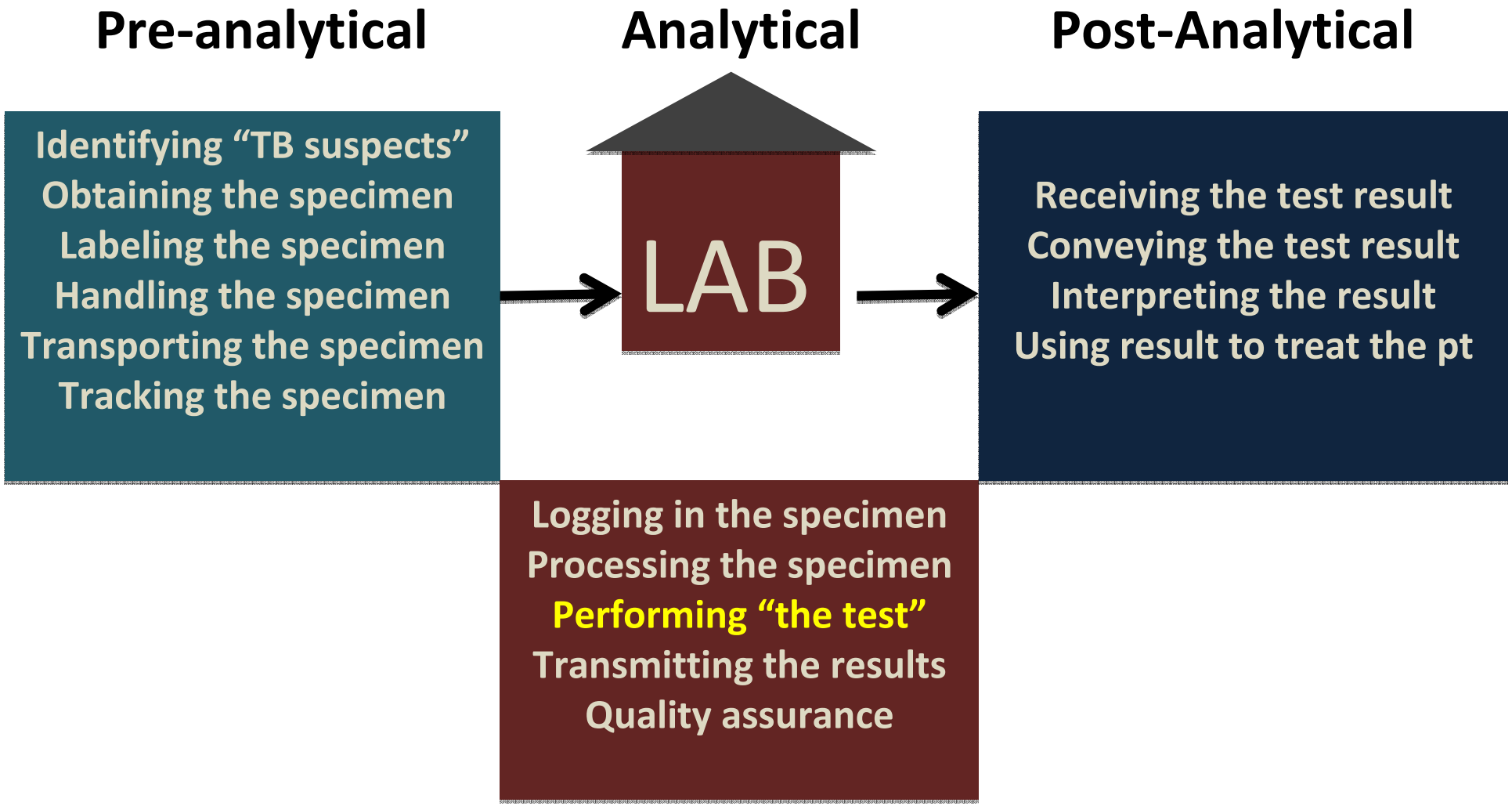
Other TB Diagnostic Tests

- **Smear microscopy improvements:** LED; concentration of bacilli; automated reading
- **Culture improvements:** Novel detection systems; novel media
- **Nucleic acid amplification for MTB detection:** Isothermal “near care”
- **Molecular for DST:** Expanded mutation capacity
- **Serology:** Proteomic approaches
- **Detection of volatiles:** Giant pouched rats; electronic noses

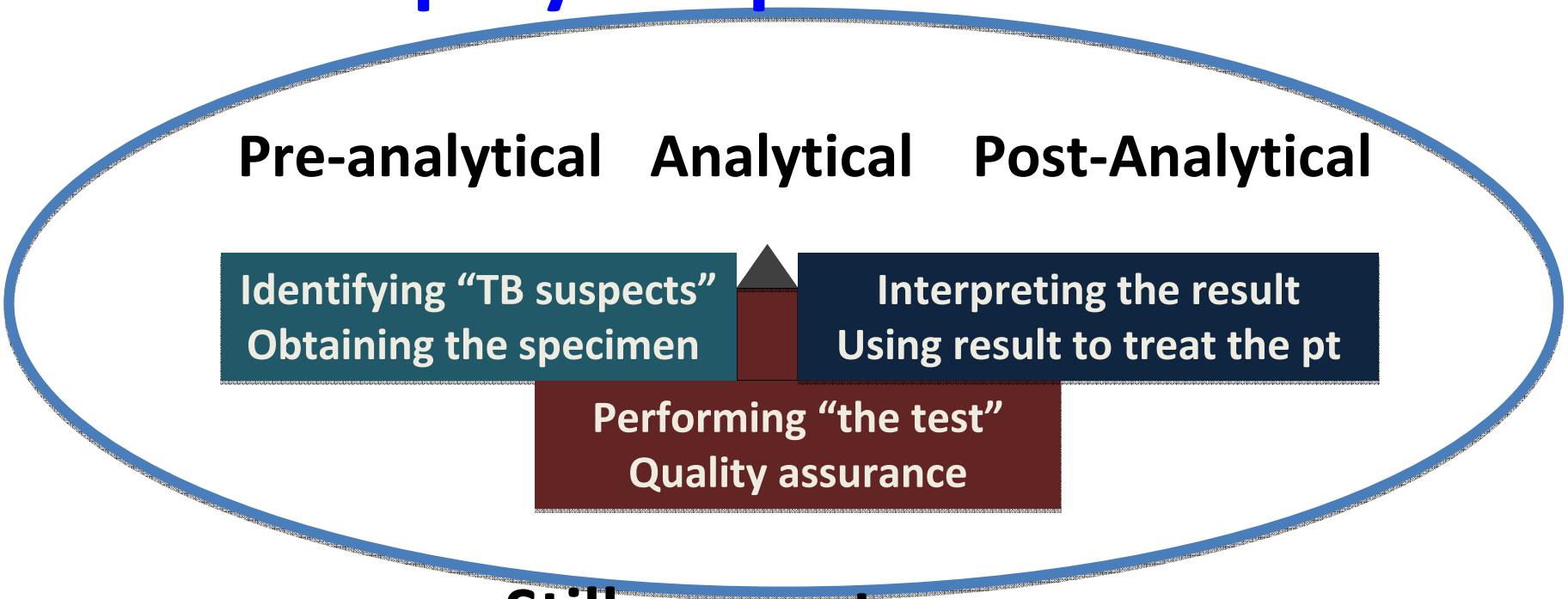


Beyond “accuracy” as measured in the lab…

Accuracy in the lab is only one step of a complex process



“near care” or “POC” tests will simplify the process BUT…



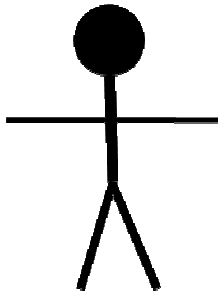
Still many steps….

opportunities & needs for operational research

around diagnostic and clinical care processes

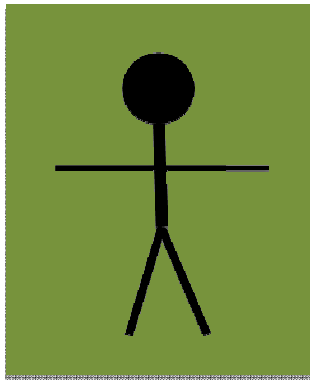
Impact: on Whom, What?

The Patient



Time to tx?
Morbidity?
Survival?

The TB/HIV Program(s)
The Health System



 # patients reached?
Costs ($ and opportunity)?

The Community

TB rates?
Rates of drug resistant TB?

Infection Control (e.g. in healthcare settings)

- TB case-finding is essential for infection control
- How can sensitive POC/near-care diagnostics open up new approaches to infection control esp. in healthcare settings?

“Deliverability”

- Can the test be rolled out to the places that matter?
- Will there be uptake?
- What is needed to sustain uptake?
- How to ensure that capacity for successful TB **treatment** keeps pace with case detection?

Important work already underway: Global Laboratory Initiative, TB REACH, PEPFAR, others

From accuracy to access: a role for advocacy and activism

- HIV/AIDS
  - Pre-2000: high ARV prices and patents limited access in developing countries
  - Post-2000: expansion started (e.g. WHO “3 by 5”)
    - Special terms in international trade laws allow manufacture of generic drugs
    - Some countries allow purchase of generic drugs from abroad
    - Brazil: legislation for free access to tx
  - **Common theme: role of civil society**
- Parallels between HIV *treatment* access and TB *diagnostic* access

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HIV TESTING IS THE ANSWER — WHAT'S THE QUESTION?

THERE is reason for concern about the false positive rate in testing for antibody to the human immunodeficiency virus (HIV). Even when the specificity of a test is high, some persons who are truly without disease will nevertheless test positive. In populations in which the prevalence of disease is low, these false positive results represent a substantial proportion of all positive results, lowering the probability that a positive

and possibly, suicide.

Yet in discussions of HIV antibody testing, the false positive rate has become a distraction, obscuring other concerns. Arguments that the false positive rate is too high sometimes mask misgivings about the social control implicit in widespread or mandatory testing, particularly screening. Conversely, arguments that a low false positive rate can be achieved seem tacitly to support aggressive testing policies. Using the false posi-

"HIV TESTING IS THE ANSWER – WHAT'S THE QUESTION?"

Robin Weiss and Samuel O. Thier, NEJM, Oct 13 1988

Acknowledgements

- NIH – TB Clinical Diagnostics Research Consortium

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