JOHNS HOPKINS UNIVERSITY

APHL

JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

Labs, Ledgers, and Lives Saved:

The Impact of Diagnostic Strategies on the Epidemiology and Economics of Tuberculosis

David Dowdy, MD, PhD

9th National Conference on Laboratory Aspects of Tuberculosis

June 8, 2015

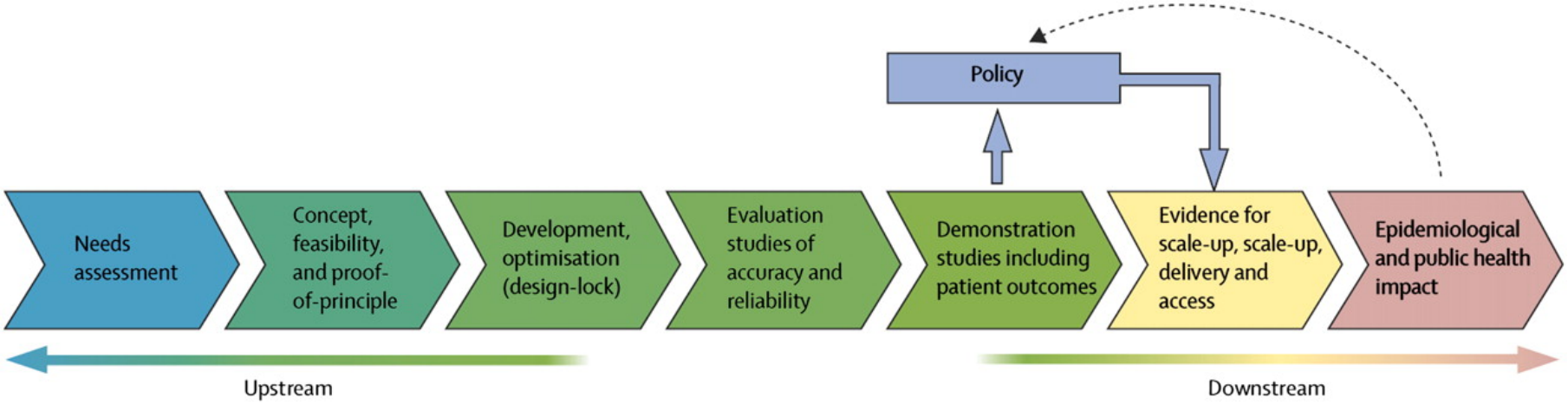
Protecting Health, Saving Lives—*Millions at a Time*

Disclosure

- No financial conflicts of interest with any commercial entity

- Funding to evaluate TB diagnostics
  - National Institutes of Health
  - Bill & Melinda Gates Foundation
  - Foundation for Innovative New Diagnostics

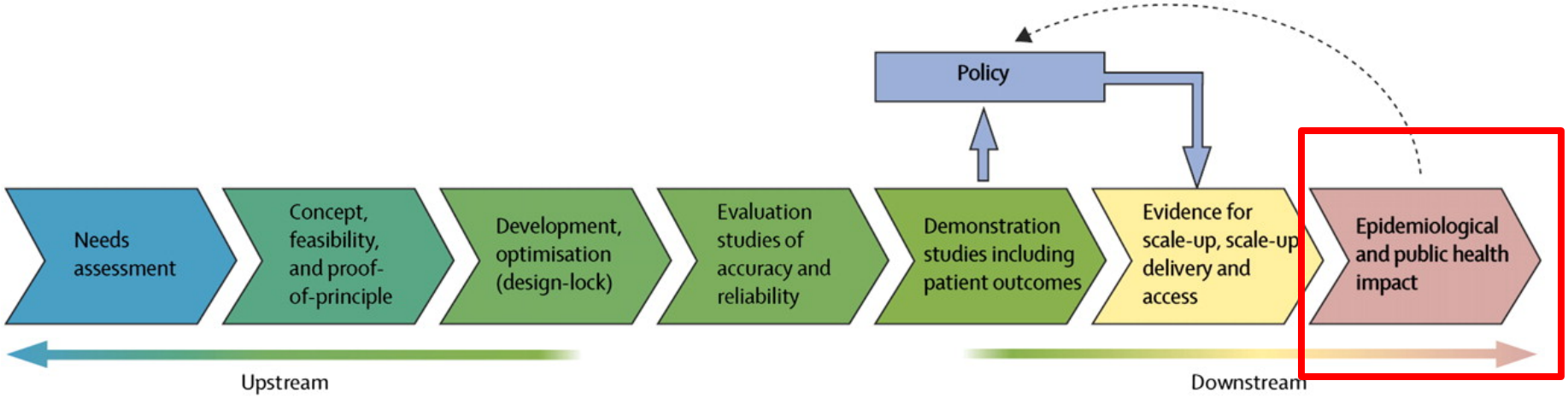
Pathway to TB Diagnostics



Cobelens et al. J Infect Dis. 2012;205:S191-S198

The Journal of Infectious Diseases

Pathway to TB Diagnostics

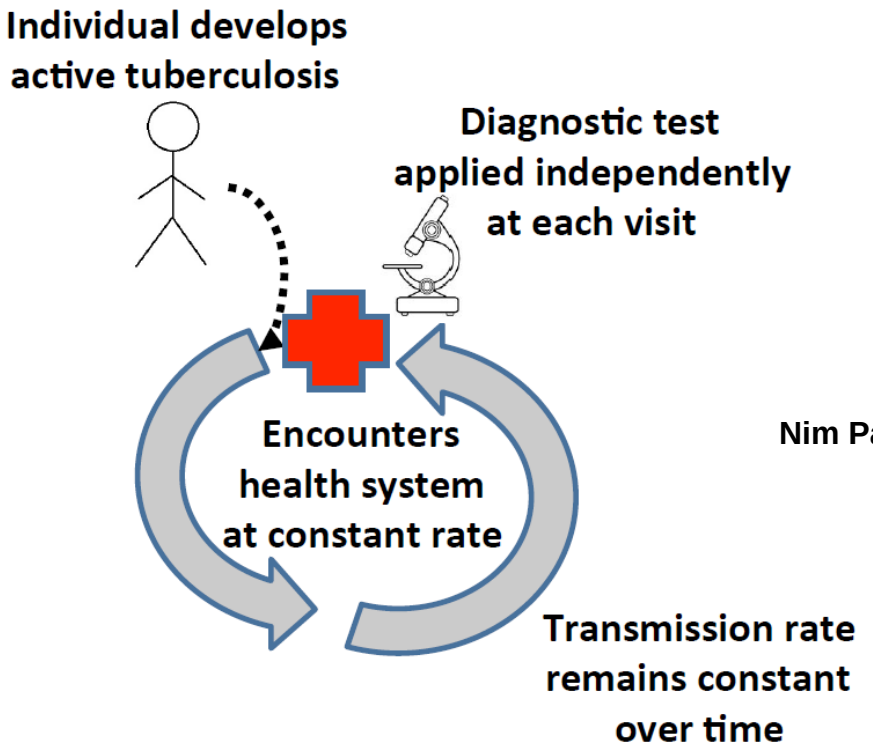


Cobelens et al. J Infect Dis. 2012;205:S191-S198

- How do we begin to think about the epidemiological and economic impact of diagnostic tests for TB?

The Journal of Infectious Diseases

The Classical View

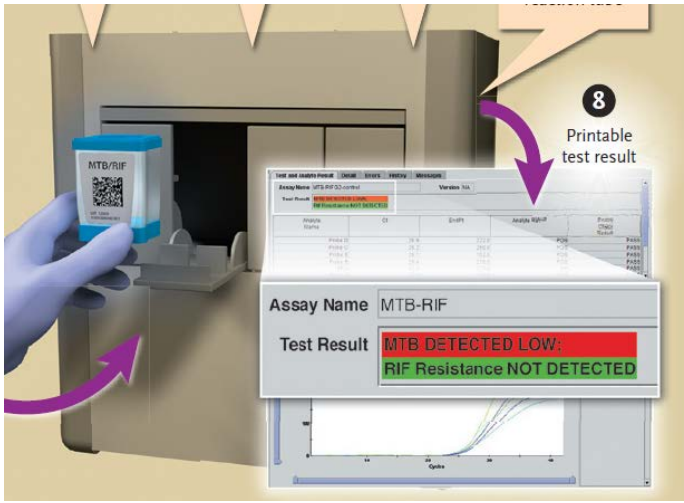


Nim Pathy and David Dowdy, under review

- The impact of a diagnostic test for TB is simply a function of its sensitivity.

Xpert MTB/RIF

- Fully automated PCR
- More accurate than sputum smear, less sensitive than culture
- Results in 2 hours, with Rif susceptibility
- FDA approved in 2013, CLIA Moderately Complex
- Endorsed by WHO for use in high-burden countries since 2010



Boehme et al, N Engl J Med 2010; 363: 105-1015.

OPEN ACCESS Freely available online

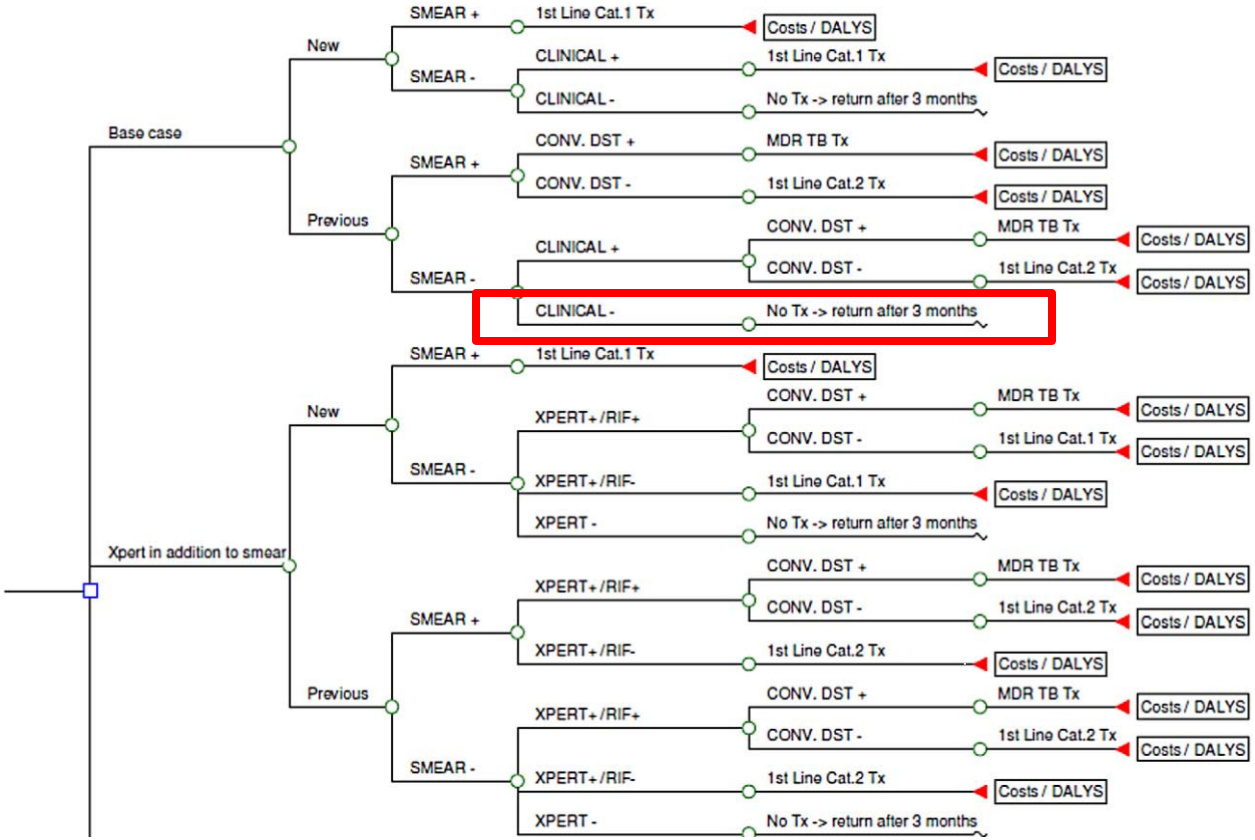
PLoS MEDICINE

Rapid Diagnosis of Tuberculosis with the Xpert MTB/RIF Assay in High Burden Countries: A Cost-Effectiveness Analysis

Anna Vassall[1,2], Sanne van Kampen[1], Hojoon Sohn[3], Joy S. Michael[4], K. R. John[5], Saskia den Boon[6], J. Lucian Davis[7], Andrew Whitelaw[8,9], Mark P. Nicol[8,9], Maria Tarcela Gler[10], Anar Khaliqov[11], Carlos Zamudio[12], Mark D. Perkins[13], Catharina C. Boehme[13], Frank Cobelens[1]*

PLoS Med 8(11): e1001120. doi:10.1371/journal.pmed.1001120

Decision Tree



Only 21% of smear/Xpert-negatives assumed to be diagnosed clinically.

Primary Results

Table 5. Cost per DALY (US$ 2010).

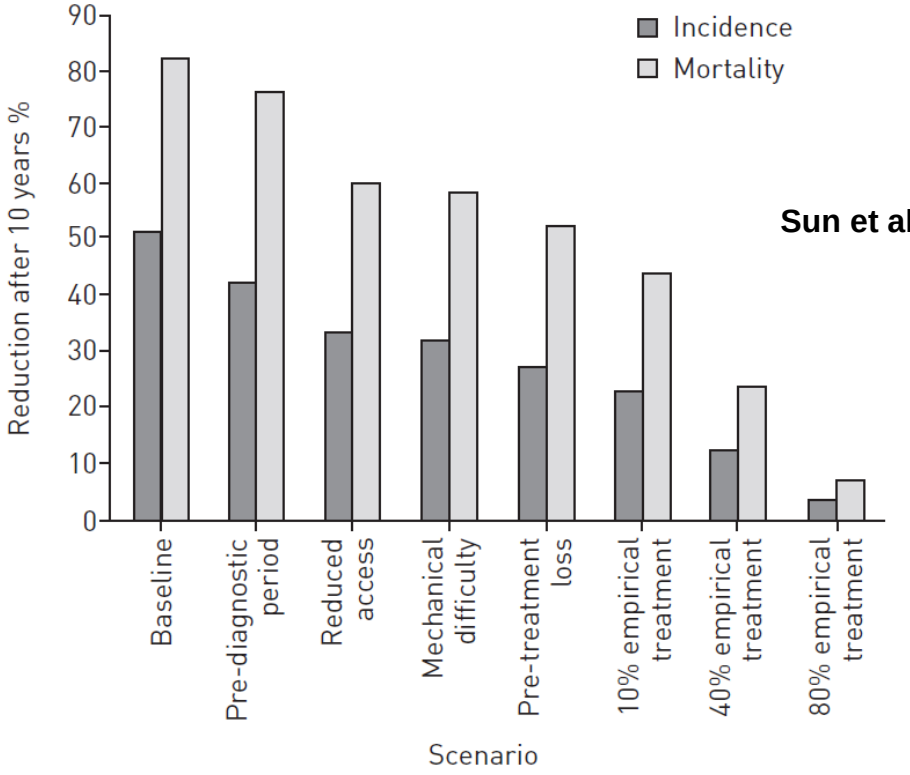
Country	Scenario	Total Cost	Total DALYS	Cost per DALY	ICER Compared to Base Case, Mean
India	Base case	513,698	17,133	30	—
	In addition to smear	664,191	19,887	33	55
	Replacement of smear	709,248	20,019	35	68
South Africa	Base case	1,084,698	15,805	69	—
	In addition to smear	1,594,276	20,420	78	110

For 10,000 people with presumptive TB:
4,600 life-years saved (DALYs averted)
Cost: $110 per DALY averted

Problem #1: South Africa is not the USA

South Africa	United States
Incidence: 1,000 per 100,000/yr	Incidence: 4 per 100,000/yr
TB Culture inconsistent	TB Culture routine
Smear+: Presumptive TB	Smear+: Possible NTM
Every generalist has seen TB	Most MDs never see TB
Xpert can be performed by RN	Xpert requires CLIA lab (where Amplicor & MTD are available)
Xpert cartridge: $10	Xpert cartridge: $71
Hospital stay: ~$100/day	Hospital stay: ~$2500/day
Overriding concern: TB/HIV mortality	Overriding concern: Fitting Xpert into cash-strapped PH system

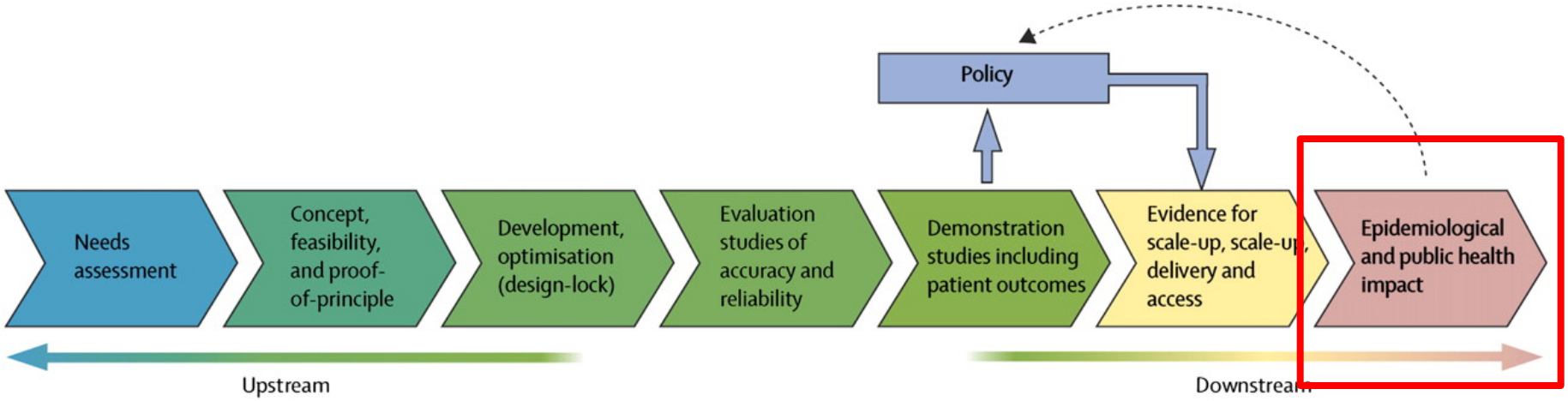
Problem #2: Projecting Impact of Diagnostic Testing isn't Simple



Sun et al, Eur Respir J 2014; 44:1366-9.

- A test projected to prevent 50% of all TB deaths under ideal assumptions may avert 3% of deaths in real-world conditions.

How Should We Think About Impact and Cost-Effectiveness of New TB Diagnostics in the USA?



Impact of GeneXpert MTB/RIF on Patients and Tuberculosis Programs in a Low-Burden Setting

A Hypothetical Trial

J. Lucian Davis[1,2], L. Masae Kawamura[3], Lelia H. Chaisson[1], Jennifer Grinsdale[3], Jihane Benhammou[4], Christine Ho[5], Anna Babst[6], Houmpheng Banouvong[3], John Z. Metcalfe[1,2], Mark Pandori[6], Philip C. Hopewell[1,2], and Adithya Cattamanchi[1,2]

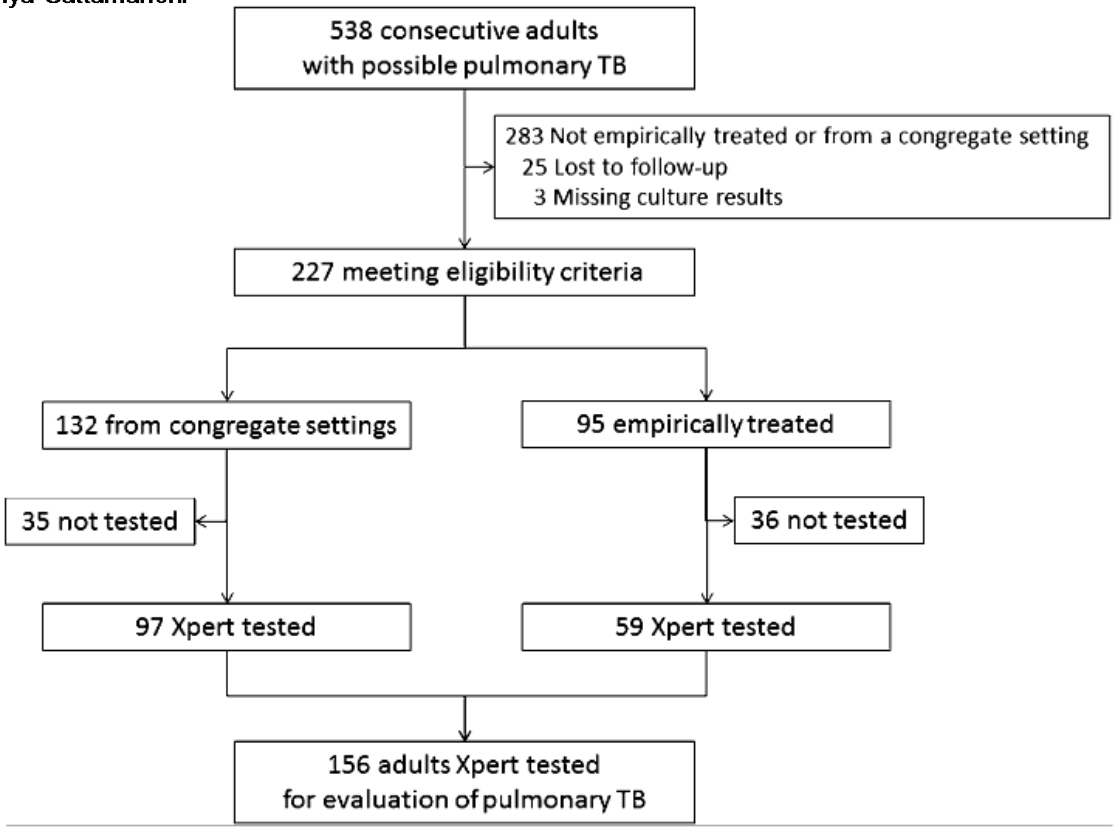
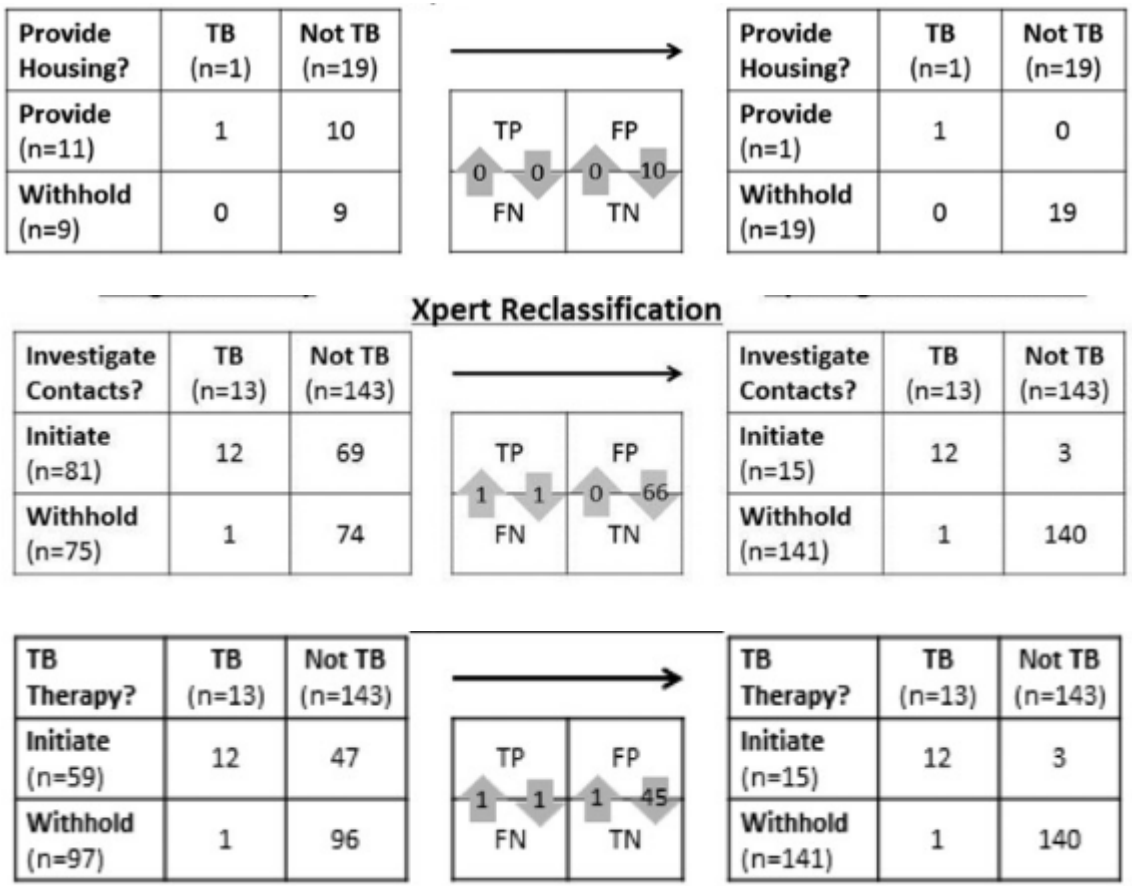


Figure 1. Patient enrollment flow diagram. TB – tuberculosis; Xpert – GeneXpert MTB/RIF.

AJRCCM 2014; 189(12):1551-59

How Might Xpert Be Useful in the USA?



Xpert may be more useful in ruling out TB (pending culture) than ruling TB in.

- Avoid unnecessary empiric treatment
- Avoid unnecessary contact investigation
- Aid public health decisions (e.g., housing)

Table 2. Impact of Xpert-guided Decisions on Individual and Total Annual Outcomes

Outcomes	Median (IQR) Individual Impact			Total Annual Impact (95% CI)		
	Standard Criteria	Xpert	Difference	Standard Criteria	Xpert	Difference
Treatment						
Mtb culture-positive						
Days of prediagnosis treatment	13 (10 to 15)	12 (9 to 15)	1 (1 to 3)	187 (86 to 288)	174 (68 to 280)	13 (−16 to 42)
Days of undertreatment	24 (—)	5 (—)	19 (—)	24 (—)	5 (—)	19 (—)
Mtb culture-negative						
Days of overtreatment	46 (45 to 49)	1 (1 to 3)	44 (43 to 47)	2,280 (2,081 to 2,479)	111 (0 to 56)	2,169 (1,938 to 2,400)
Contact investigation*						
Index case *Mtb* culture-positive						
Number of TB contacts investigated	2 (1 to 4)	1 (1 to 3)	—	30 (14 to 46)	23 (11 to 34)	—
Number of TB contacts not investigated	12 (—)	5 (—)	—	12 (—)	5 (—)	—
Index case *Mtb* culture-negative						
Number of non-TB contacts investigated	1 (1 to 1)	1 (1 to 7)	—	99 (79 to 119)	9 (0 to 35)	—
Subsidized housing						
Mtb culture-positive						
Nights of early housing	6 (—)	6 (—)	0 (—)	6 (—)	6 (—)	0 (—)
Nights of housing missed	0	0	0	0	0	0
Mtb culture-negative						
Nights of unnecessary housing	47 (46 to 49)	1 (1 to 4)	46 (38 to 47)	495 (387 to 603)	30 (6 to 54)	465 (348 to 582)

All assume that clinicians (and lawyers) will actually trust Xpert…

Translating Into Cost-Effectiveness

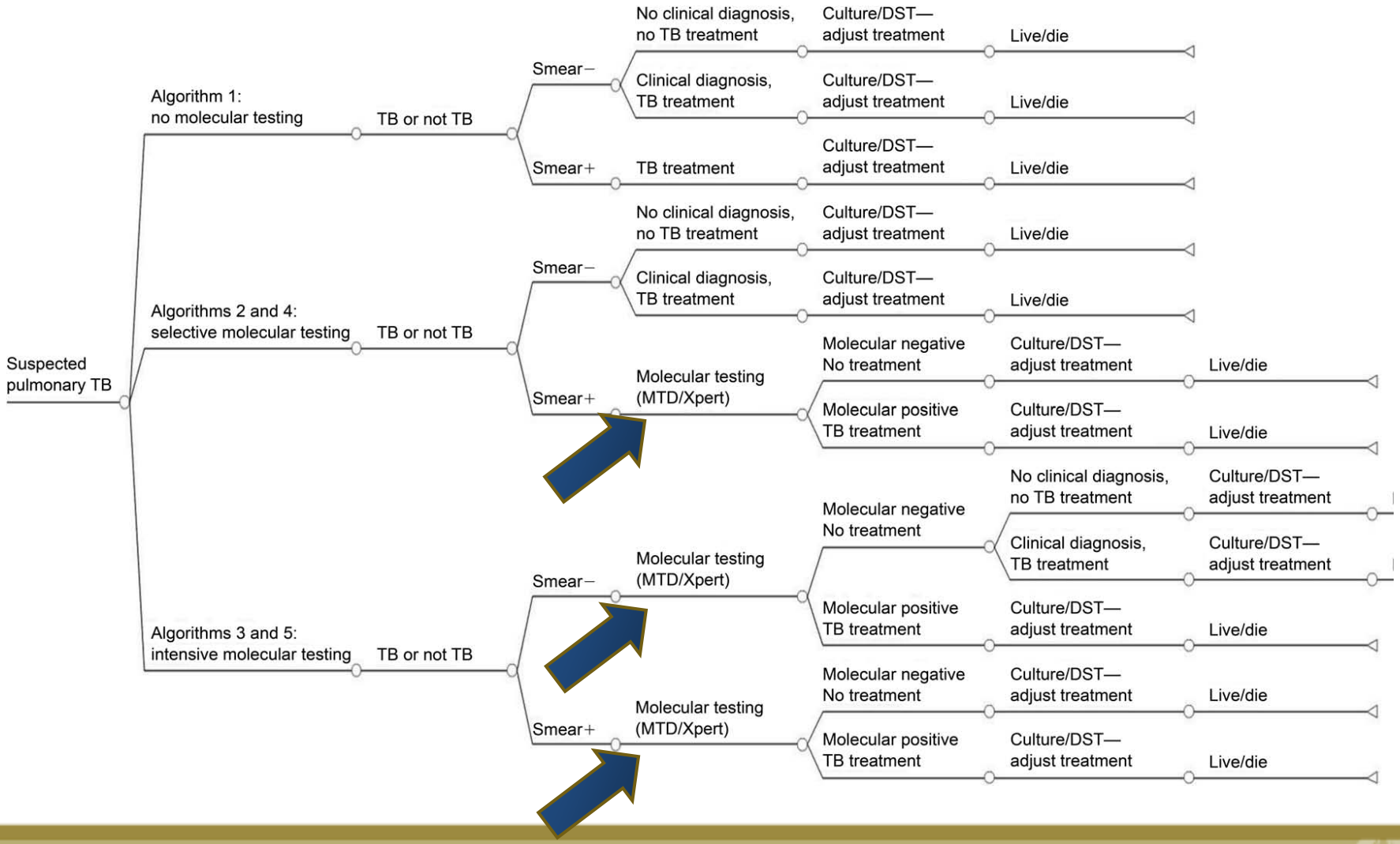
INT J TUBERC LUNG DIS 17(10):1328–1335

http://dx.doi.org/10.5588/ijtld.13.0095

Cost-effectiveness of Xpert® MTB/RIF for diagnosing pulmonary tuberculosis in the United States

H. W. Choi,* K. Miele,* D. Dowdy,† M. Shah*‡

Model Diagram



Key Parameters

Variable	Base case	Low	High	Reference
Laboratory costs, US$*				
Smear microscopy	4.07	2.35	5.95	Calculated
Mycobacterial culture	35.56	17.29	52.60	Calculated
DST	101.68	19.60	166.37	Calculated
MTD®	91.49	26.08	320.42	Calculated
Xpert® MTB/RIF	98.10	20.24	838.46	Calculated
Treatment costs, US$				
Anti-tuberculosis treatment course (drug-susceptible TB, 6 months)	9037†	3069	53401	BCHD†, 15, 16
Hospitalization costs per day	2469	1161	2975	17, 18
MDR-TB treatment	57889†	40133	204862	BCHD†, 15, 19
Epidemiology and diagnostic and treatment parameters				
Prevalence of TB among TB suspects in the United States (HIV-positive TB suspects)§	0.02 (0.062)	0.01 (0.03)	0.30 (0.30)	1, 20, 21‡
MDR-TB prevalence among TB cases in the United States	0.011	0.009	0.075	1
Probability of hospitalization during initial TB evaluation	0.20	0	1.0	BCHD, 15, 22
Mortality of untreated smear-positive TB (smear-negative TB)¶	0.70 (0.20)	0.53 (0.10)	0.86 (0.30)	23, 24
Mortality of treated drug-susceptible TB (MDR-TB)¶	0.05 (0.08)	0.01 (0.05)	0.20 (0.50)	1

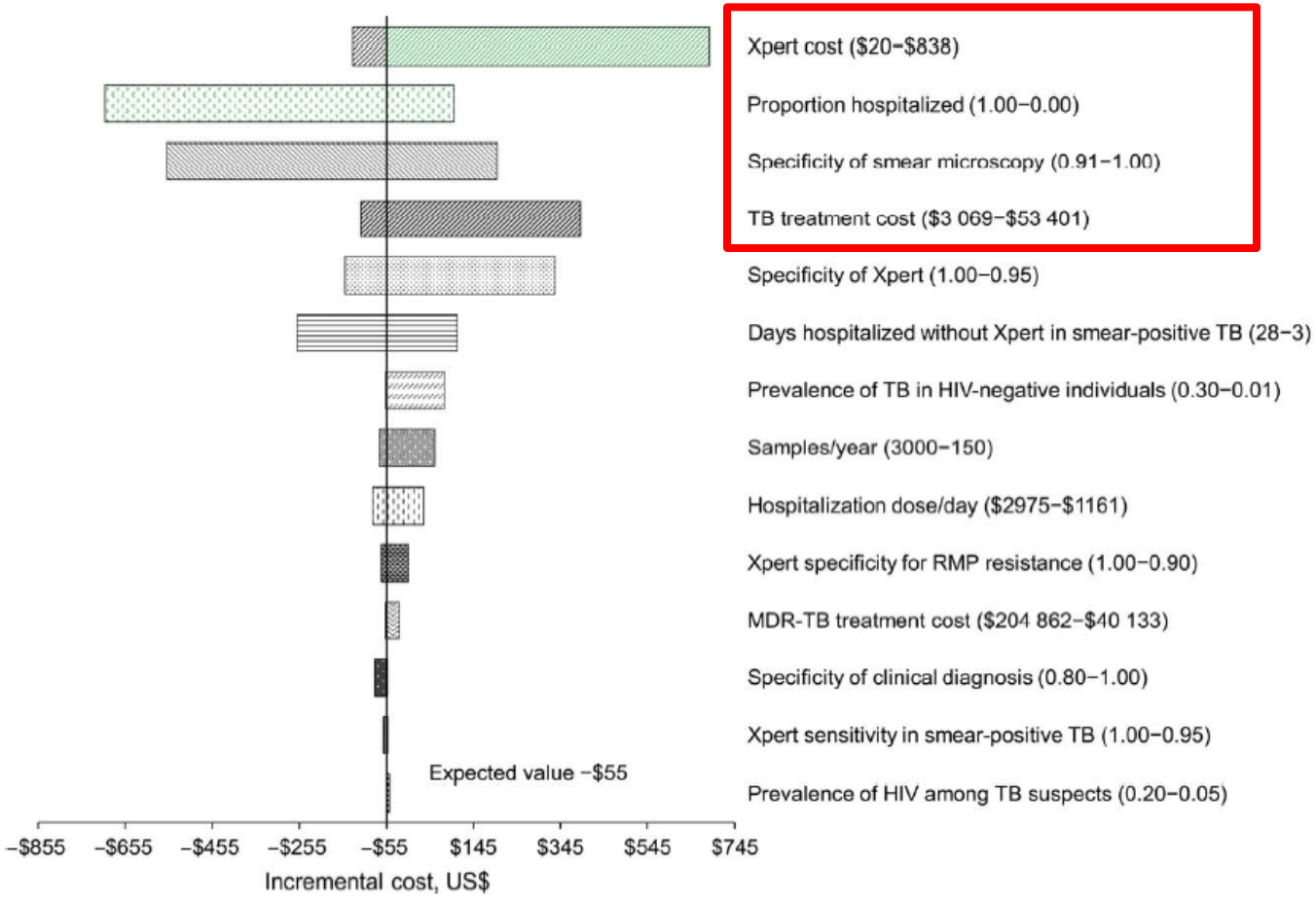
$100 per test sounds like a lot…until compared to the cost of a hospital day.

Cost-Effectiveness

Costs and effects	Algorithm 1 no molecular	Algorithm 2 selective MTD®	Algorithm 3 intensive MTD®	Algorithm 4 selective Xpert®	Algorithm 5 intensive Xpert®
Total laboratory costs per TB suspect, US$	157.64	161.80	249.13	162.10	255.75*
Incremental laboratory costs, US$	Reference	4.16	91.49	4.46	98.11
Total health care costs per TB suspect, US$†	2727.68	2479.63	2653.08	2481.71	2672.79
Incremental total costs, US$	Reference	−248.05	−74.60	−245.97	−54.89
QALYs accrued per TB suspect	22.08622	22.08771	22.09133	22.08780	22.09254
Incremental QALYs per 1000 suspects	Reference	1.49	5.11	1.58	6.32‡
Average time to diagnosis among TB cases, days§	16.30	13.31	3.92	6.03	2.71
TB cases diagnosed by molecular testing, %	0	75.50	88.00	75.50	92.00
ICER, US$ per QALY gained¶	Dominated¶	Reference	47 914	23 111	39 992
ICER, US$ per QALY gained	—	—	Reference	—	16 289
ICER, US$ per QALY gained	—	—	—	Reference	40 312

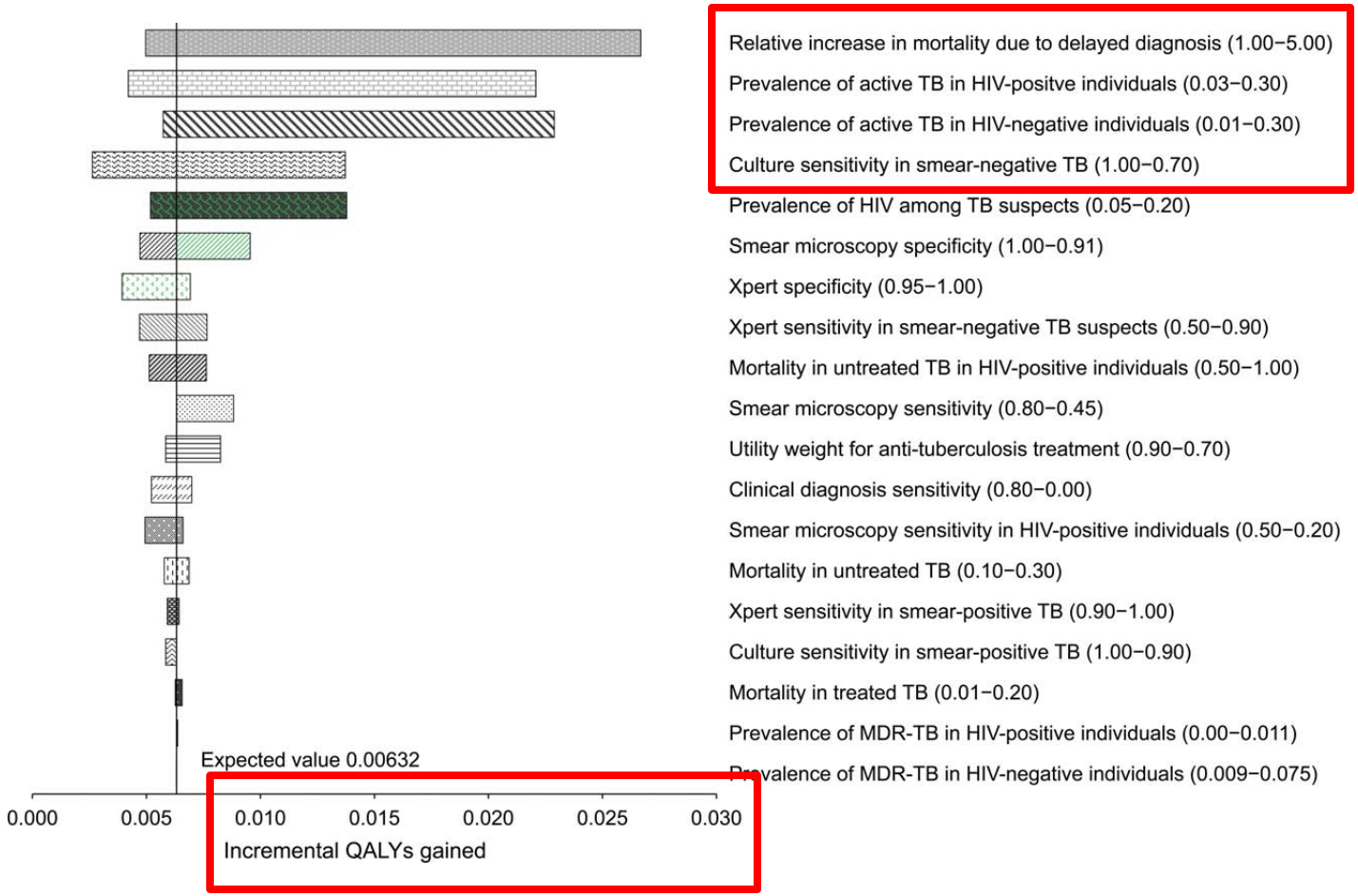
What may save the healthcare system money may still be costly to labs.
Effectiveness is small (5-6 QALYs per 1000 people with TB symptoms).
Difference between MTD and Xpert is even smaller.
With these caveats, Xpert does appear cost-effective (<$50,000/QALY).

Drivers of Cost



Major avertible costs are hospitalization of patients with possible TB and treatment of smear-positive NTM.

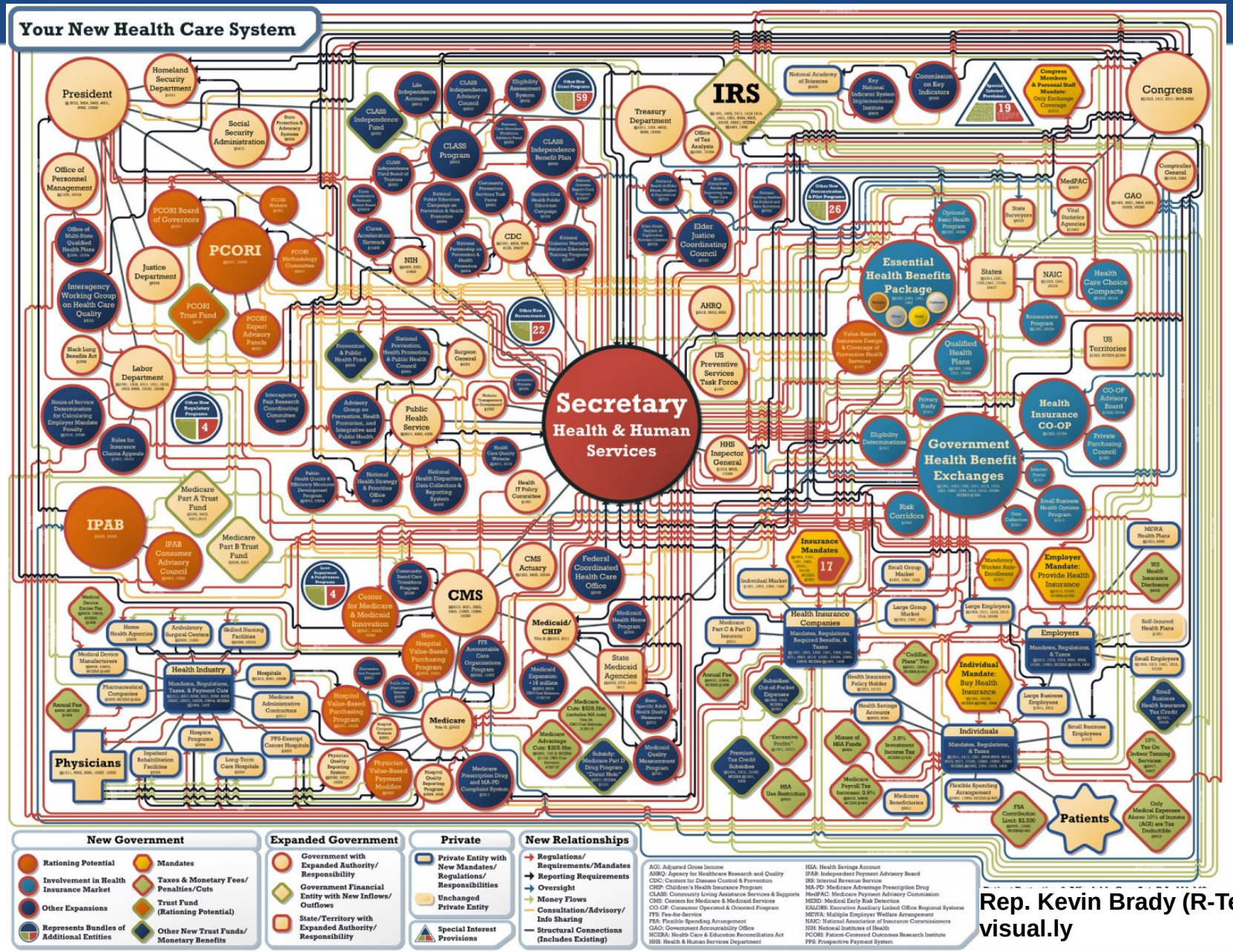
Drivers of Effectiveness



Potential health benefit if delayed diagnosis leads to death…but the magnitude of that benefit is relatively small.

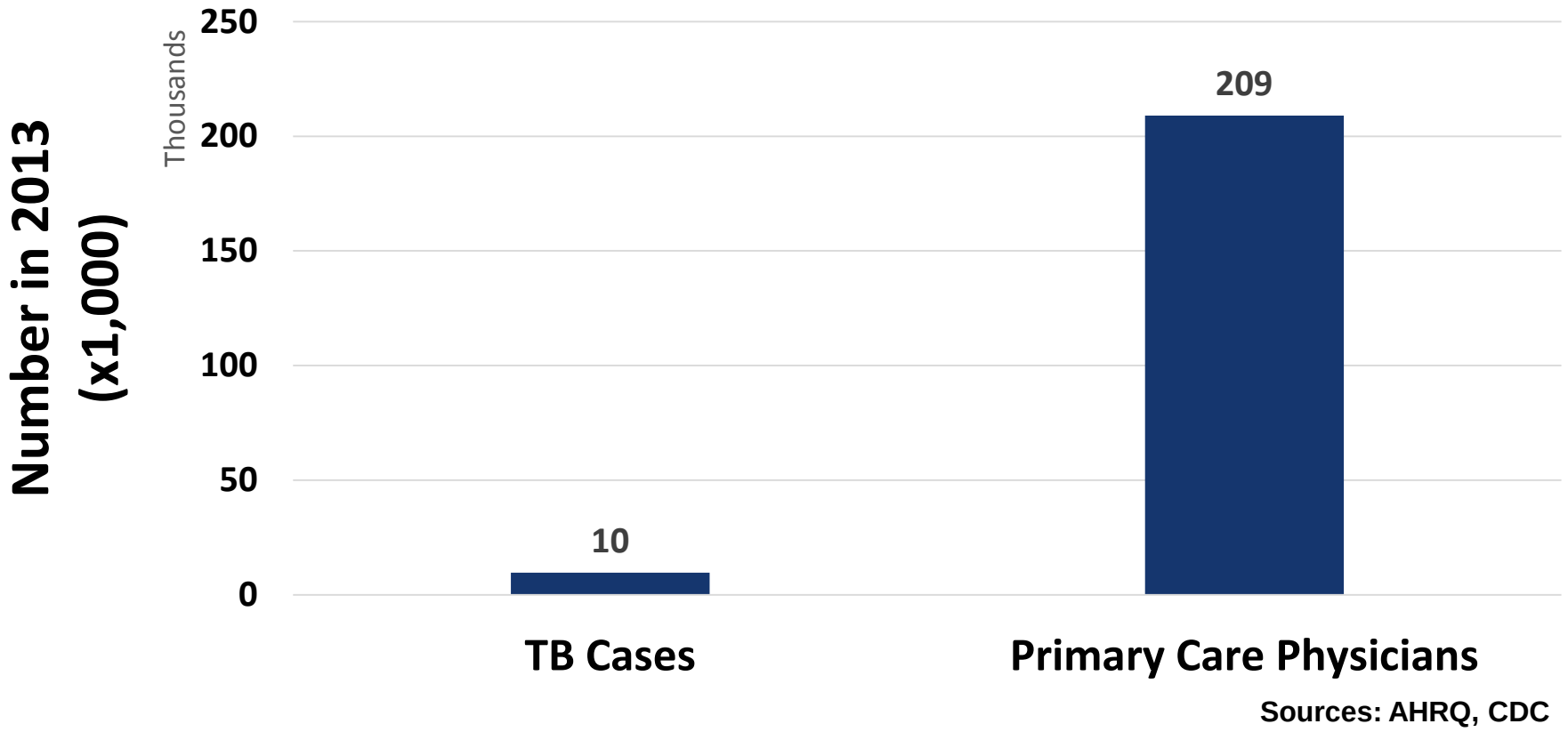
It's Not the Test, It's the System.

- Xpert (and MTD) are costly to labs but save the system money.
  - Implications for implementation when cost is borne by the public health lab system but savings accrue to hospitals?
- Molecular testing of smear-positives makes sense (to society).
  - Xpert vs. MTD: will matter to some labs, not to others (ex.: number of cartridges used, existing equipment)
- What needs to be done to derive maximum impact and cost-effectiveness from molecular TB testing?
  - Not "make a more sensitive test"
  - Rather "make a more sensible system"



Rep. Kevin Brady (R-Texas, visual.ly

Why Public Health Labs?



The average PCP may see 1 case of TB every 20 years.

Interpretation is Often Challenging

Table Clinical characteristics of three selected patients diagnosed as having pulmonary tuberculosis by Xpert® MTB/RIF

Characteristics	Patient 1	Patient 2	Patient 3
Age, years	28	66	61
Sex	Female	Male	Female
Race	Asian	African-American	African-American
TB risk factors	Born in high-burden TB area, chronic glucocorticoid use	Incarcerated, pulmonary TB contact	Recent history of pulmonary TB, chronic alcohol use, chronic smoker, malnutrition
HIV testing	Negative	Negative	Negative
TST	0 mm	15 mm	Not performed
IGRA	Indeterminate	Not performed	Not performed
AFB smear microscopy	2+	1+	Negative
Xpert result	MTC-positive, RMP-resistant	MTC-positive, RMP-resistant	MTC-positive, RMP-susceptible
Xpert cartridge used	G3	G3	G4
Mycobacterial culture/susceptibilities	Pre-XDR-TB	Drug-susceptible TB	No growth

TB = tuberculosis; HIV = human immunodeficiency virus; TST = tuberculin skin test; IGRA = interferon-gamma release assay; AFB = acid-fast bacilli; MTC = *Mycobacterium tuberculosis* complex; RMP = rifampin; XDR-TB = extensively drug-resistant TB.

Lippincott et al, Int J Tuberc Lung Dis 2015; 19:273-275

In settings where the pre-test probability of TB (and MDR-TB) is low, the probability that a positive result is false-positive (for TB or rifampin resistance) may be high.

In Other Words…

- Public health labs may be the best places to perform new tests for TB.
  - Other labs may not have the volume to make such tests cost-effective
  - Nor the expertise to advise as to appropriate interpretation
- But the benefit of these tests is largely an economic benefit to hospitals (and society), not a public health one.
  - Clinical cases are often complex.
  - Early discharge may be beneficial to hospitals and patients.
  - Rarely is a novel test going to diagnose a case that would otherwise be missed, thereby averting transmission.
- *Can we design a system in which these realities are aligned?*

Making a Smarter System: One Example

OPEN ACCESS Freely available online

PLOS ONE

Rapid Molecular Testing for TB to Guide Respiratory Isolation in the U.S.: A Cost-Benefit Analysis

Alexander J. Millman[3,5], David W. Dowdy[6], Cecily R. Miller[4], Robert Brownell[3], John Z. Metcalfe[1,2,3], Adithya Cattamanchi[1,2,3], J. Lucian Davis[1,2,3]*

MAJOR ARTICLE

Xpert MTB/RIF Assay Shortens Airborne Isolation for Hospitalized Patients With Presumptive Tuberculosis in the United States

Christopher K. Lippincott,[1] Melissa B. Miller,[2] Elena B. Popowitch,[3] Colleen F. Hanrahan,[4] and Annelies Van Rie[4]

[1]Institute for Global Health and Infectious Diseases and [2]Department of Pathology and Laboratory Medicine, University of North Carolina at Chapel Hill; [3]Clinical Microbiology/Immunology Laboratories, University of North Carolina Health Care, Chapel Hill; and [4]Department of Epidemiology, University of North Carolina at Chapel Hill

Xpert for Triage of Airborne Isolation

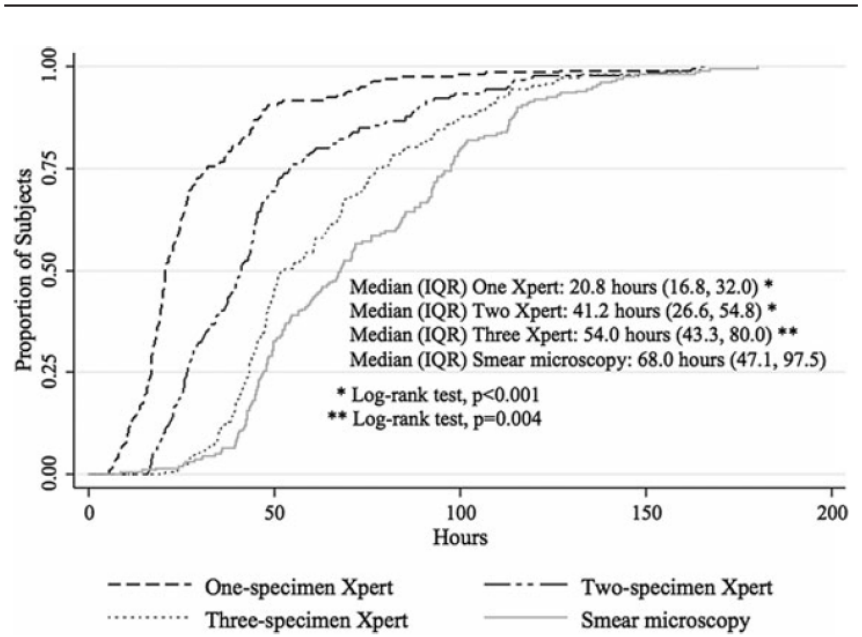


Figure 3. Kaplan-Meier curve comparing airborne infection isolation duration for the Xpert MTB/RIF assay strategies on 1 specimen (n = 201), 2 specimens (n = 180), and 3 specimens (n = 148) to the smear microscopy–based strategy (n = 201). Abbreviation: IQR, interquartile range.

UNC: Xpert MTB/RIF shortens time to discontinuation of airborne isolation by 48 hours.

- 27 hours if 2 Xpert tests are performed.

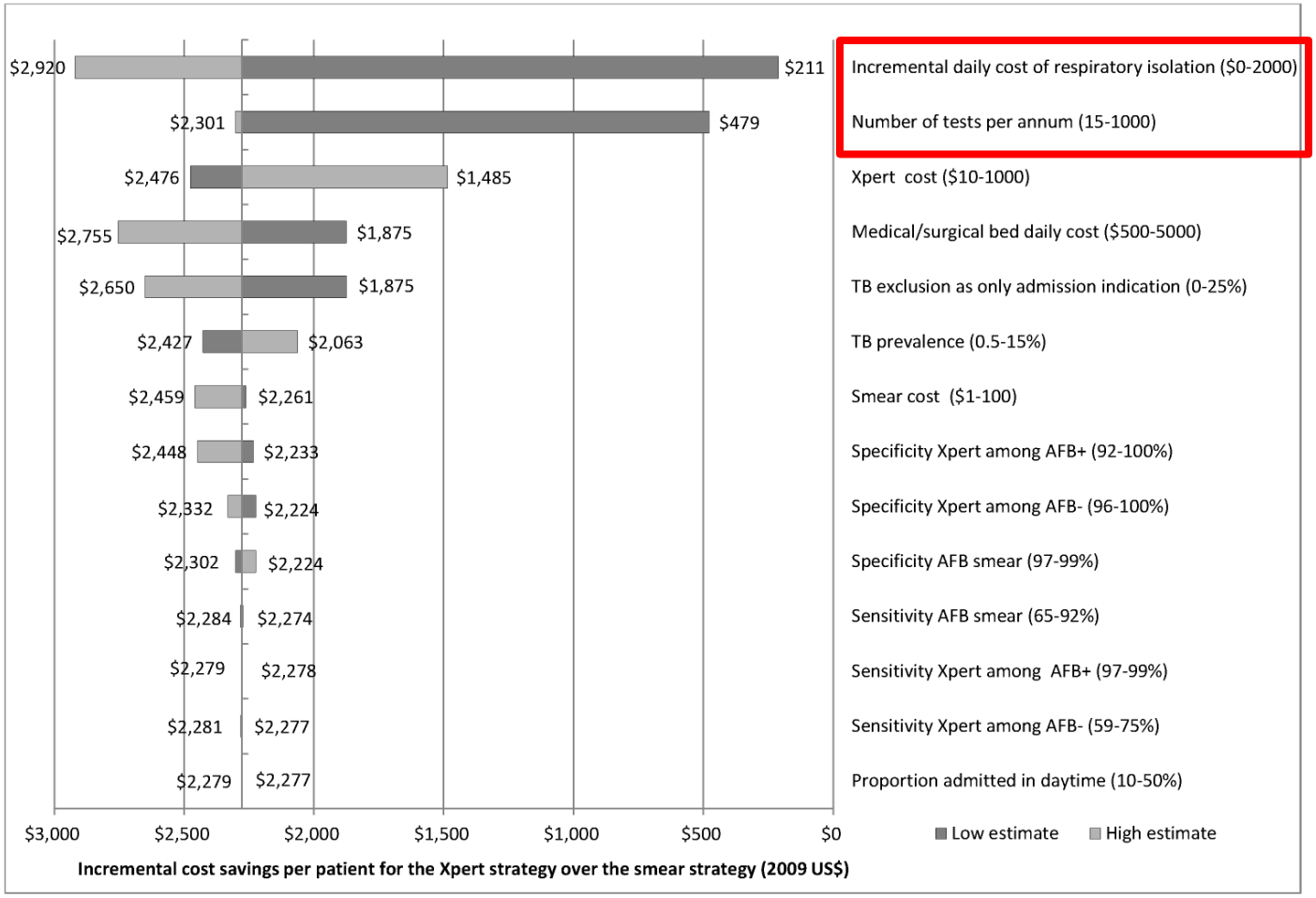
Outcomes Per Patient

Outcome	Smear Strategy	Xpert Strategy	Difference
Length of Stay*			
Isolation room	2.7	1.4	1.3
Standard room	3.2	4.4	−1.2
Total	5.9	5.8	0.1
Costs†			
Isolation room	$10,483	$5,305	$5,178
Standard room	$7,285	$9,980	−$2,695
Diagnostic testing	$15	$218	−$203
Total	$17,783	$15,503	$2,278

SFGH: Xpert can avert 1 isolation day per patient.

- Cost of Xpert testing ($218/test) is much less than the cost of isolation.
- Therefore Xpert is cost-saving to the system (but not to the lab) in most cases.

Drivers of Cost Savings



Whether the strategy makes sense depends on the incremental cost of isolation and being able to perform a sufficient volume of testing.

TBTC 34

- Multicenter study of 633 patients in airborne infection isolation for concern of TB.
- Xpert strategies were more accurate than 3 smears.

	AFB POSITIVE	1 XPERT POSITIVE	p value	2 XPERTS, AT LEAST ONE POSITIVE	p value
2 AFB SMEARS					
ALL n = 91	62/91 (68.1%)*	75/88 (85.2%)[a]	p=0.001	82/90 (90.1%)[b]	p<0.001
AFB POSITIVE n=62		59/61 (96.7%)[b]		62/62 (100%)	
AFB NEGATIVE n=29		16/27 (59.3%)[c]		20/28 (71.4%)[b]	
3 AFB SMEARS					
ALL n = 53	32/53 (60.4%)**	41/50 (82.0%)[a]	p=0.006	46/52 (88.5%)[b]	p<0.001
AFB POSITIVE n=32		30/31 (96.8%)[b]		32/32 (100%)	
AFB NEGATIVE n=21		11/19 (57.9%)[c]		14/20 (70.0%)[b]	

p value for comparison of AFB smear vs. Xpert, * AFB+ 61/88 (69.3%) for 1 Xpert comparison and 62/90 (68.9%) for 2 Xperts comparison, ** AFB+ 31/50 (62.0%) for 1 Xpert comparison and 32/52 (61.5%) for 2 Xperts comparison

Luetkemeyer et al, Abstract 824, CROI 2015

Updated FDA/CDC Guidance

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 64 / No. 7
February 27, 2015

The Food and Drug Administration (FDA) has cleared the Xpert MTB/RIF Assay (Cepheid; Sunnyvale, California) with an expanded intended use that includes testing of either one or two sputum specimens as an alternative to examination of serial acid-fast stained sputum smears to aid in the decision of whether continued airborne infection isolation (AII) is warranted for patients with suspected pulmonary tuberculosis (*1*). This change reflects the outcome of a recent multicenter international study demonstrating that negative Xpert MTB/RIF Assay results from either one or two sputum specimens are highly predictive of the results of two or three negative acid-fast sputum smears.*

Xpert for Discontinuing Airborne Infection Isolation

- Xpert can be cost-saving when used in specific circumstances.
  - If isolation costs outweigh lab costs of performing the test, then Xpert will almost certainly be cost-saving.

- Cost-effectiveness depends on tradeoffs of lab testing vs. isolation cost, not sensitivity of Xpert or prevalence of TB.
  - Xpert to rule out infectious TB, not rule it in
  - May not be a favorable ratio for hospitals with low volume of TB rule-out admissions and low incremental cost of isolation

Looking Ahead: Impact of Emerging Tests

- **Next-generation/whole-genome sequencing**
  - Can we quantify the impact of information gained for purposes of improving public health activities (e.g., contact investigation)?
- **Rapid molecular DST**
  - What is the benefit of getting the right drug profile at the time of treatment initiation?
- **More sensitive molecular tests for TB**
  - Will these assays make a difference in systems where culture is already routinely performed?
- **Making a case for TB elimination**
  - What are the costs and benefits of doing so?

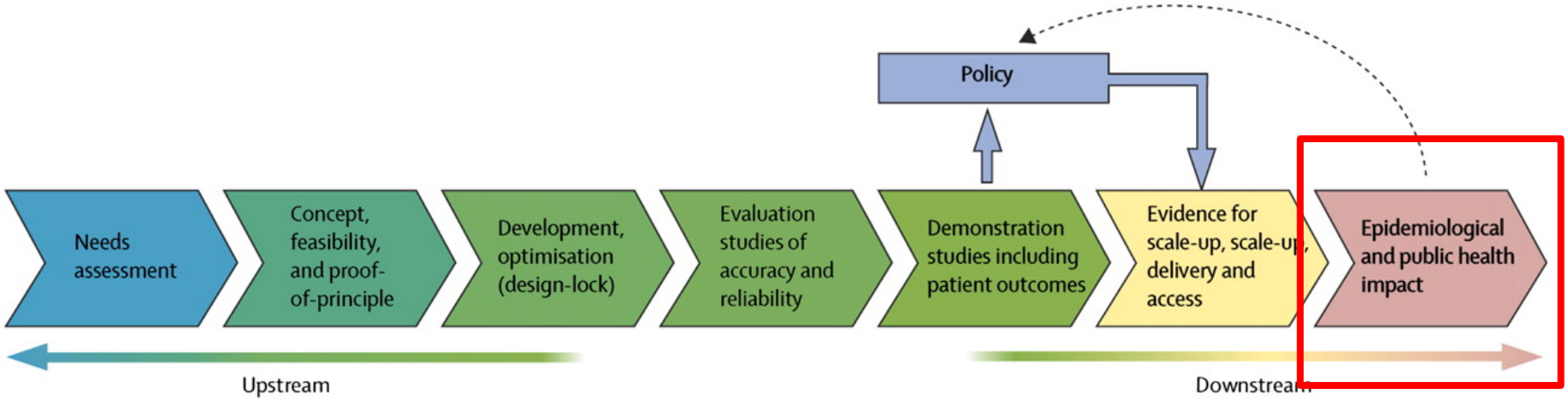
Conclusions

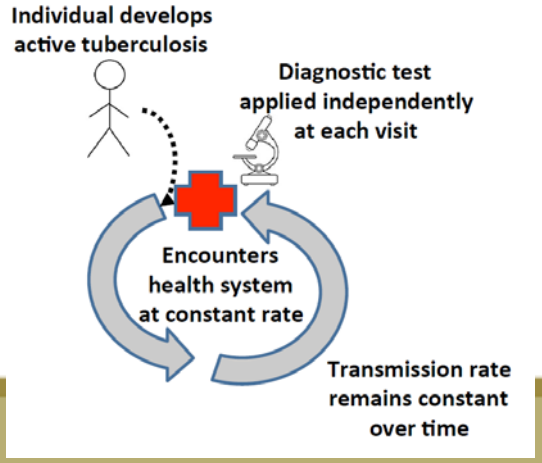
- Xpert MTB/RIF and other molecular tests are likely to be used in the USA for **rule-out** of infectious TB, rather to rule-in TB.

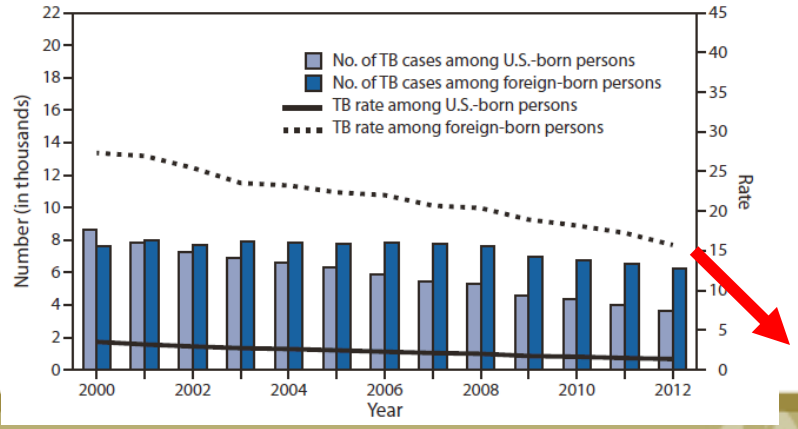
- Impact and cost-effectiveness therefore depend on **tradeoffs between lab testing and healthcare costs**.
  - Challenging to weigh societal value when public health system, labs, and hospitals are financed in different ways.

- If we are to optimize the impact of novel diagnostic strategies for TB, public health labs must work with other stakeholders to **design a smarter system**.

The ongoing challenge: think of tests in terms of impact, not just accuracy!







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  - Maunank Shah
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  - Luke Davis (now at Yale)
  - Adithya Cattamanchi
  - Alex Millman (now with EIS)

- APHL
  - Will Murtaugh and the conference organizers