



JOHNS HOPKINS
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Introduction to Cost-Effectiveness Analysis David Dowdy, MD PhD
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Protecting Health, Saving Lives—*Millions at a Time*

Presentation Outline

- Introduction to cost-effectiveness analysis (CEA)
- In the context of diagnostic tests for TB



“First we’re going to run some tests to help pay off the machine.”



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

Anna Vassall^{1,2}, Sanne van Kampen¹, Hojoon Sohn³, Joy S. Michael⁴, K. R. John⁵, Saskia den Boon⁶, J. Lucian Davis⁷, Andrew Whitelaw^{8,9}, Mark P. Nicol^{8,9}, Maria Tarcela Gler¹⁰, Anar Khaliqov¹¹, Carlos Zamudio¹², Mark D. Perkins¹³, Catharina C. Boehme¹³, Frank Cobelens^{1*}

Abstract

Background: Xpert MTB/RIF (Xpert) is a promising new rapid diagnostic technology for tuberculosis (TB) that has characteristics that suggest large-scale roll-out. However, because the test is expensive, there are concerns among TB program managers and policy makers regarding its affordability for low- and middle-income settings.

Methods and Findings: We estimate the impact of the introduction of Xpert on the costs and cost-effectiveness of TB care using decision analytic modelling, comparing the introduction of Xpert to a base case of smear microscopy and clinical diagnosis in India, South Africa, and Uganda. The introduction of Xpert increases TB case finding in all three settings; from 72%–85% to 95%–99% of the cohort of individuals with suspected TB, compared to the base case. Diagnostic costs (including the costs of testing all individuals with suspected TB) also increase: from US\$28–US\$49 to US\$133–US\$146 and US\$137–US\$151 per TB case detected when Xpert is used “in addition to” and “as a replacement of” smear microscopy, respectively. The incremental cost effectiveness ratios (ICERs) for using Xpert “in addition to” smear microscopy, compared to the base case, range from US\$41–\$110 per disability adjusted life year (DALY) averted. Likewise the ICERs for using Xpert “as a replacement of” smear microscopy range from US\$52–\$138 per DALY averted. These ICERs are below the World Health Organization (WHO) willingness to pay threshold.

Conclusions: Our results suggest that Xpert is a cost-effective method of TB diagnosis, compared to a base case of smear microscopy and clinical diagnosis of smear-negative TB in low- and middle-income settings where, with its ability to substantially increase case finding, it has important potential for improving TB diagnosis and control. The extent of cost-effectiveness gain to TB programmes from deploying Xpert is primarily dependent on current TB diagnostic practices. Further work is required during scale-up to validate these findings.



How Do We Determine if Xpert MTB/RIF is Cost-Effective?

- Consider two scenarios:
 - TB diagnosis without Xpert
 - TB diagnosis with Xpert
- Add up **costs** for each scenario
 - Costs of the machine & cartridges, but also...
 - Costs of treatment (incl. false-positives) & additional testing
 - Costs of overhead, maintenance, staffing, sputum cups, etc.
 - Costs to patients?
- Add up **effectiveness** for each scenario
 - How should we measure effectiveness?
 - More useful outcomes are harder to measure
 - Diagnoses made -> treatments completed -> lives saved -> DALYs/QALYs
- Measure **incremental cost-effectiveness**
 - Is switching to Xpert worth the cost?



A Word on Costs

- Economists measure costs as opportunity (economic) costs.
 - Lost benefit of a resource if used for best alternative use
 - Compared with financial cost = what is actually paid
 - Often not the actual price paid (financial cost)
 - Donated goods
 - Volunteer time
 - Distorted prices (price you pay isn't what something is worth)
- Why does this matter?
 - Economists like to believe they have society's interests at heart.
 - Not interested in how much Xpert will cost Cepheid, or even a TB program
 - Question is: "If Xpert is used, how much would society lose, in terms of other things it could do with its resources instead?"
 - Money is a proxy for resource availability, not the object of the analysis.
 - » "\$1,000" does not mean \$1,000, but rather the resources that \$1,000 could buy.
 - » *Is it worth it to use a given quantity of resources to obtain a given amount of health?*



Opportunity Cost

- **Scenario**

- You pay \$15, non-refundable, to see a movie (2 hrs).
- If you weren't watching a movie, you would be walking outside in the park, right next to the theater.
- The park costs \$1, but you would be willing to pay up to \$10 for a two-hour visit.
- Immediately upon seeing the movie introduction, you realize with 100% certainty that you are going to hate the movie. If you had known this before buying your ticket, you wouldn't even have paid 1 cent.
- The 3rd alternative is to sit at home – no cost, no fun.

- **From an economics perspective, what should you do?**



Opportunity Cost

- Scenario

- You pay \$15, non-refundable, to see a movie (2 hrs).
- If you weren't watching a movie, you would be walking outside in the park, right next to the theater.
- The park costs \$1, but you would be willing to pay up to \$10 for a two-hour visit. *Every person decides how valuable their time is!*
- Immediately upon seeing the movie introduction, you realize with 100% certainty that you are going to hate the movie. If you had known this before buying your ticket, you wouldn't even have paid 1c.
- The **best** alternative would have been to go directly to the park.

- What is the societal cost...

- Stay and watch the movie: $\$15 + \10
- Leave and go to the park: $\$15 + \1



Opportunity Cost

- Scenario

- You pay \$15, non-refundable, to use Xpert MTB/RIF for TB diagnosis.
- If you weren't using Xpert, you would be using smear.
- Smear costs \$1 in supplies, but also requires labor that could perform \$10 worth of lab work otherwise, even if you don't pay for that.

- What is the societal cost...

- Xpert: \$15
- Smear: \$10 + \$1
- Incremental cost of Xpert is \$4.



Costs: Other Considerations

- **Inflation and discounting**

- Inflation: \$20 will buy less next year than this year.
 - Important to specify the year of currency for any costs
- Assume you know that \$20 this year will be worth the same as \$21 next year (5% inflation rate).
 - Which would you rather have: \$20 in your hand, or the promise of \$21 next year?
 - How much in next year's money is \$20 today worth to you?

- **Capital vs. recurrent costs**

- Must pay “up front” for some items (equipment, buildings)
- These items will last a certain amount of time
- Paying \$100,000 for a machine today that will last 5 years is not the same as paying \$20,000 every year
 - Because of inflation and discounting



Costs: Other Considerations

- **Fixed vs. variable costs**

- Cost per Xpert test:
 - **Lab Space (Xpert machine?)** – costs the same amount no matter how many tests are run
 - **Xpert cartridge** – cost depends entirely on how many tests are run
 - **Staff training** – cost depends partially on how many tests are run
- In general, must calculate unit costs:
(variable cost) + (fixed cost/number of units)

- **Perspective**

- Costs that matter to society might not matter to the healthcare system
- Labs may be more worried about some costs than clinics
- *The perspective of the person making the scale-up decision is generally different from the ideal perspective – how to manage this?*



Costs: Other Considerations

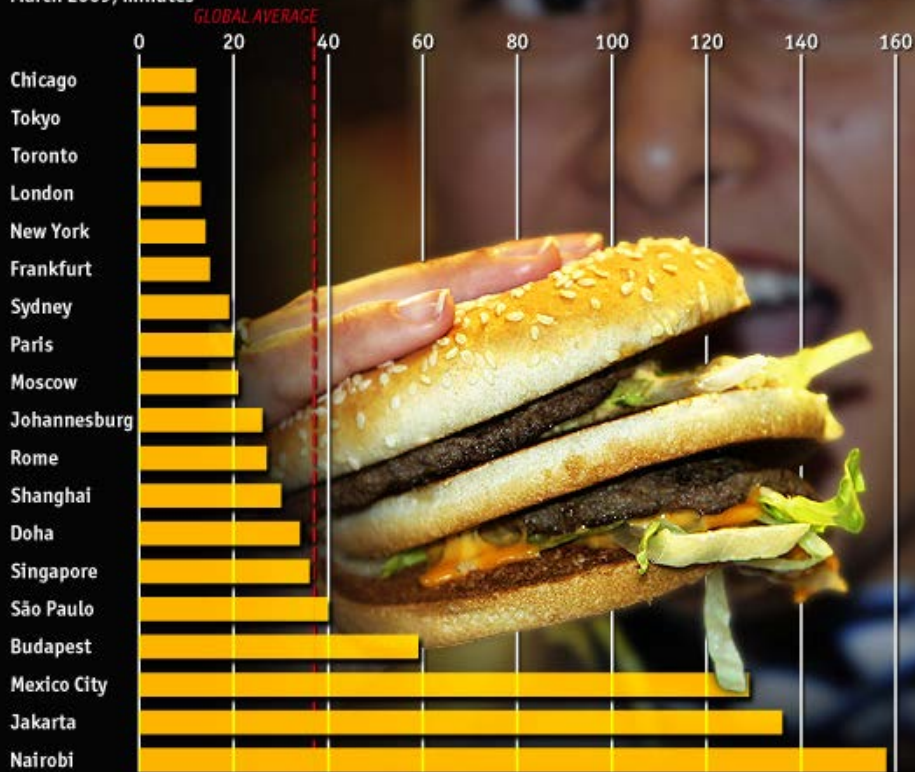
- **Currency conversion**

- 1 US\$ might officially exchange for 400 Kwacha in Malawi
- But 1 US\$ will buy less in the US than MK400 will buy in Malawi
 - *Labor in the US is much more expensive (some Malawians make K20,000/mo for full-time work), so all goods created with that labor are more expensive too.*
- Some costs depend on local “purchasing power”
 - *Malawian staff are paid in Kwa, not US\$*
 - *If I take 1 US\$ and exchange it for Kwa, I get more labor in Malawi than in the USA*
- Other costs depend on exchange rate
 - *Xpert machines are bought on the international market, in US\$*
 - *If I take \$100,000 and exchange it for Kwa, I get the same number of Xpert machines (and have to pay the money changers)*
- Important to specify the currency used, and how it is converted
 - *“International \$” = based on purchasing power parity*
 - *“US\$” = based on exchange rates*



Working time needed to buy a Big Mac*

March 2009, minutes



*For worker earning average net wage weighted across 14 professions

Source: UBS

Big Mac index

Local currency under (-) / over (+) valuation against the dollar



*At market exchange rate on March 16th. Weighted average of member countries. Average of four cities.

Source: McDonald's; The Economist

Costs: TB Diagnosis Example

Table 2. Cost of diagnostic tests at the study sites (2010 US\$).

Diagnostic Test	Type of Laboratory	Costs per Test (2010 US\$)		
		India	South Africa	Uganda
AFB Smear (one smear)	Peripheral/hospital	1.13	1.58	1.63
Xpert (current pricing) US\$19.4 including transport	Peripheral/hospital	22.63	25.90	27.55
Xpert (volume>1.5 million/y) US\$15.5 including transport	Peripheral/hospital	18.73	22.00	23.61
Xpert (volume>3.0 million/y) US\$11.7 including transport	Peripheral/hospital	14.93	18.20	19.85
Culture (LJ)	Reference	13.56	—	15.45
Culture (MGIT)	Reference	—	15.24	18.95
Culture + DST (LJ)	Reference	22.33	—	23.98
Culture + DST (MGIT)	Reference	—	41.17	44.88
DST (MGIT + LPA)	Reference	—	33.01	38.82
DST (LPA), on sputum	Reference	—	20.23	21.84

Table 3. Cost of Xpert (current pricing) by input type (2010 US\$).

Input Type	Costs per Test (2010 US\$)		
	India	South Africa	Uganda
Overhead	0.18	0.88	0.40
Building space	0.02	0.08	0.12
Equipment	2.84	3.50	7.00
Staff	0.11	1.82	0.24
Reagents and chemicals	19.40	19.40	19.40
Consumables	0.07	0.22	0.38
Total	22.63	25.90	27.55

doi:10.1371/journal.pmed.1001120.t003



Cost: Summary

- To estimate the cost of Xpert (or another TB diagnostic) need unit costs for:
 - Staff
 - Lab Space
 - System/Cartridges
 - Patient Time (if a societal analysis)
 - etc.
- For each cost, must consider:
 - Opportunity (not financial) costs
 - Perspective (patient vs. health system vs. society)
 - Inflation & discounting, fixed vs. variable, currency conversion, etc.
- **Combine these costs to estimate the cost per test.**
 - Often as a function of key variables (e.g., volume)



From Cost to Effectiveness

- Options for effectiveness measures:
 - TB diagnoses made
 - What if I'm comparing GXP to MDR-TB/HIV-TB?
 - TB deaths averted
 - What if I'm comparing to prostate cancer?
 - Years of life gained
 - What if I'm comparing to depression?
 - Health utility
 - “Adjusted” years of life, where:
 - 1 = Life lived in perfect health
 - 0 = Death



Measuring Health Utility

- **Standard Gamble**

- “I will offer you a bet. If you win the bet, you live the rest of your life in perfect health, instead of your current health state. If you lose, you die instantly. Would you take this bet if your risk of dying was 1 in 100? 1 in 20? 1 in 10?”

- **Time-Tradeoff**

- “If you have 100 years left to live in your current health state and could trade those years for a smaller number of years in perfect health, would you trade them for 99 years? 95 yrs? 90 yrs?”

- **Visual Analogue Scale**

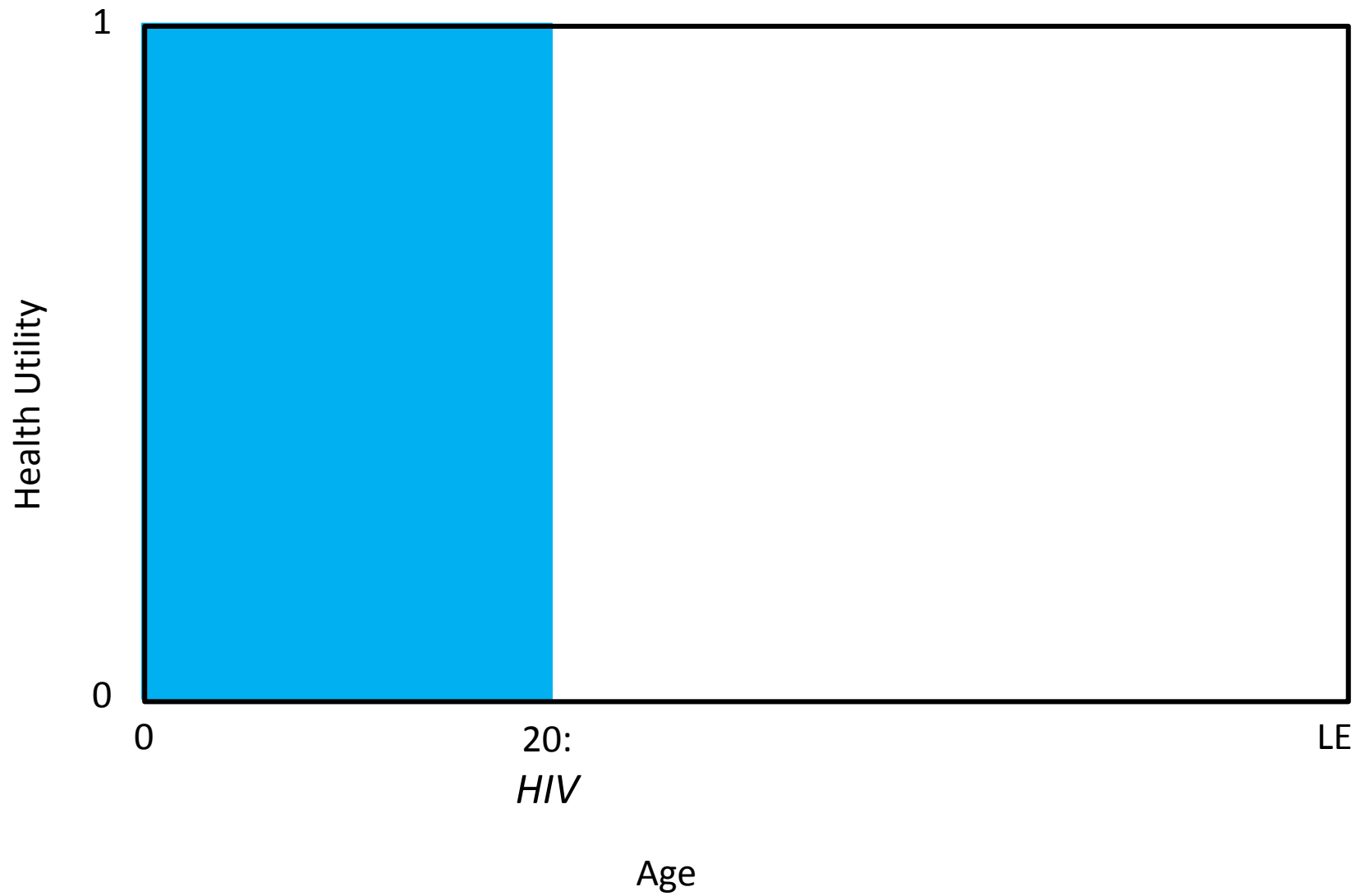
- “Using this ‘thermometer,’ rate your current quality of life from 0 to 100.”

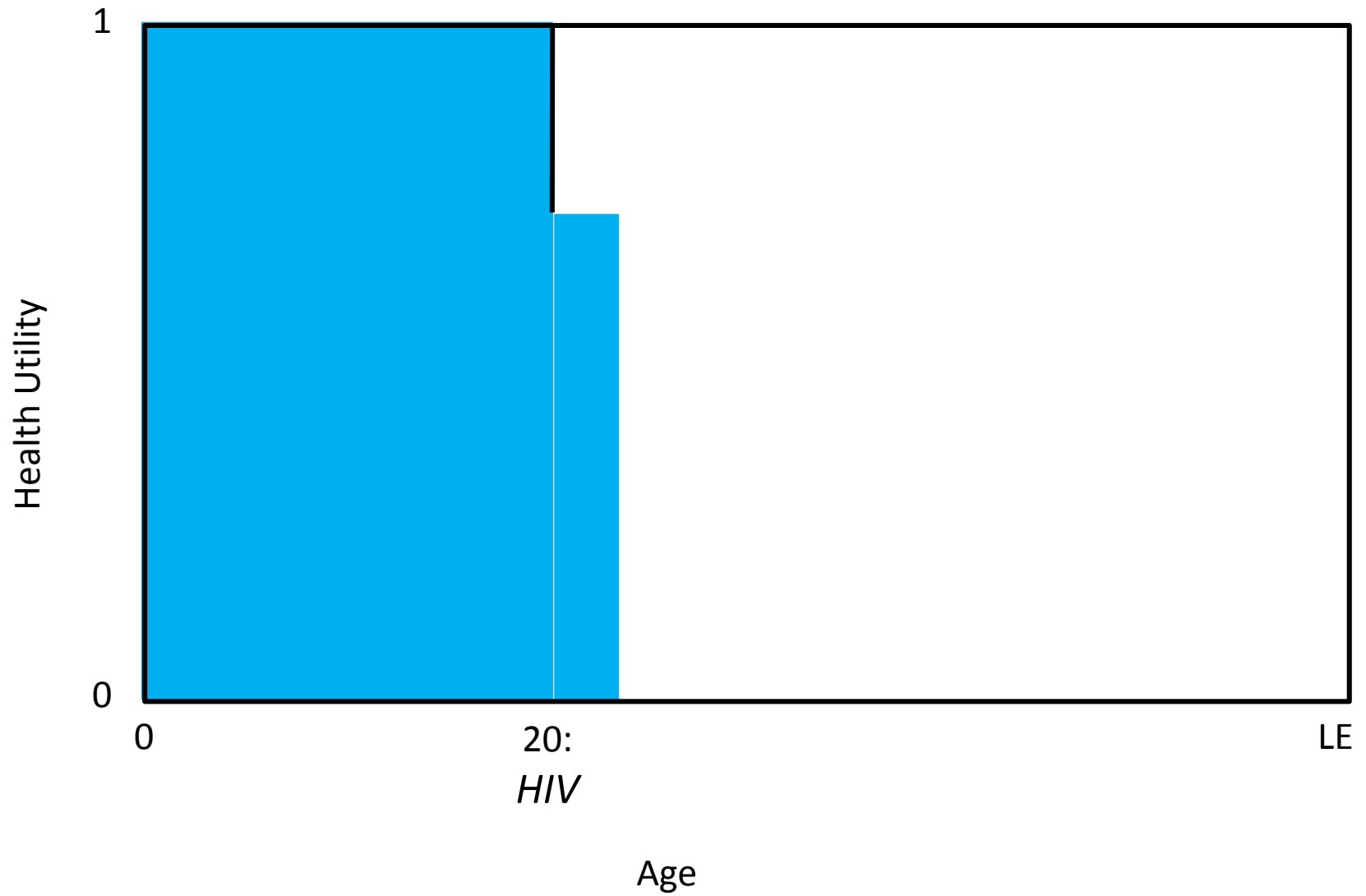


Utility Measures: DALYs & QALYs

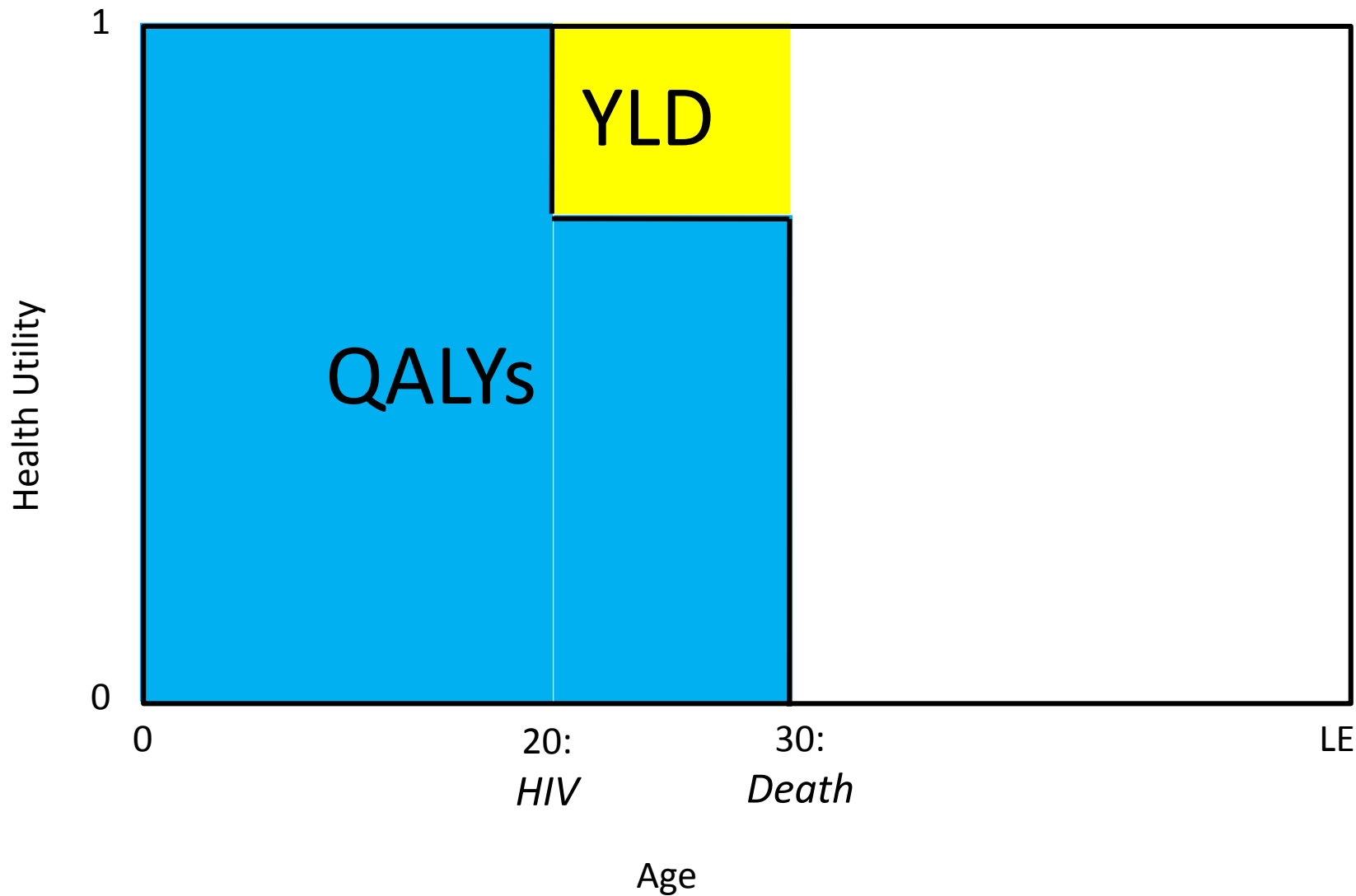
- **DALY = “Disability-Adjusted Life Year”**
 - “Disability weights” ($1 - \text{utility}$) assigned using standard scenarios
 - Do not change from one setting to another
 - Age & sex can be incorporated, also discounting, but nothing else
 - Standardized formula available
 - Calculate as years of life lost (YLL) + years of life with disability (YLD)
 - DALYs are bad = want to avert them
- **QALY = “Quality-Adjusted Life Year”**
 - More of a “pure” utility measure
 - Ask people in your cohort (or people like them) to answer traditional utility questions for each health state
 - Each year in that health state is weighted by this value
 - Takes into account all external factors that weigh into decisions

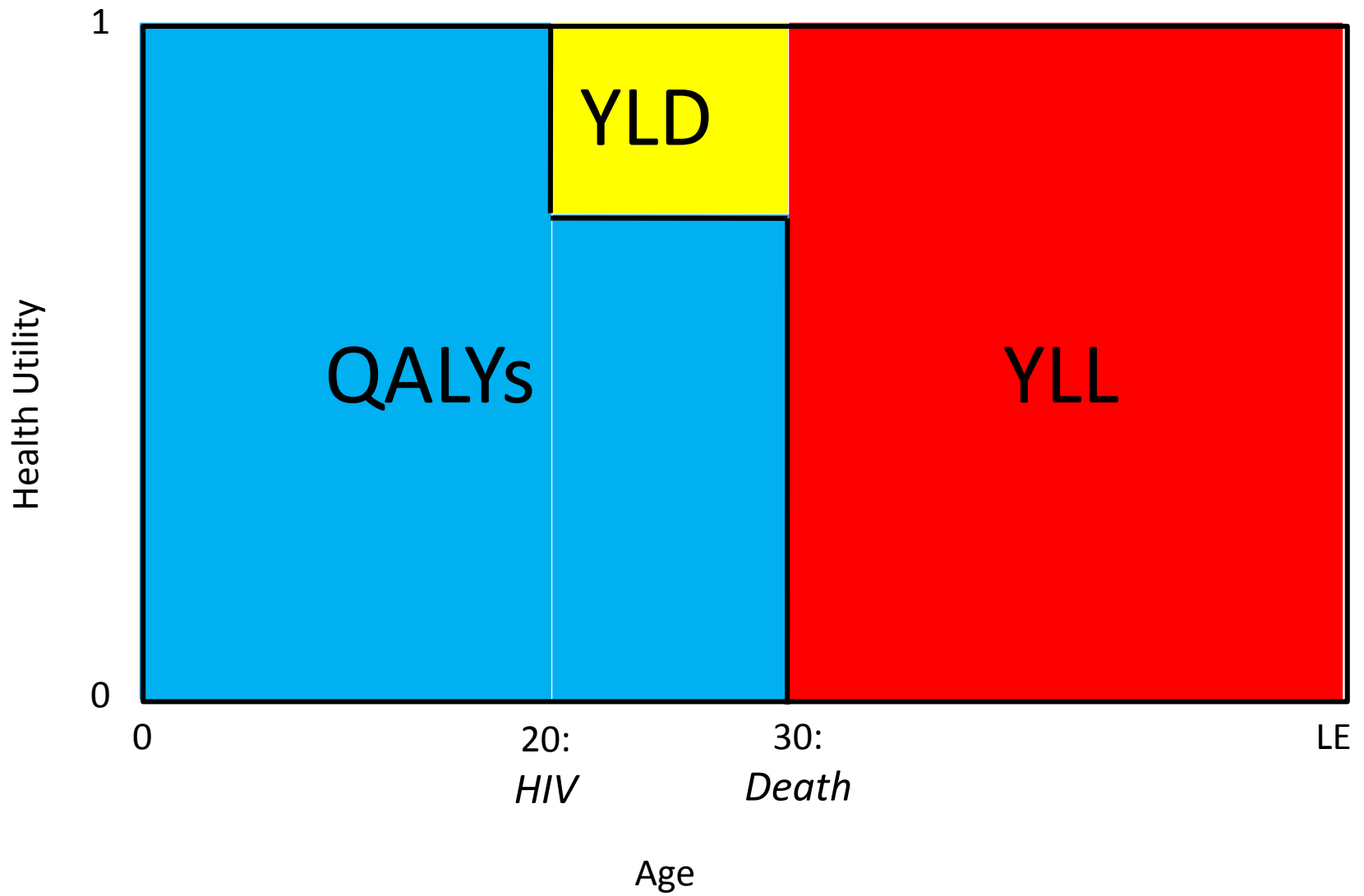


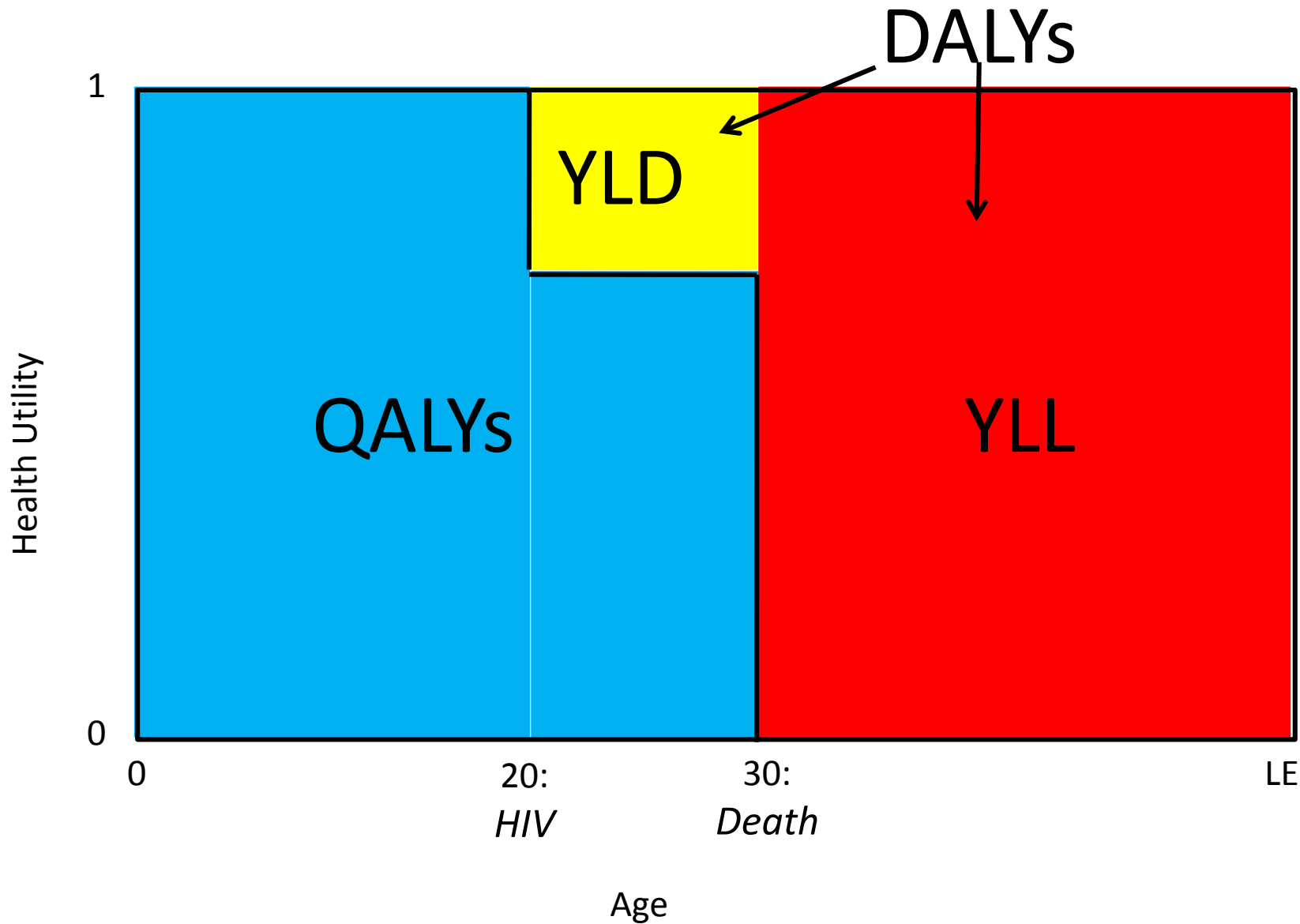












Caveats

- **Previous graphs were for illustration only: QALYs and DALYs are not interchangeable!**
- Utility measured using different techniques
 - Standardized scenarios (DALYs) vs. local preference surveys (QALYs)
- Age weighting and discounting incorporated into DALYs in standard fashion.
 - QALYs depend on responses (difficult to get kids to respond)
- DALYs meant to be globally transportable, QALYs usually setting-specific.
- *All this being said, (1 – DALY) and QALY measurements, if done well, are usually not dramatically different.*
 - Similar thresholds often used



Measuring Cost-Effectiveness: *Incremental Cost-Effectiveness Ratio (ICER)*

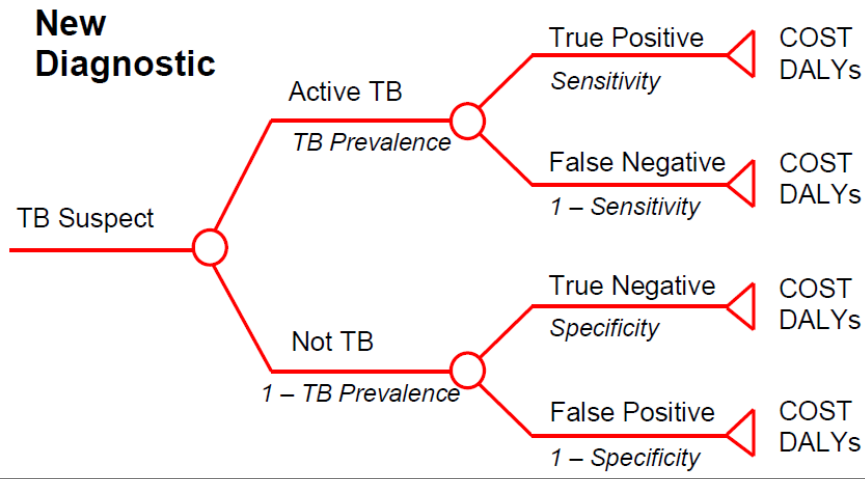
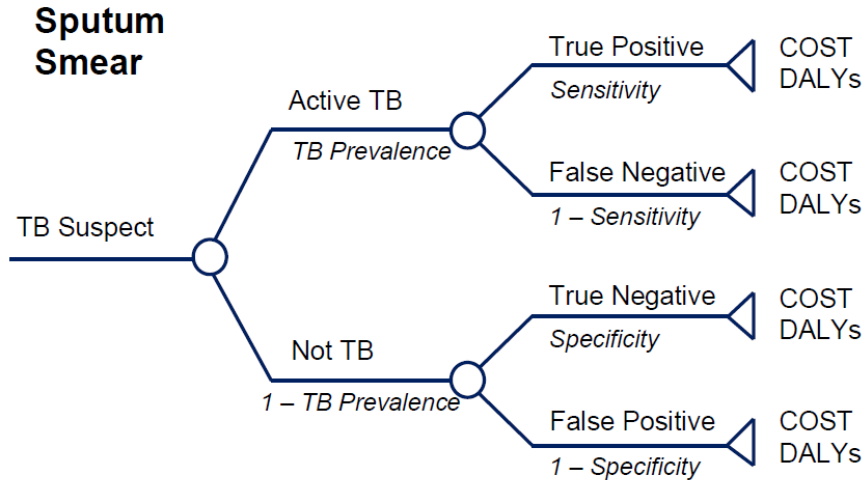
$$\frac{C_{\text{GXP}} - C_{\text{smear}}}{E_{\text{GXP}} - E_{\text{smear}}}$$

How much does it **COST** to
SWITCH from smear to Xpert?

How much **MORE EFFECTIVE** is
Xpert than smear?



CEA of TB Diagnostics: Prototype Model



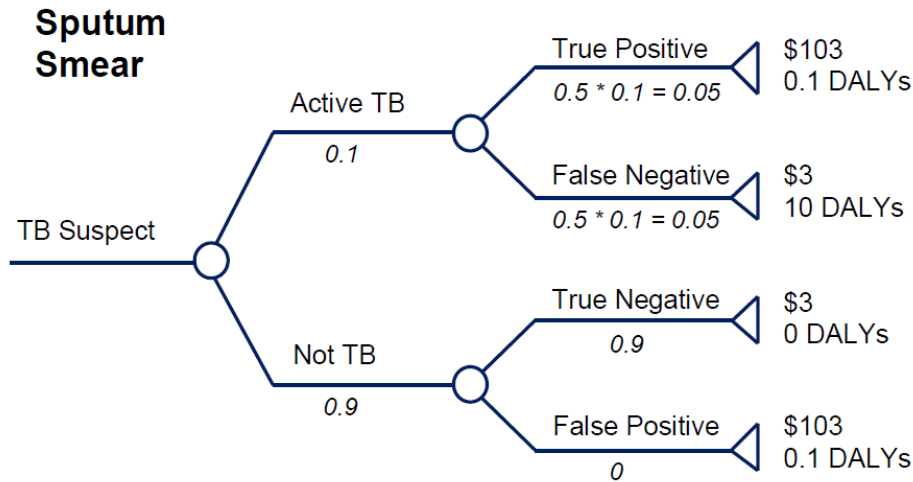
$$\text{Mean Cost} = \Sigma(\text{Cost} * \text{Probability})$$

$$\text{Mean Effectiveness} = \Sigma(\text{DALYs} * \text{Probability})$$

$$\text{Incremental Cost-Effectiveness Ratio (ICER)} = \frac{(\text{Cost of New Test} - \text{Cost of Smear})}{(\text{Effectiveness of New Test} - \text{Effectiveness of Smear})}$$



Add in Some Realistic Numbers



TB Prevalence: 0.1

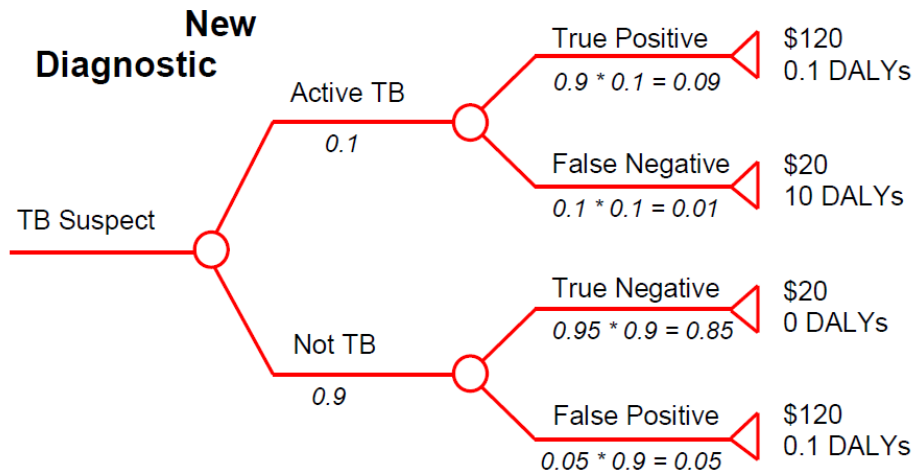
Smear Sensitivity: 0.5
Smear Specificity: 1.0

New Test Sensitivity: 0.9
New Test Specificity: 0.95

Cost of Smear: \$3

Cost of New Test: \$20

Cost of TB Treatment: \$100

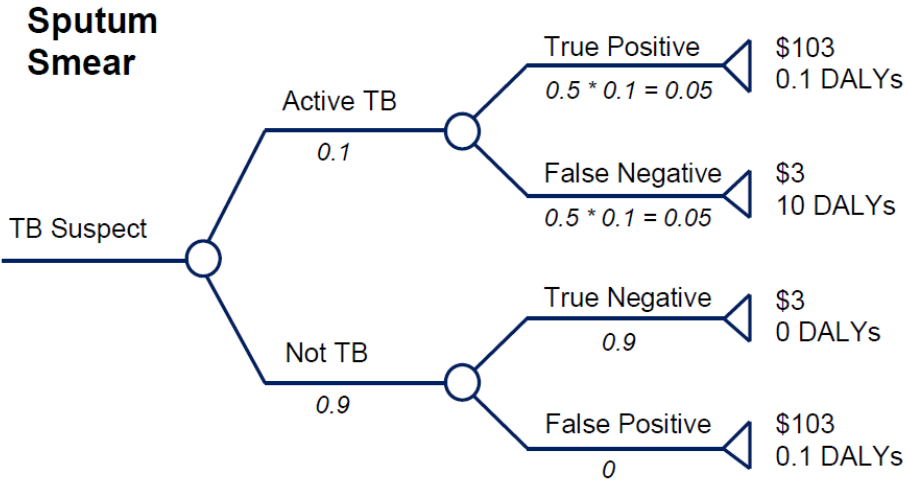


DALYs for Untreated TB: 10
(20 years * 50% risk of death)

DALYs for TB Treatment: 0.1
(6 months * 20% QOL loss)



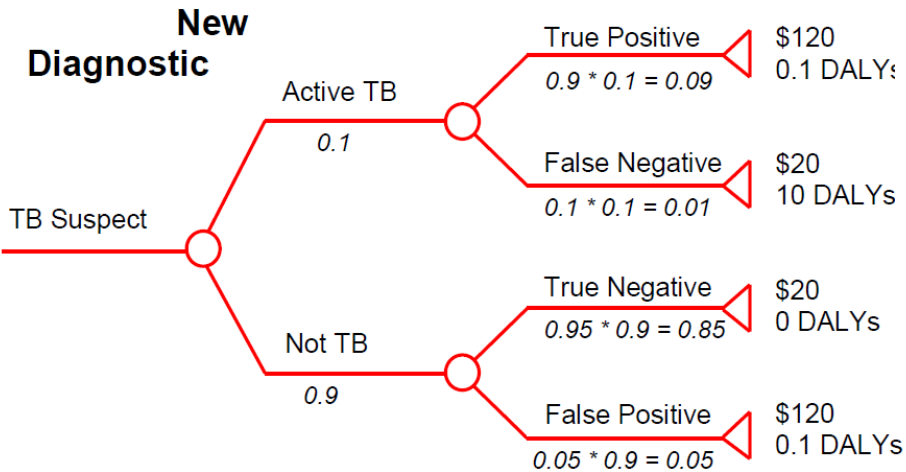
Add in Some Realistic Numbers



Mean Cost = $\Sigma(\text{Cost} * \text{Probability})$
Mean Effectiveness = $\Sigma(\text{DALYs} * \text{Probability})$

Incremental Cost-Effectiveness Ratio (ICER) =

$$\frac{(\text{Cost of New Test} - \text{Cost of Smear})}{(\text{Effectiveness of New Test} - \text{Effectiveness of Smear})}$$



Mean Cost:
 $(\$103 * 0.05) + (\$3 * 0.05) + (\$3 * 0.9) + (\$103 * 0) = \$8$ (smear)
 $(\$120 * 0.09) + (\$20 * 0.01) + (\$20 * 0.85) + (\$120 * 0.05) = \$34$ (new test)

Mean Effectiveness = $\Sigma(\text{DALYs} * \text{Probability})$
 $(0.1 * 0.05) + (10 * 0.05) + (0 * 0.9) + (0.1 * 0) = 0.505$ (smear)
 $(0.1 * 0.09) + (10 * 0.01) + (0 * 0.85) + (0.1 * 0.05) = 0.114$ (new test)

Incremental Cost-Effectiveness Ratio (ICER) =
 $(\$34 - \$8) / (0.114 - 0.505) = \$66$ per DALY averted



What is “Cost-Effective”?

- Ideally, society’s value for a DALY averted/QALY gained
 - If you can deliver a QALY for fewer resources, then it’s worth doing.
- But this may differ according to whose DALYs they are...
 - Should a DALY in the USA be worth more than one in Uganda?
- ...and available resources
 - Often have many “cost-effective” options from which to choose!
- WHO standard for “highly cost-effective”: <GDP per capita
 - Malawi: \$900; USA: \$44,000
 - \$50,000/QALY as one benchmark in the USA, £20-30,000 often used in the UK.
 - *Often cited as the “dialysis threshold,” but no supporting data, is staying constant*



CEA: Summary

- **Costs**
 - Difference between prices and opportunity costs
- **Effectiveness**
 - Utility is more useful, but harder to measure
 - DALYs and QALYs as common metrics
- **Cost-Effectiveness Analysis**
 - Importance of incremental analysis
 - Simple decision analysis gives us “ballpark” ranges
 - Thresholds commonly used but have no supporting data



Challenges in Economic Evaluation of Diagnostic Tests

OPEN ACCESS Freely available online

PLOS MEDICINE

Essay

Is Scale-Up Worth It? Challenges in Economic Analysis of Diagnostic Tests for Tuberculosis

David W. Dowdy^{1*}, Adithya Cattamanchi², Karen R. Steingart³, Madhukar Pai⁴

- 3 CHALLENGES:
- **Representing the diagnostic process**
- **Converting diagnosis to health**
- **Incorporating transmission effects**

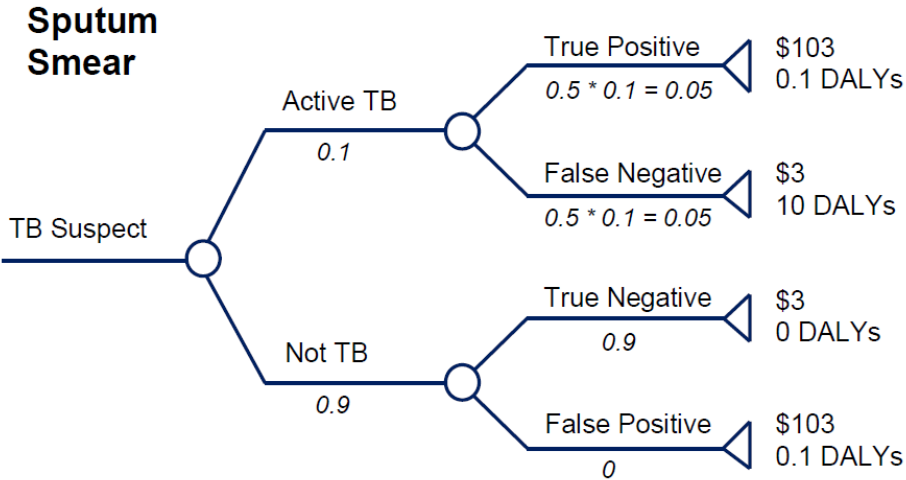


Challenge #1: Representing the Diagnostic Process

- Most TB models assume that a patient receives a diagnosis and is treated/suffers outcomes accordingly.
- In reality, many steps happen in between.
 - **Diagnostic delay:** time of diagnosis as important as correct diagnosis
 - **Loss to follow-up:** diagnostic results not acted upon
 - **Repeat diagnosis:** false-negatives may return to clinic
 - **Other conditions:** inappropriate TB diagnoses may increase morbidity from other diseases
- Failure to incorporate these steps likely results in overestimation of diagnostics' cost-effectiveness.



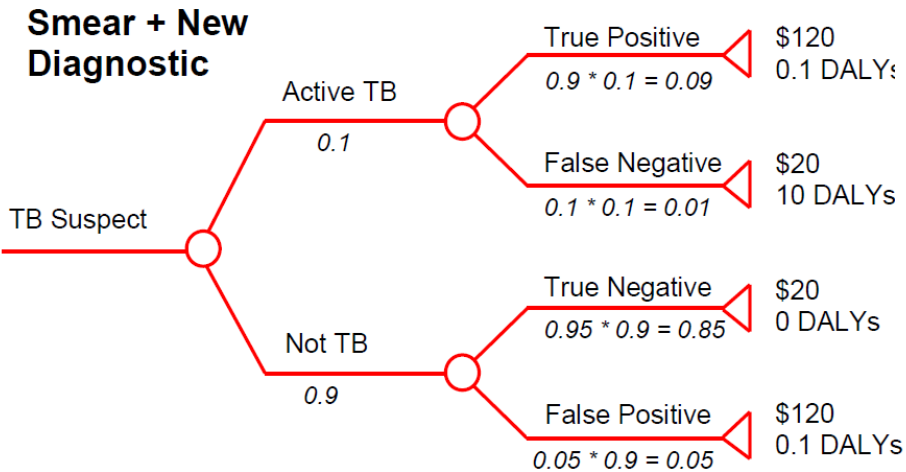
Take This Good Test...



Mean Cost = $\Sigma(\text{Cost} * \text{Probability})$
Mean Effectiveness = $\Sigma(\text{DALYs} * \text{Probability})$

Incremental Cost-Effectiveness Ratio (ICER) =

$$\frac{(\text{Cost of New Test} - \text{Cost of Smear})}{(\text{Effectiveness of New Test} - \text{Effectiveness of Smear})}$$



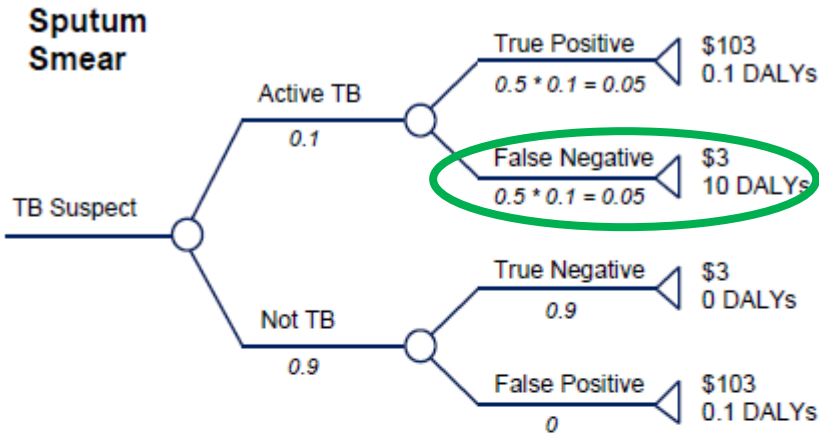
Mean Cost:
 $(\$103 * 0.05) + (\$3 * 0.05) + (\$3 * 0.9) + (\$103 * 0) = \$8$ (smear)
 $(\$120 * 0.09) + (\$20 * 0.01) + (\$20 * 0.85) + (\$120 * 0.05) = \$34$ (new test)

Mean Effectiveness = $\Sigma(\text{DALYs} * \text{Probability})$
 $(0.1 * 0.05) + (10 * 0.05) + (0 * 0.9) + (0.1 * 0) = 0.505$ (smear)
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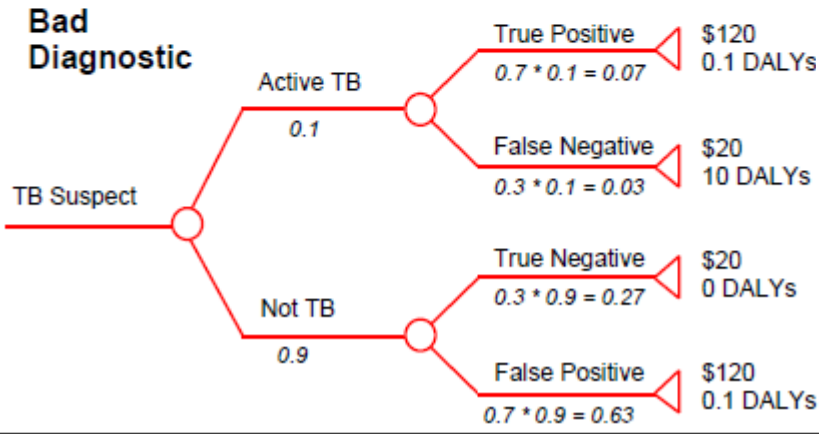
Incremental Cost-Effectiveness Ratio (ICER) =
 $(\$34 - \$8) / (0.114 - 0.505) = \$66$ per DALY averted



...and Replace it with a Bad One



Sensitivity = 70%
Specificity = 30%
(i.e., randomly treat 70% of all pts)
Cost = \$20



Mean Cost:
 $(\$103 * 0.05) + (\$3 * 0.05) + (\$3 * 0.9) + (\$103 * 0) = \$8$ (smear)
 $(\$120 * 0.07) + (\$20 * 0.03) + (\$20 * 0.27) + (\$120 * 0.63) = \$90$ (new test)

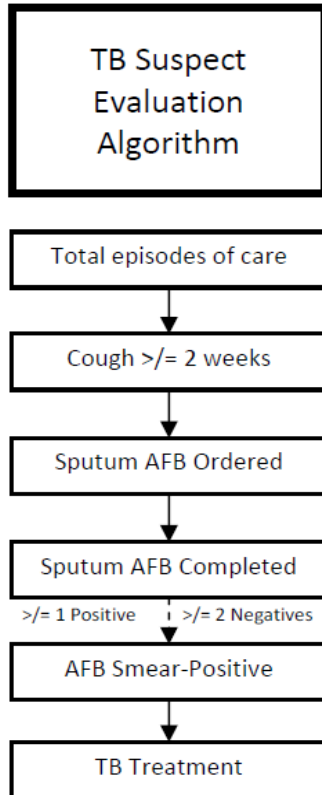
Mean Effectiveness = $\Sigma(\text{DALYs} * \text{Probability})$
 $(0.1 * 0.05) + (10 * 0.05) + (0 * 0.9) + (0.1 * 0) = 0.505$ (smear)
 $(0.1 * 0.07) + (10 * 0.03) + (0 * 0.27) + (0.1 * 0.63) = 0.370$ (new test)

Incremental Cost-Effectiveness Ratio (ICER) =
 $(\$90 - \$8) / (0.370 - 0.505) = \$607$ per DALY averted

\$670/DALY = Highly Cost-Effective in Most Settings



Link from Diagnosis to Treatment in Uganda



Indicator	Numbers, by quarter				Proportions*, by quarter				p-Value
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	
	14,852	14,652	17,369	16,036	--	--	--	--	--
	365	280	349	294	2.5%	2.0%	2.1%	1.8%	0.27
1	75	111	211	155	21%	40%	60%	53%	0.014
2	55	90	168	119	73%	81%	80%	77%	0.85
	7	19	30	25	13%	21%	18%	21%	0.25
3	5	13	23	21	71%	68%	77%	84%	0.016

Cumulative Probability of Being Diagnosed with and Treated for TB ⁺	11%	22%	37%	34%	0.005
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- Davis JL et al, AJRCCM 2011



Challenge #1: Summary

- The diagnostic process is dynamic, not static.
 - Patients who are not diagnosed do not just go home to die.
 - But most CEA models assume static outcomes
- Diagnostics in the lab are different from diagnostics in the field.
 - Not everyone who should get the test does
 - Not every result is translated into clinical benefit
- Economic models that fail to incorporate these realities will misrepresent the true cost-effectiveness of diagnostic tests.



Challenge #2: Converting Diagnosis to Health

- Diagnostic tests are designed to detect disease, not treat it.
 - Yet many diagnostic tests are implemented on the assumption that they will reduce population-level morbidity & mortality.
- Why might diagnosis not translate into more QALYs?
 - Link between diagnosis and treatment fails.
 - Patients would get treated in the absence of the test.
 - Patients are diagnosed too late for the diagnostic test to help.
 - Sickest patients incrementally diagnosed
 - Patients who are diagnosed wouldn't suffer any consequences.
 - Most well patients incrementally diagnosed
 - Patients are diagnosed and treated for one condition but suffer consequences of another.
 - Patients with disease are usually the most immunocompromised, etc.



ORIGINAL ARTICLE

Mortality Results from a Randomized Prostate-Cancer Screening Trial

Gerald L. Andriole, M.D., E. David Crawford, M.D., Robert L. Grubb III, M.D.,

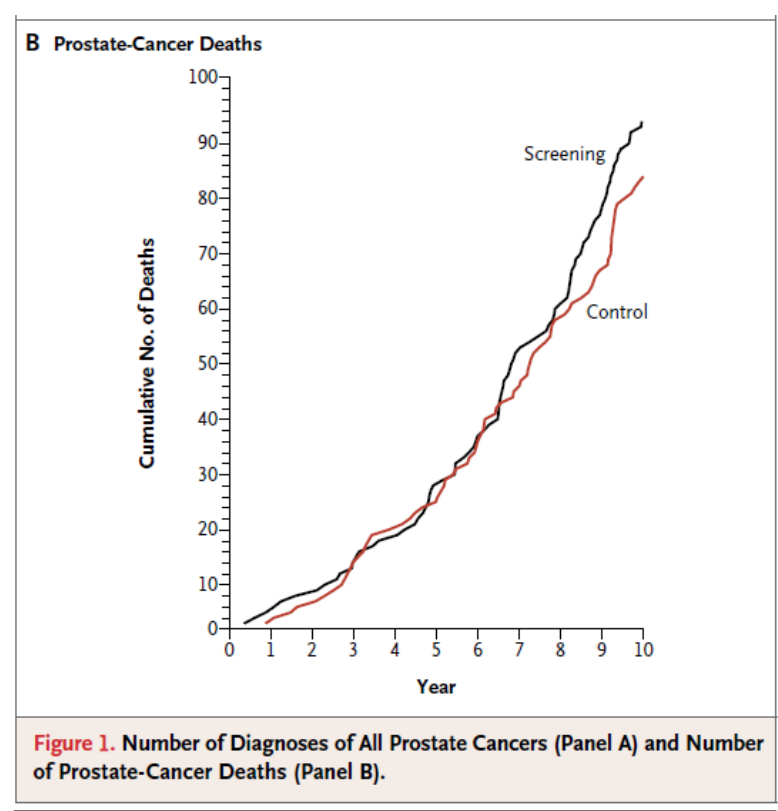
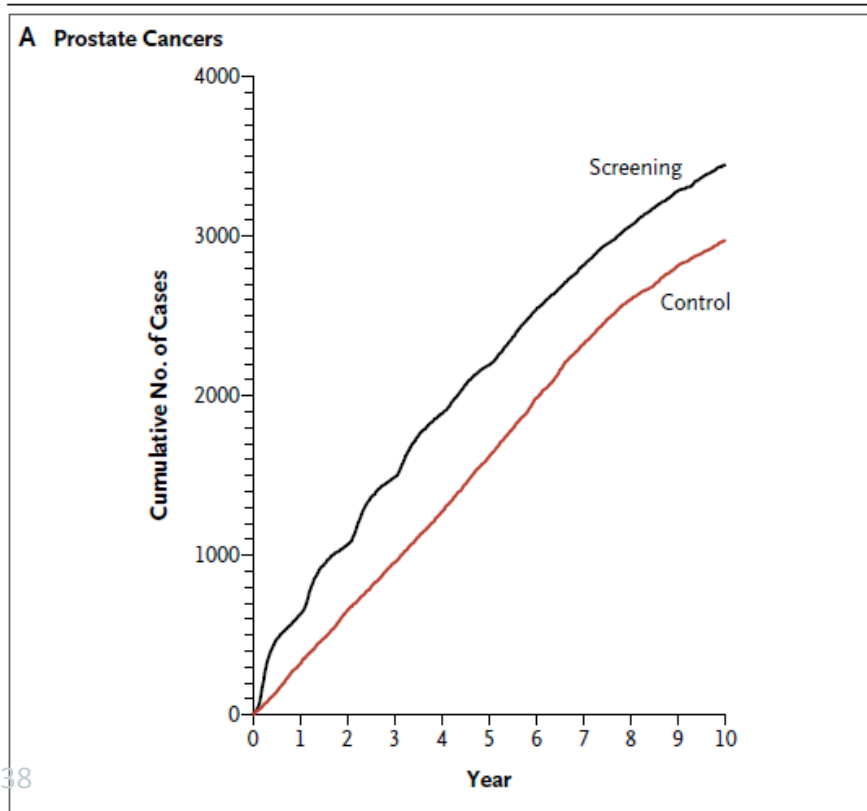


Figure 1. Number of Diagnoses of All Prostate Cancers (Panel A) and Number of Prostate-Cancer Deaths (Panel B).

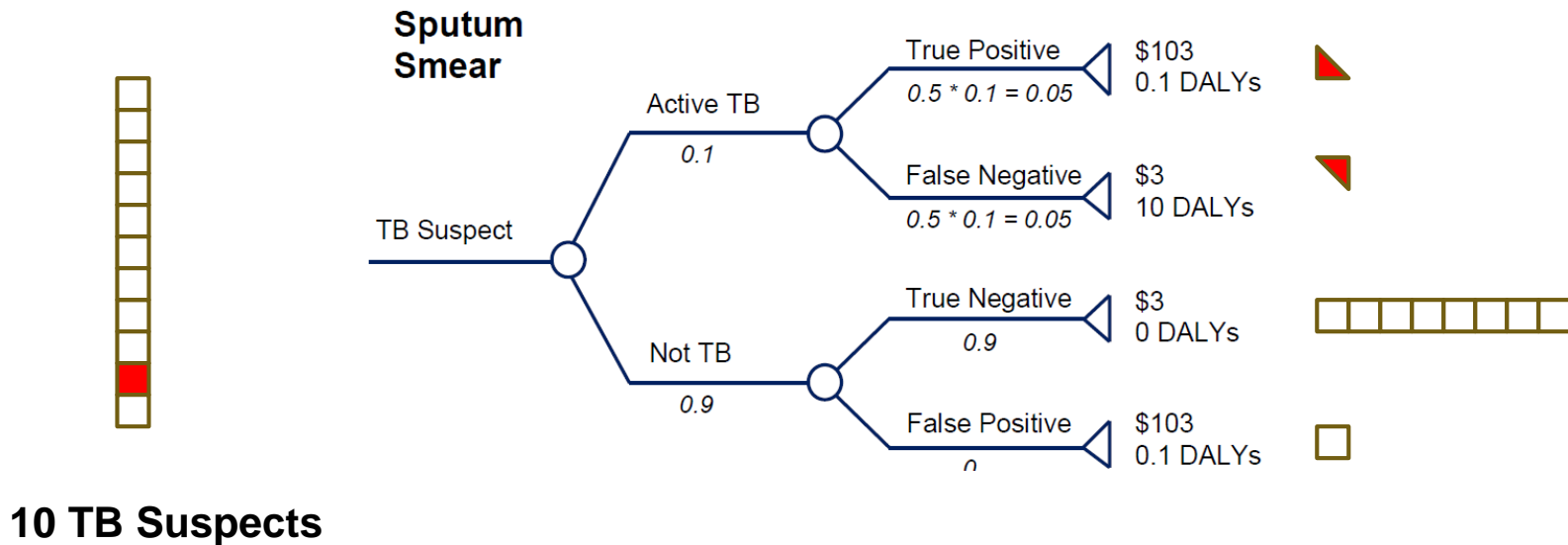
Challenge #2: Summary

- There is no guarantee that improved diagnosis leads to better health.
 - Prostate cancer as a clear example
- We must make choices in the meantime with the data that we have.
 - Requires modeling with assumptions of uncertain validity
- Cost-effectiveness estimates are only as good as the corresponding effectiveness data.
 - As better effectiveness data come out, we must be willing and able to revise our cost-effectiveness estimates accordingly.



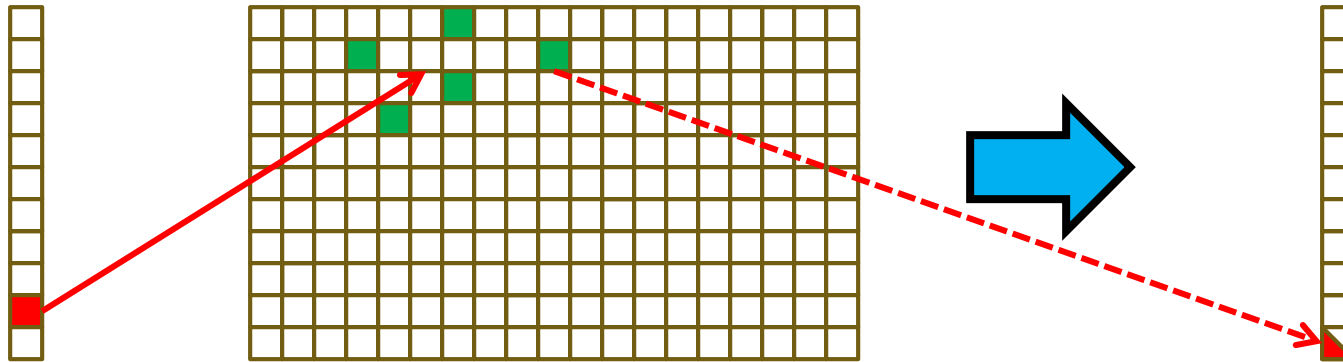
Challenge #3: Incorporating Transmission Effects

- Many diagnostic tests (esp. point-of-treatment/POC) are adopted in the hope that they will reduce transmission.
- There is no guarantee that this will happen!



Early Diagnosis

(e.g., Active TB Case-Finding)



10 TB Suspects

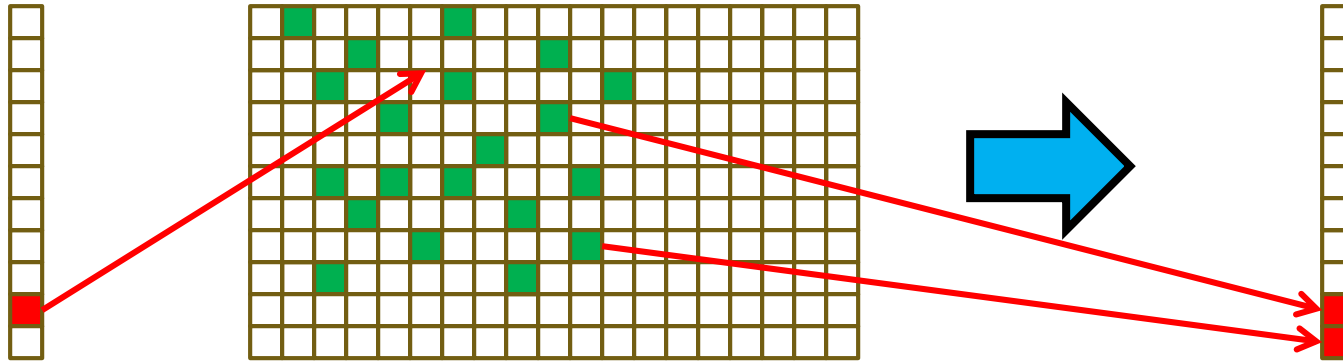
190 Contacts
5 Secondary Infections

Next 10 TB Suspects
Only 0.5 TB Cases



Late Diagnosis

(e.g., Passive TB Case-Finding)



10 TB Suspects

190 Contacts
20 Secondary Infections

Next 10 TB Suspects
2 TB Cases



Challenge #3: Summary

- Decision analysis describes what happens to a cohort of selected individuals.
 - By design, does not incorporate people outside the cohort
 - Can be expanded to an extent (e.g., Markov models of the entire population), but ultimately is limited in evaluating transmission effects
- Transmission modeling has largely been developed outside the field of health economics.
 - Transmission modelers are traditionally applied mathematicians, whereas health economists are trained in economics.



Summary:

Challenges of CEA for Diagnostic Tests

- **Representing the diagnostic process**
 - Diagnosis is a complex and dynamic process.
- **Converting diagnosis to health**
 - Many steps lie in between successful diagnosis of an individual and reduced morbidity/mortality in a population.
- **Incorporating transmission effects**
 - Knowing what will happen to one cohort may tell you nothing about what will happen to the next cohort.

