

Sensitivity Analysis & Probabilistic Analysis

Day 4

Agenda

- Sensitivity analyses
- Probabilistic analyses

Sensitivity Analysis

- Vary input parameters within plausible ranges
- For which values is each strategy optimal?
 - Threshold analysis
- Deterministic sensitivity analysis (DSA)
 - One-way analysis: vary one parameter, hold rest fixed
 - Two-way analysis: vary two parameters, hold rest fixed
- Probabilistic sensitivity analysis (PSA) = Probabilistic analysis (PA)
 - Simultaneously vary input parameters by randomly sampling from appropriate probability distributions
 - How often is each alternative cost-effective?
 - What strategy has the highest **expected** net benefit

Threshold Analysis

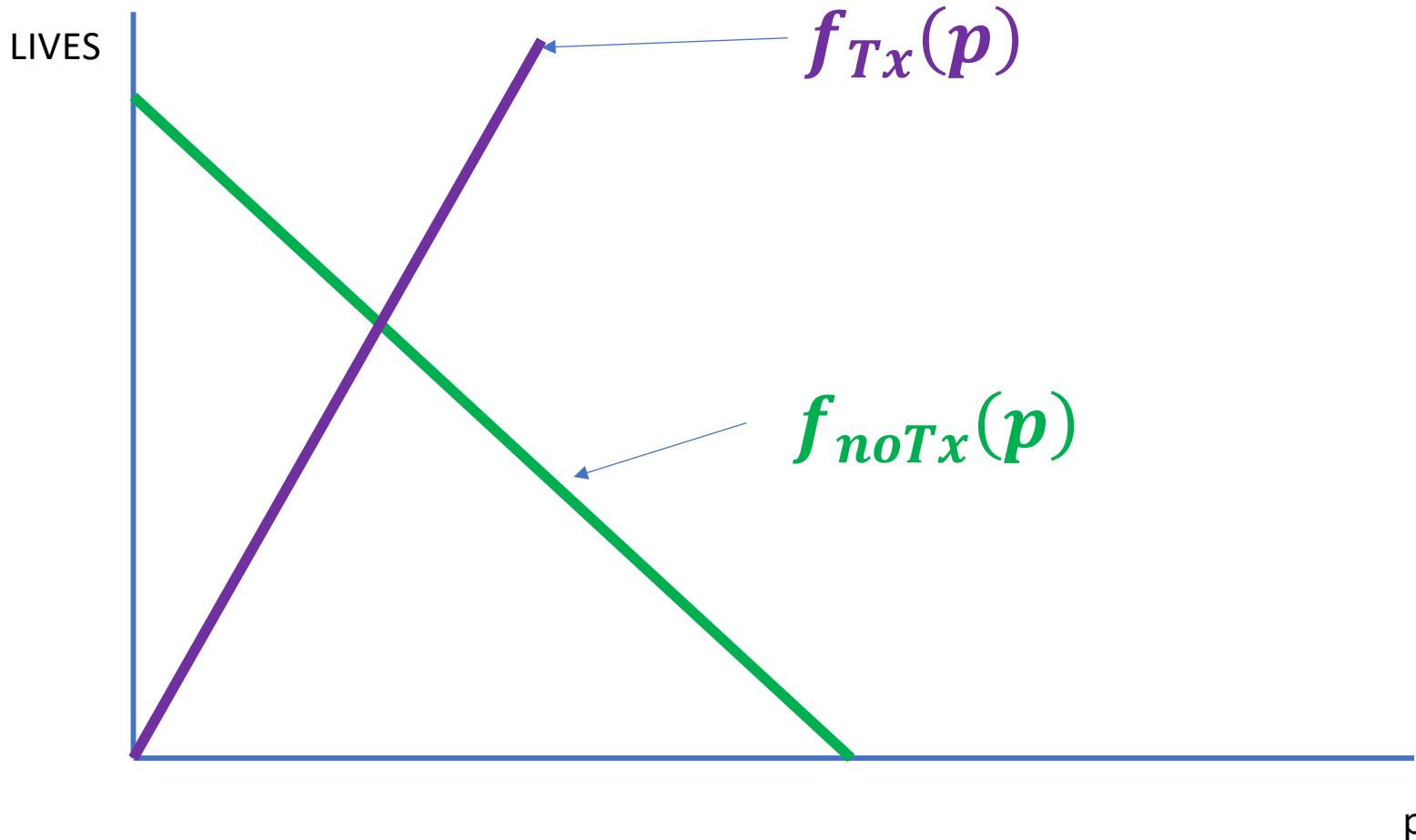
Simple Threshold Analysis

$$f_{noTx}(p) = -p + 0.4$$
$$f_{Tx}(p) = 2p$$

- The functions' output is the number of lives saved.
- When does the treatment provide more lives saved?

* Assume the functions are actually $\max(f(p), 0)$ – they never go negative

Simple threshold analysis



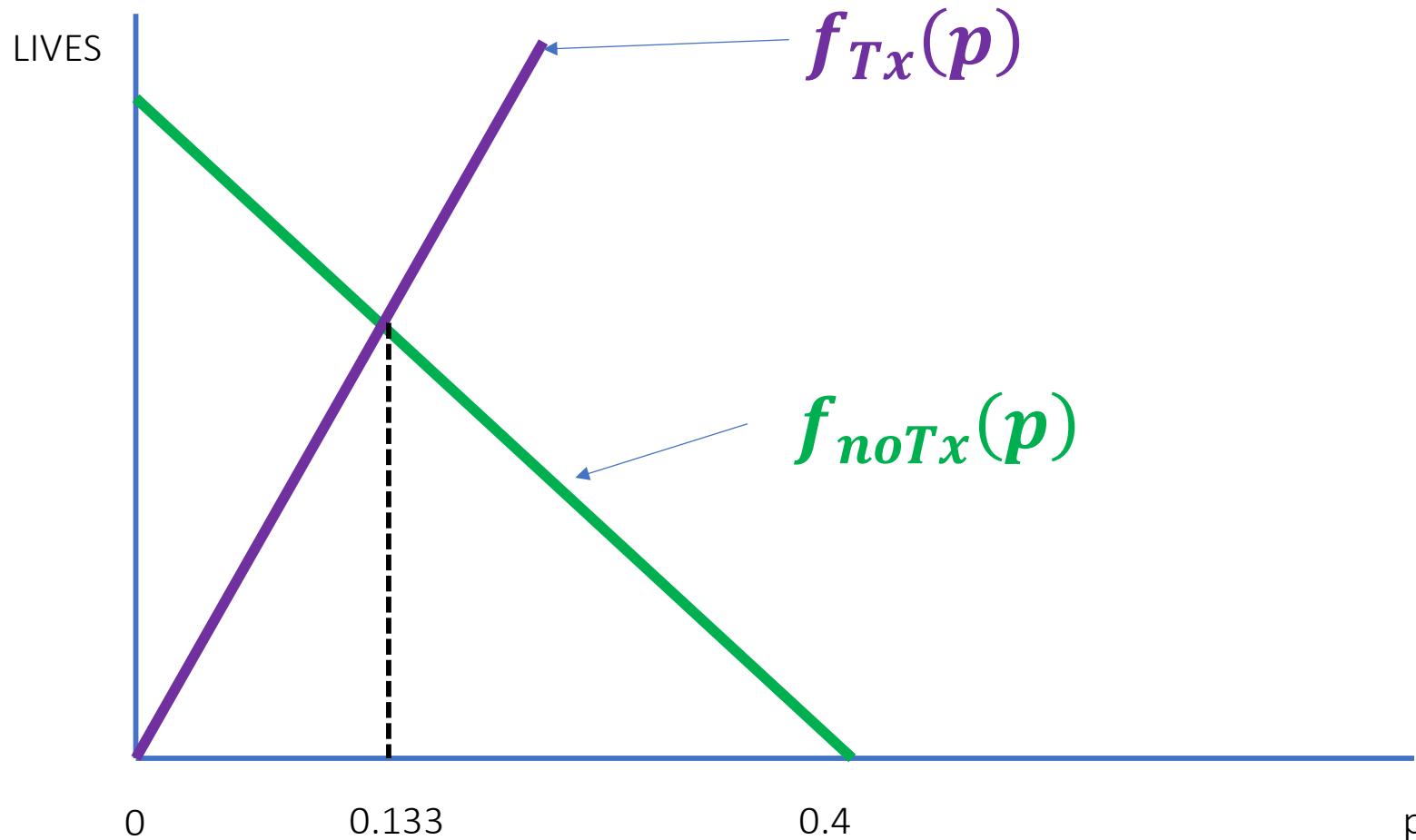
Simple threshold analysis

$$\begin{aligned}f_{noTx}(p) &=? f_{Tx}(p) \\-p + 0.4 &= 2p \\3p &= 0.4 \\p &= 0.133\end{aligned}$$

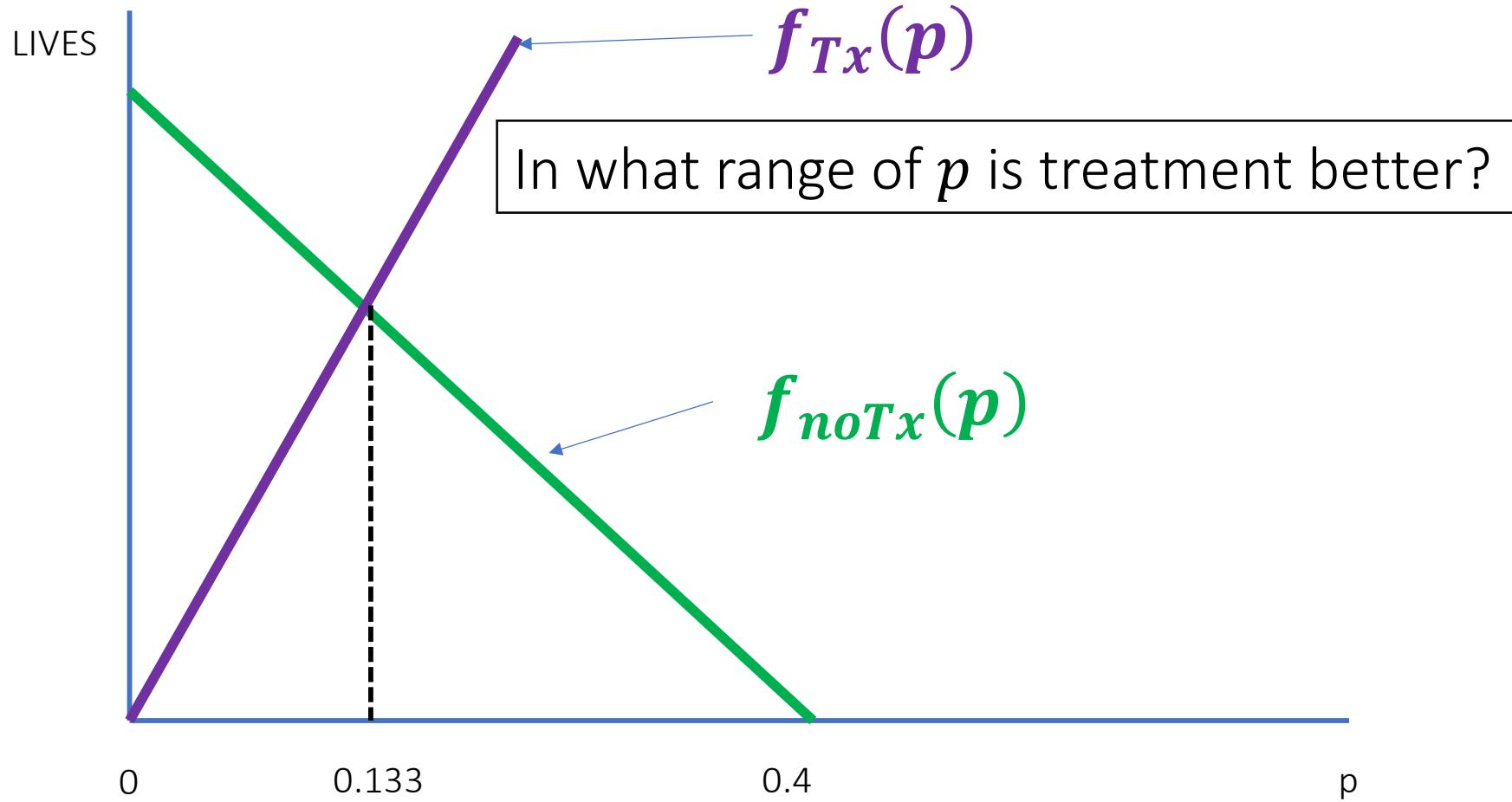
The threshold: $p = 0.133$

MEANING: Point at which both give the same # of lives saved
=> We are indifferent between Tx's

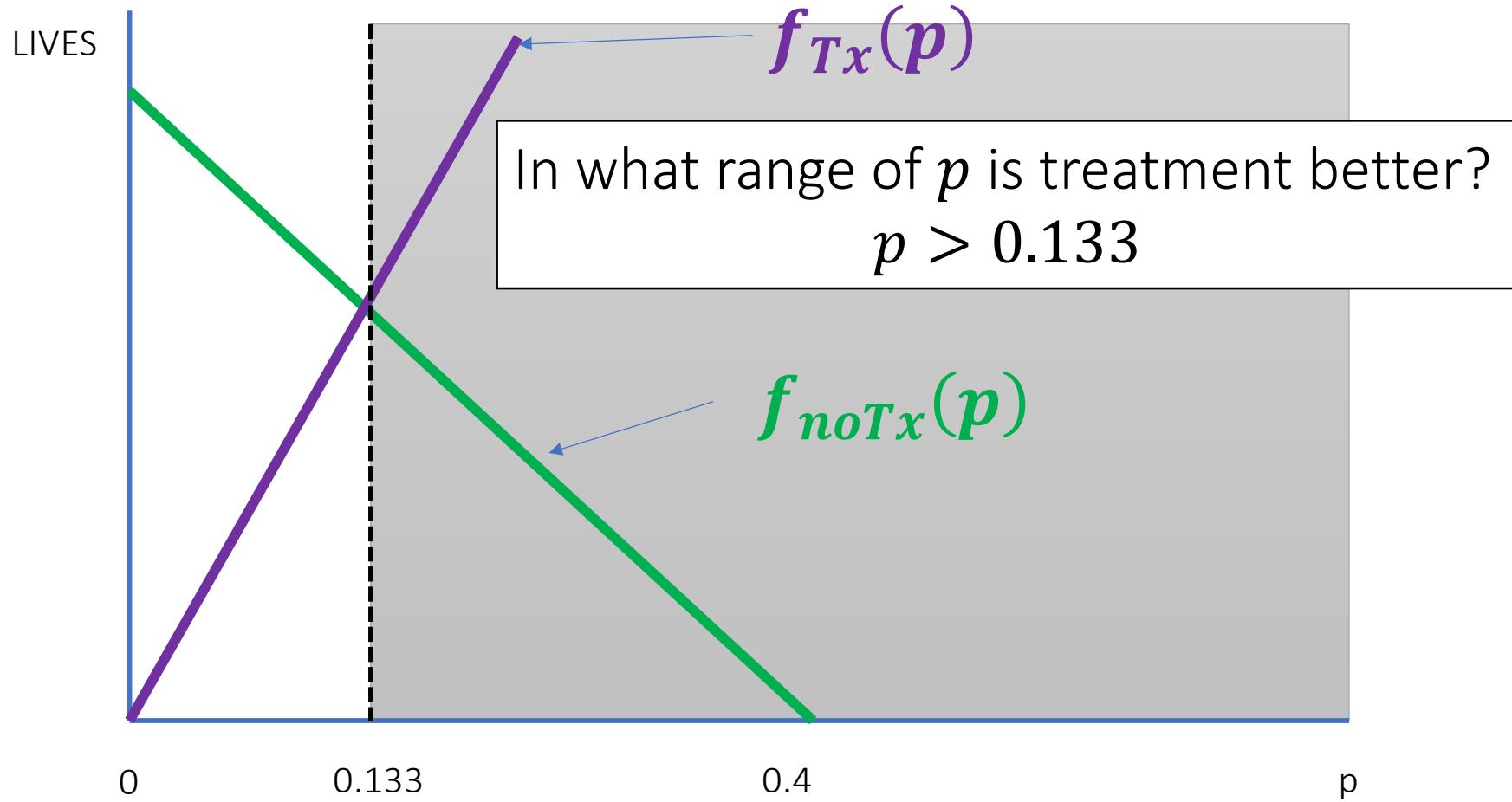
Simple threshold analysis



Simple threshold analysis



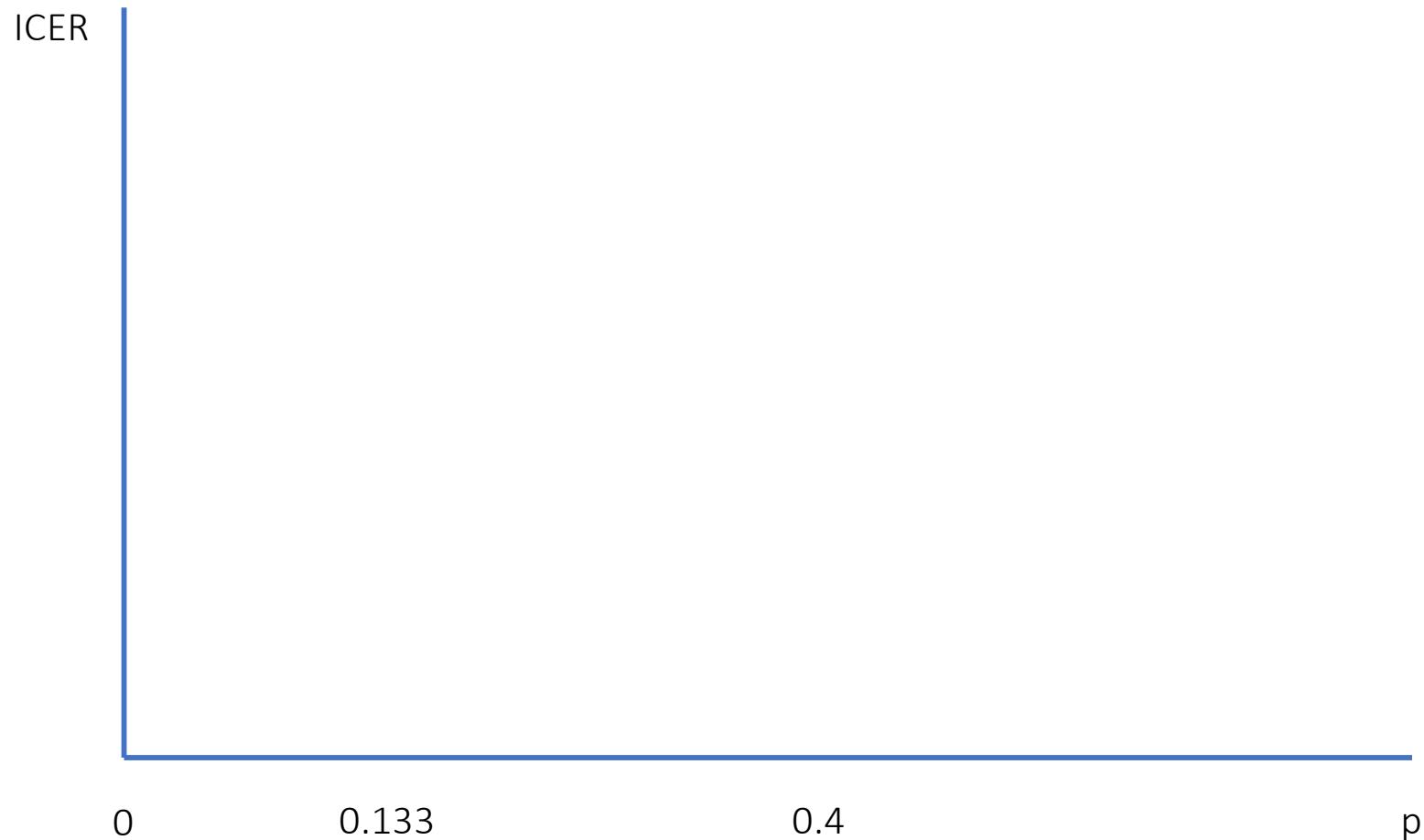
Simple threshold analysis



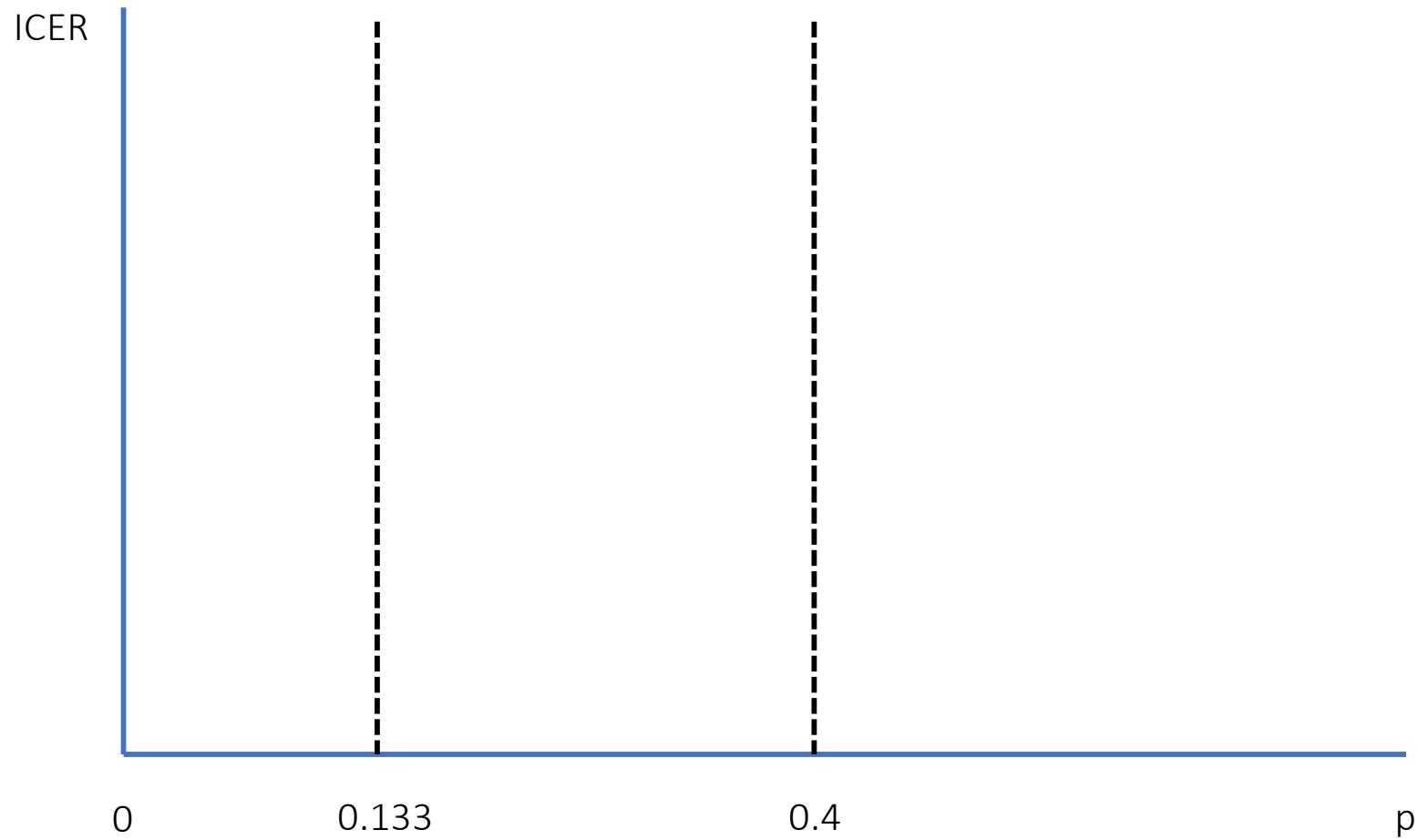
Aside: cost-effectiveness

- The example had only 1 output
 - Benefit: measured in lives saved
- What about cost-effectiveness?
 - Each function has two outputs: (costs and QALYs)
- For each value of p, compute costs & QALYs
 - C_{notx} , Q_{notx} , C_{tx} , Q_{tx}
 - Assess dominance and compute ICERs
 - *For example: assume $C_{\text{tx}} > C_{\text{notx}}$*

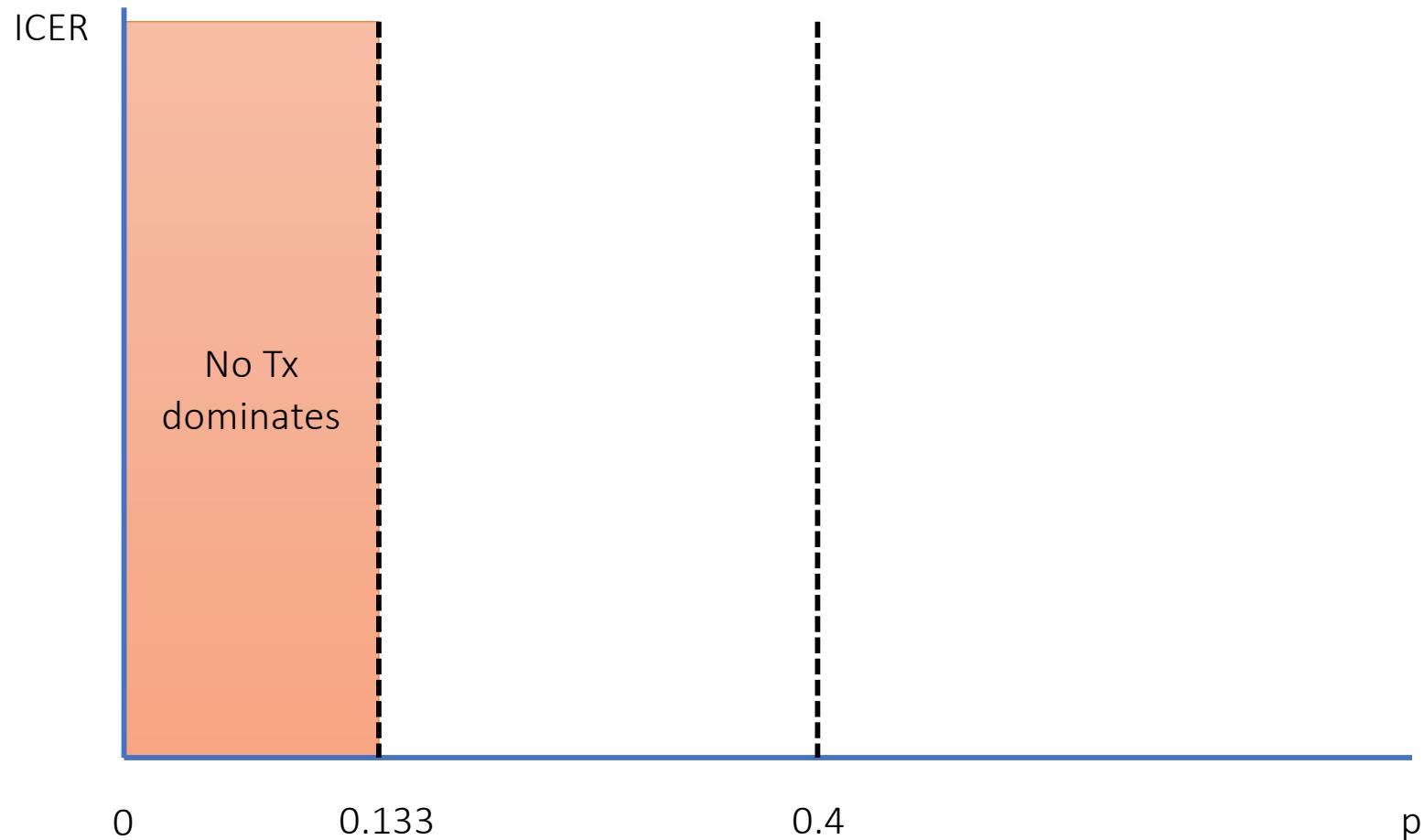
Aside: cost-effectiveness



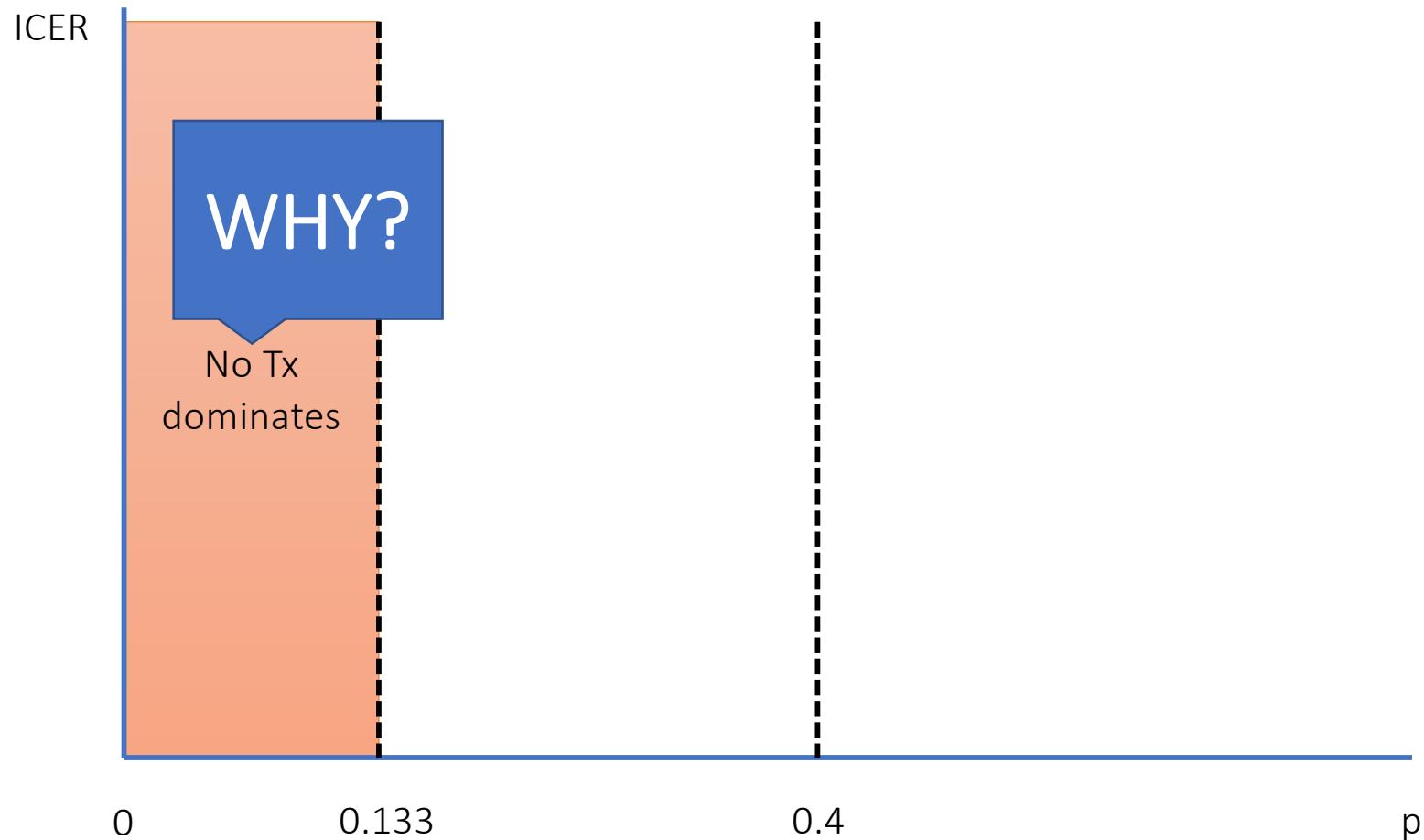
Aside: cost-effectiveness



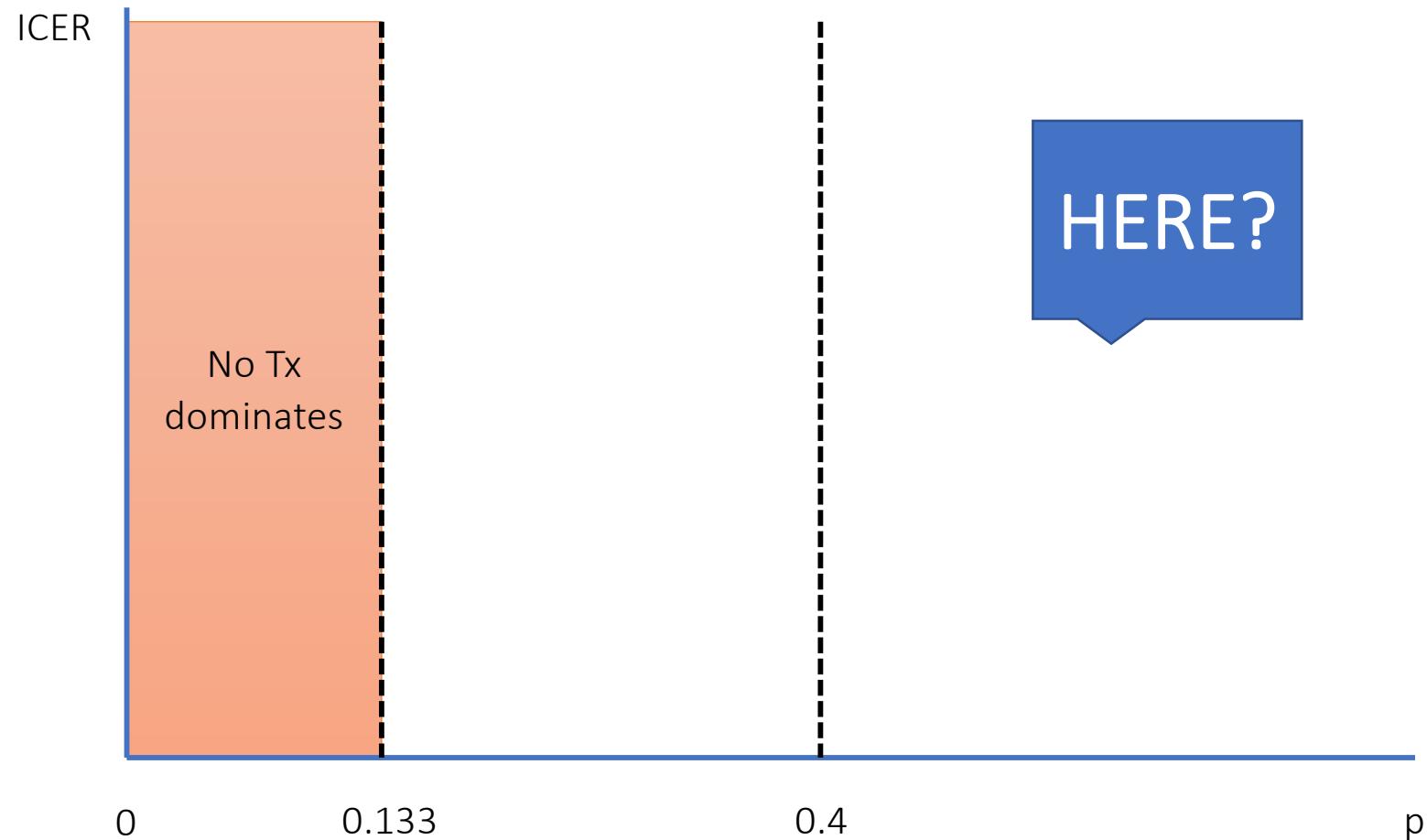
Aside: cost-effectiveness



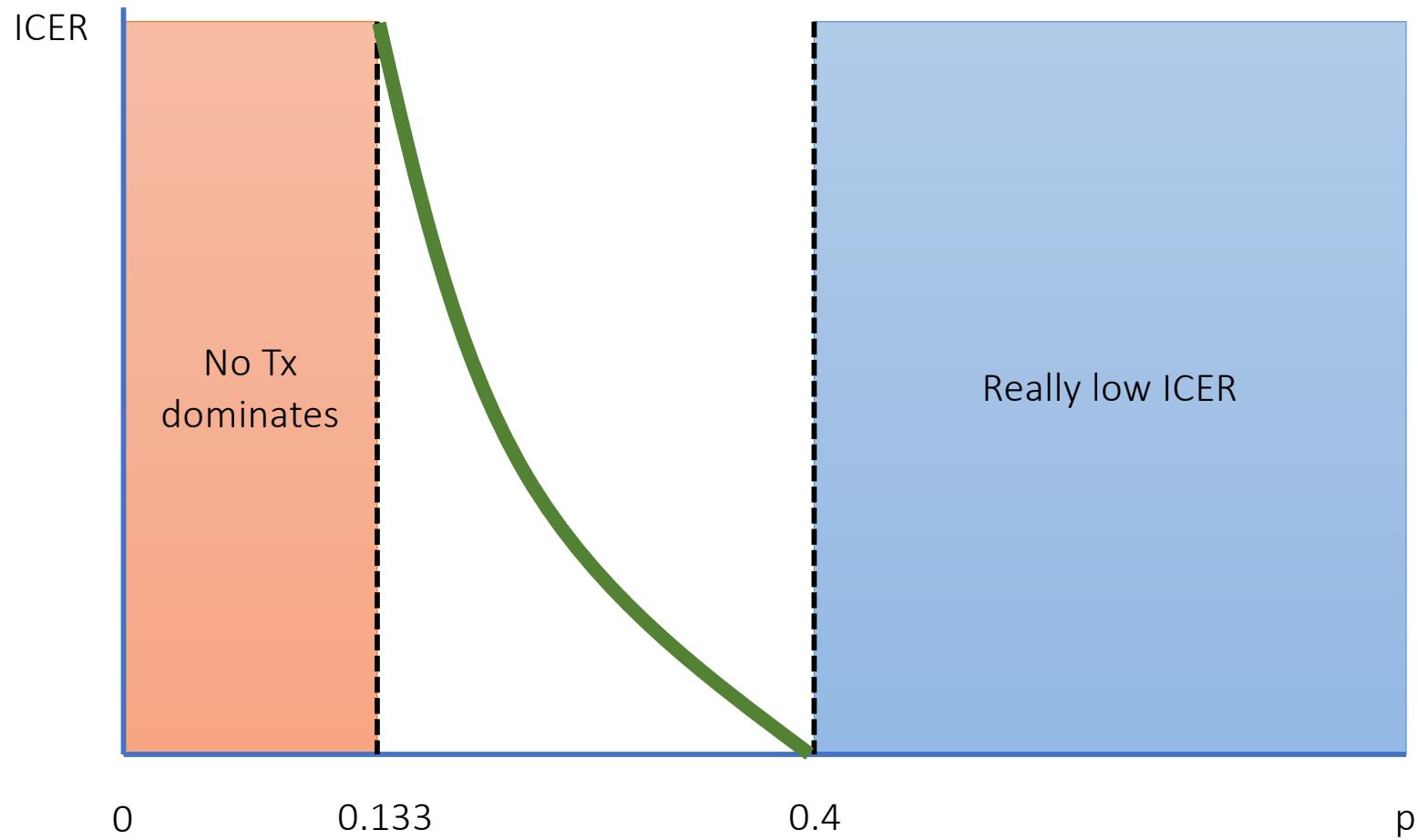
Aside: cost-effectiveness



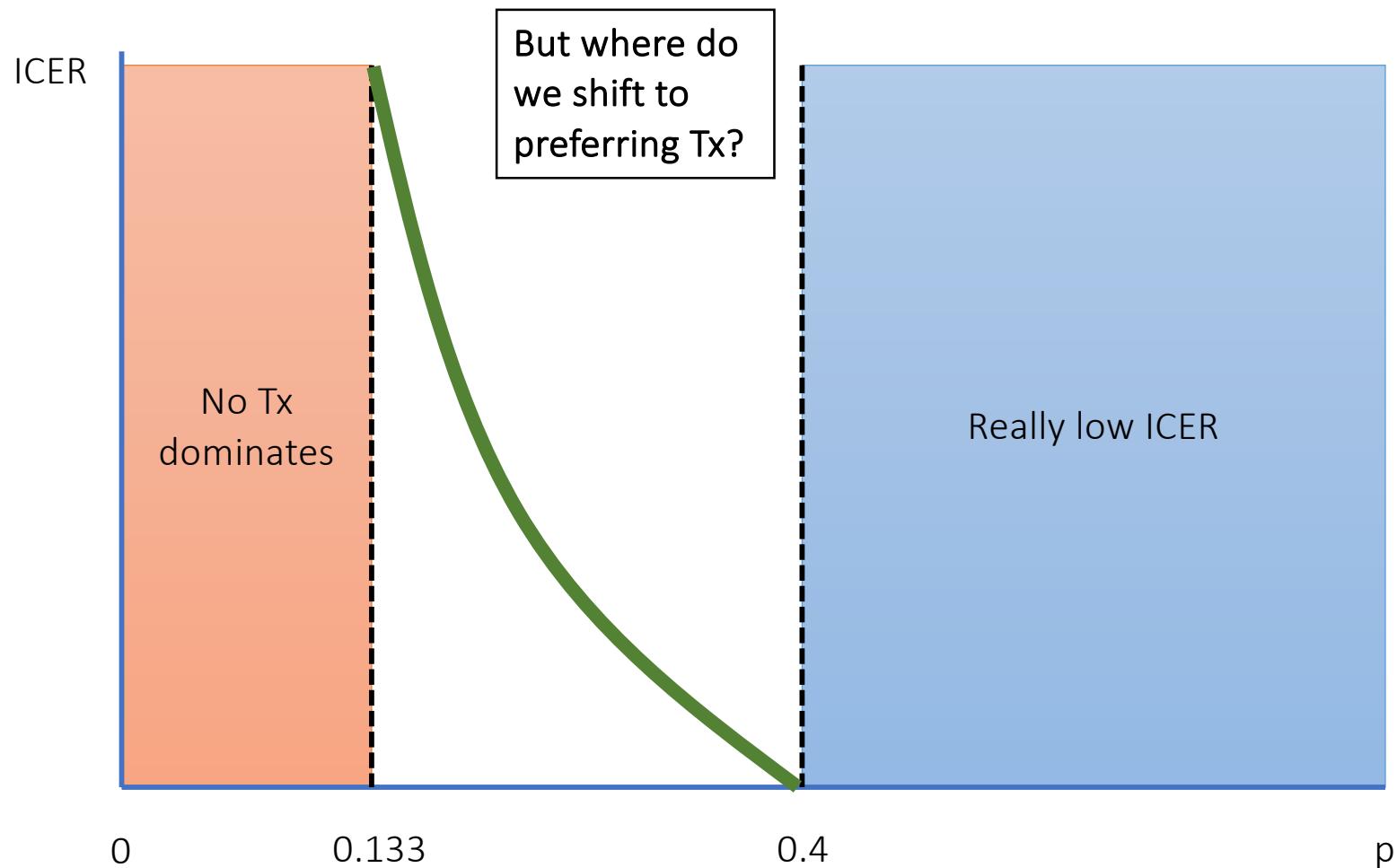
Aside: cost-effectiveness



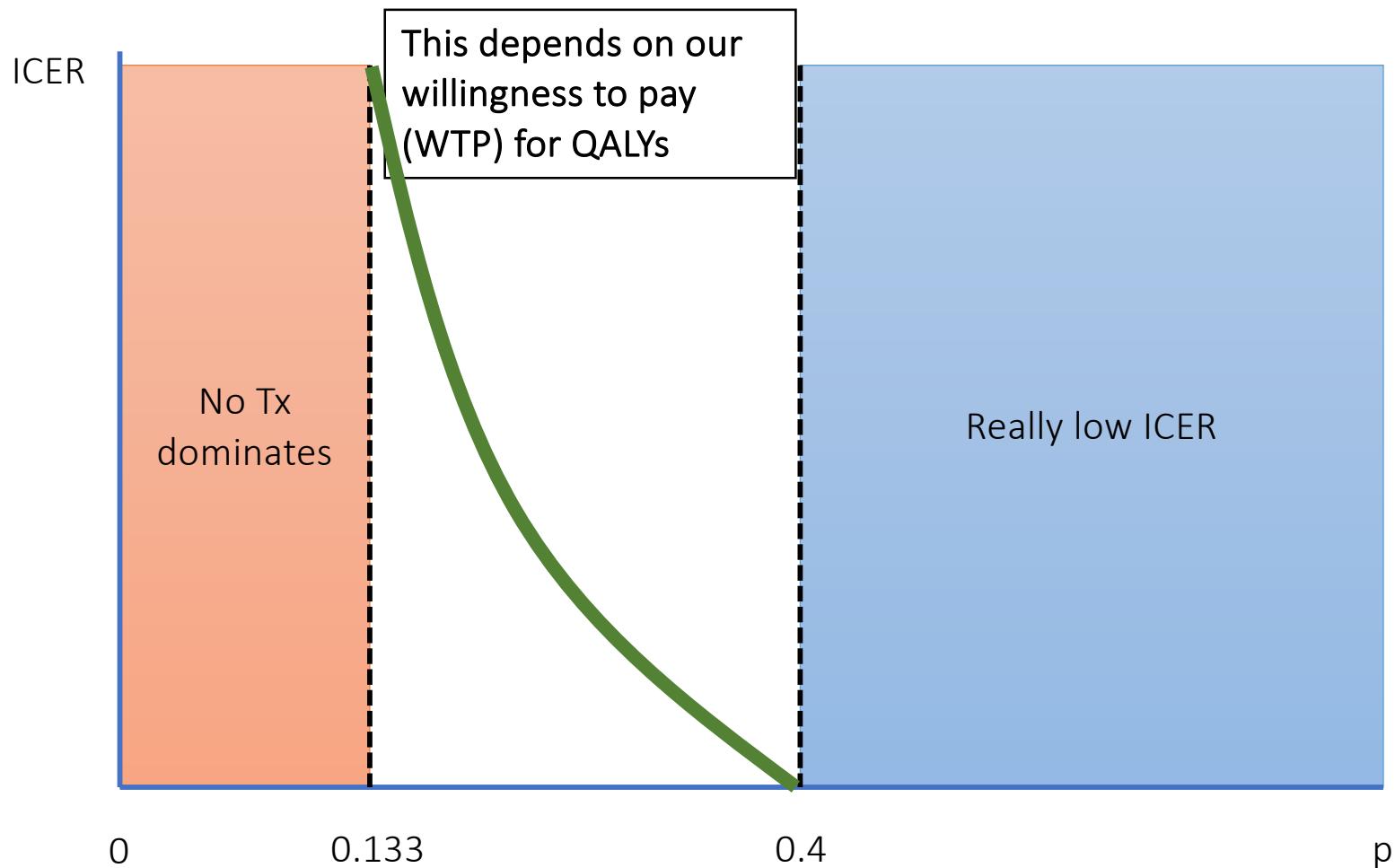
Aside: cost-effectiveness



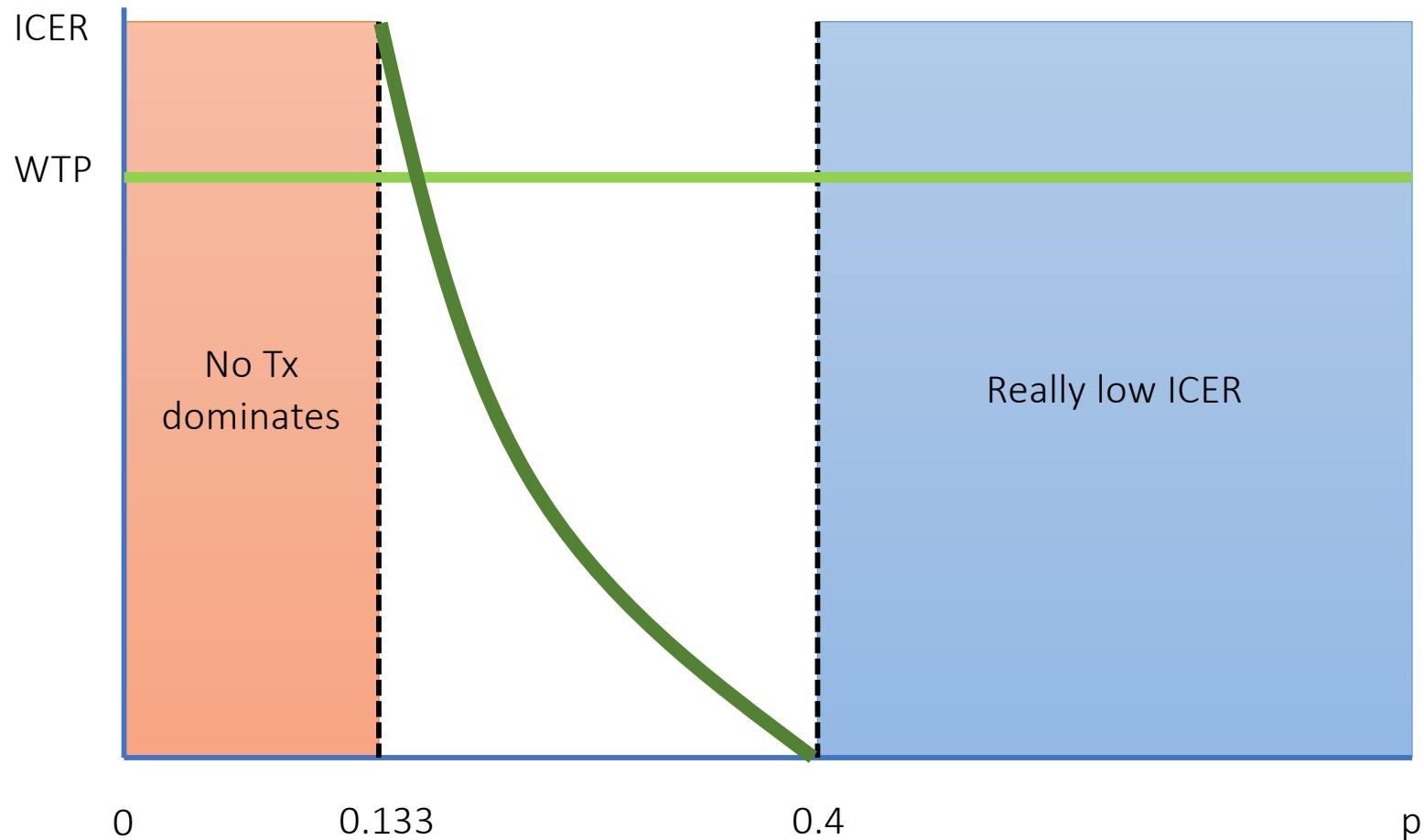
Aside: cost-effectiveness



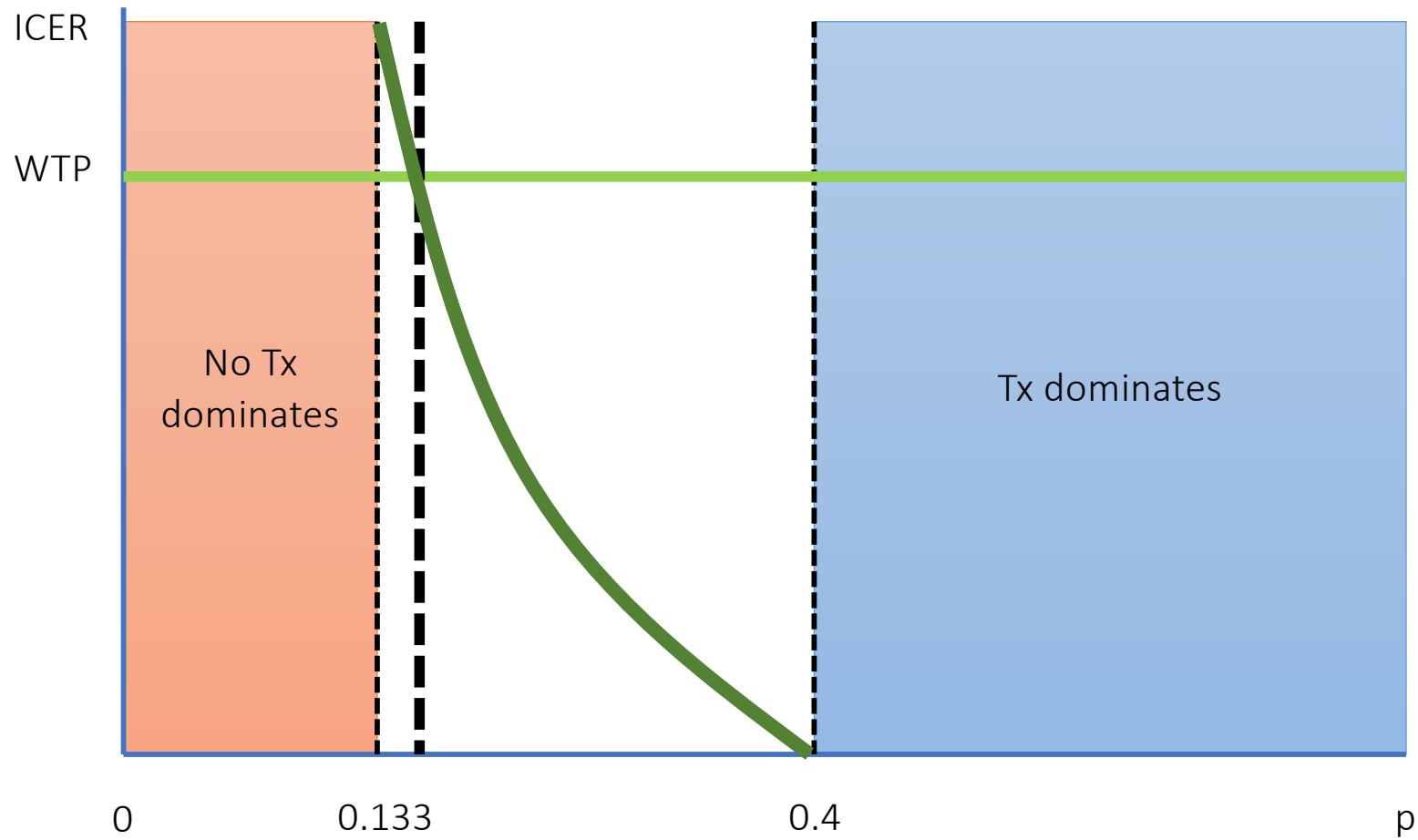
Aside: cost-effectiveness



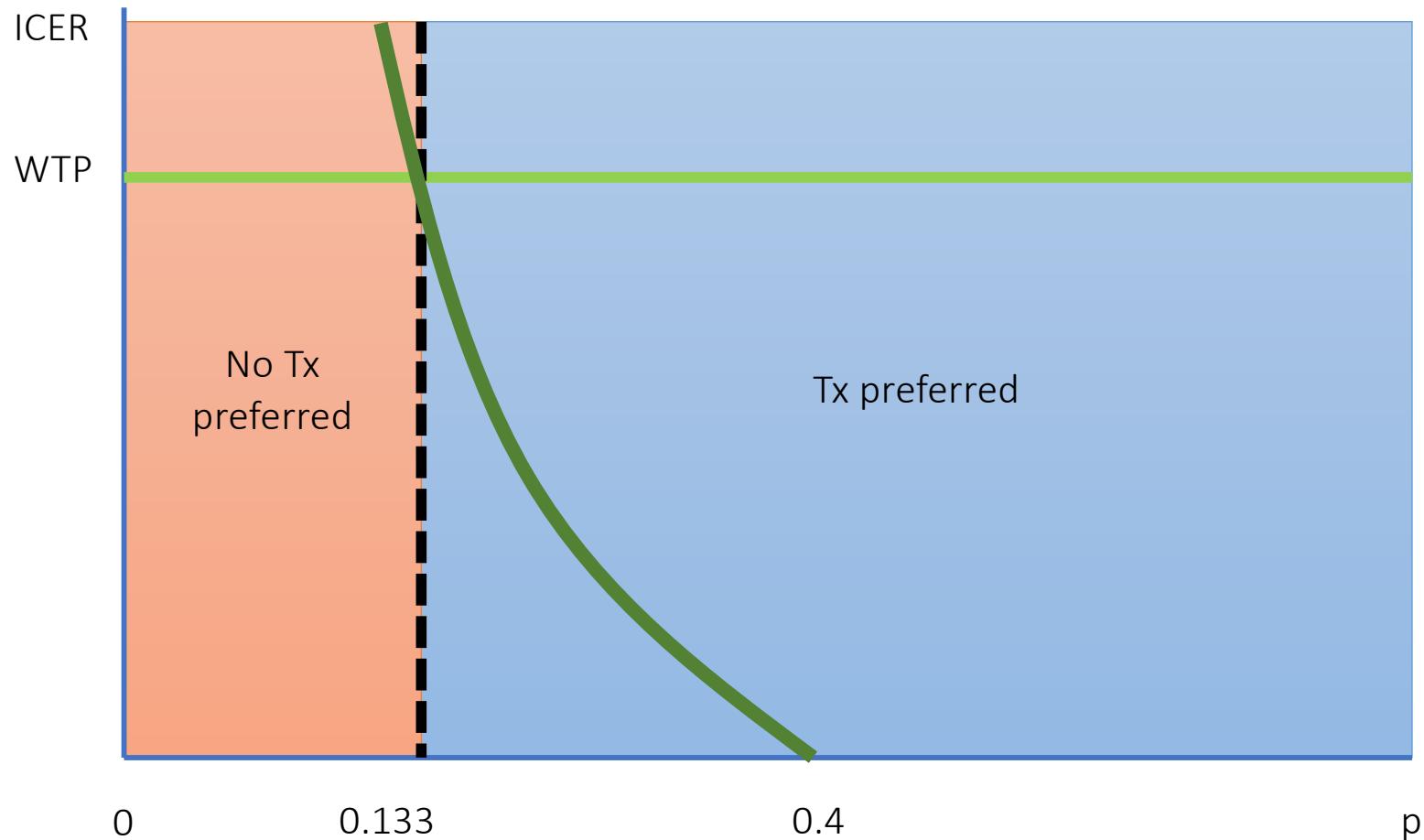
Aside: cost-effectiveness



Aside: cost-effectiveness



Aside: cost-effectiveness



Deterministic Sensitivity Analysis

One-Way Sensitivity Analysis (OWSA)

- Systematically vary a single parameter over range of uncertainty, keeping all others fixed

$p_{PCed} = 30\%$, $p_{PCed} = 40\%$, $p_{PCed} = 50\%$, etc...

- For each parameter value, calculate the expected outcomes under each strategy
- Identify which strategy is preferred for each parameter value

One-Way Sensitivity Analysis (OWSA)

Probability of early detection (Primary care)
30%
35%
40%
45%
50%
55%
60%
65%

One-Way Sensitivity Analysis (OWSA)

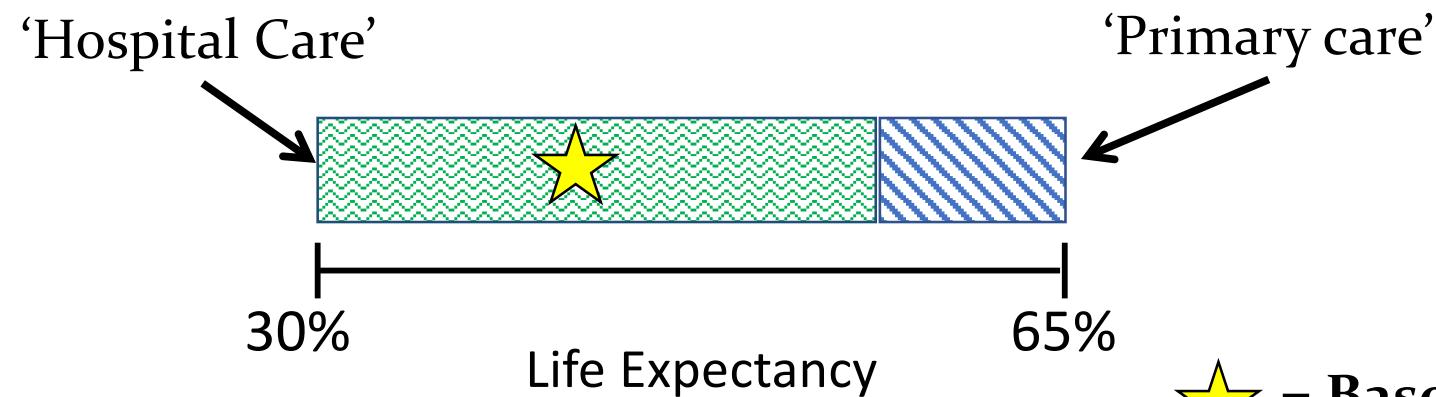
Probability of early detection (Primary care)	Life Expectancy		
	Routine practice	Primary Care	Hospital Care
30%			
35%			
40%			
45%			
50%			
55%			
60%			
65%			

One-Way Sensitivity Analysis (OWSA)

Probability of early detection (Primary care)	Life Expectancy		
	Routine practice	Primary Care	Hospital Care
30%	3.1	2.8	3.7
35%	3.1	3.1	3.7
40%	3.1	3.4	3.7
45%	3.1	3.7	3.7
50%	3.1	4.0	3.7
55%	3.1	4.3	3.7
60%	3.1	4.6	3.7
65%	3.1	4.9	3.7

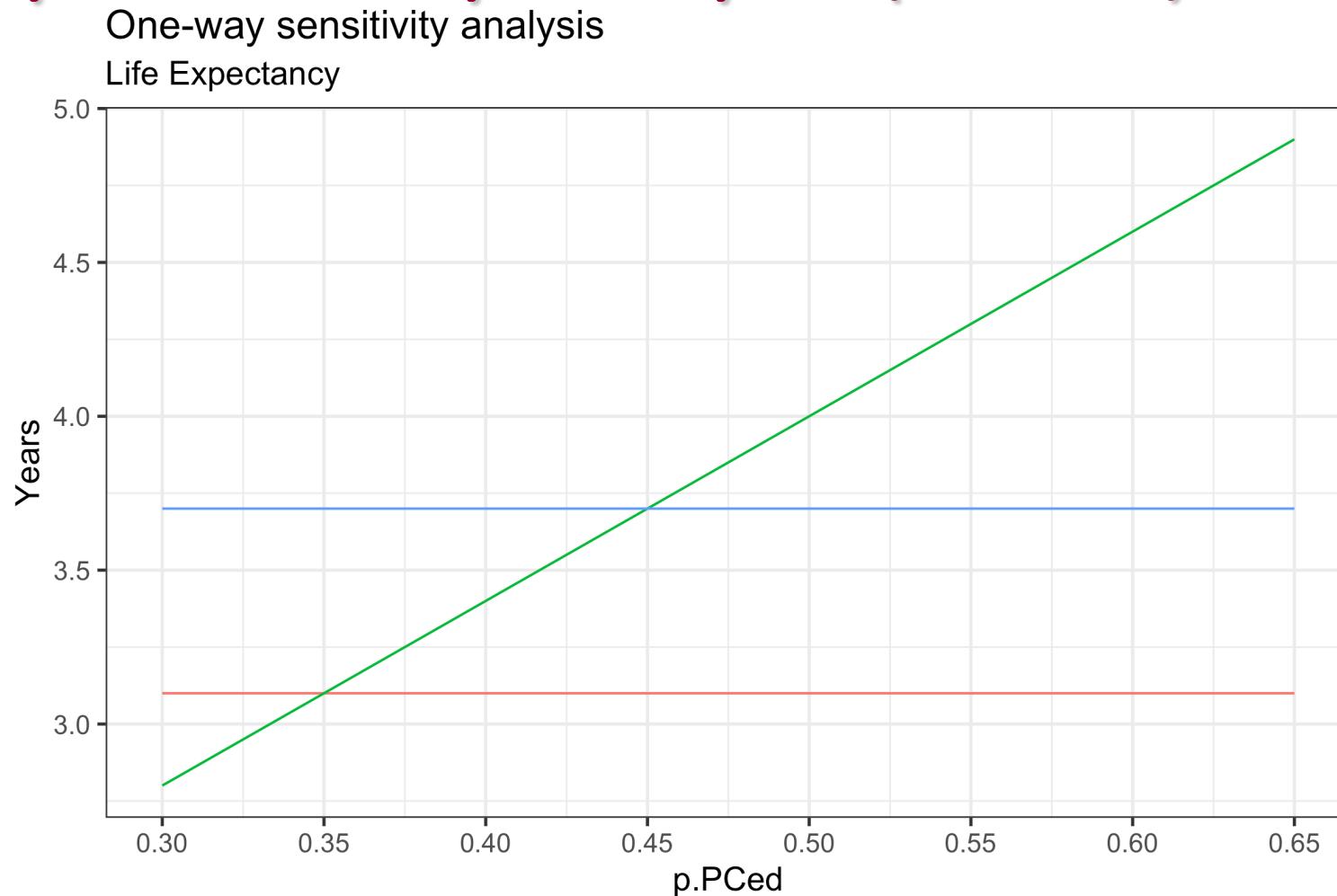
One-Way Sensitivity Analysis (OWSA)

- Systematically vary a single parameter over range of uncertainty, keeping all others fixed
 - p.PCed = 30%, p.PCed = 40%, p.PCed = 50%, etc...
- For each parameter value, calculate the expected outcomes under each strategy
- Identify which strategy is preferred



★ = Base case
Stanford Health Policy

One-Way Sensitivity Analysis (OWSA)



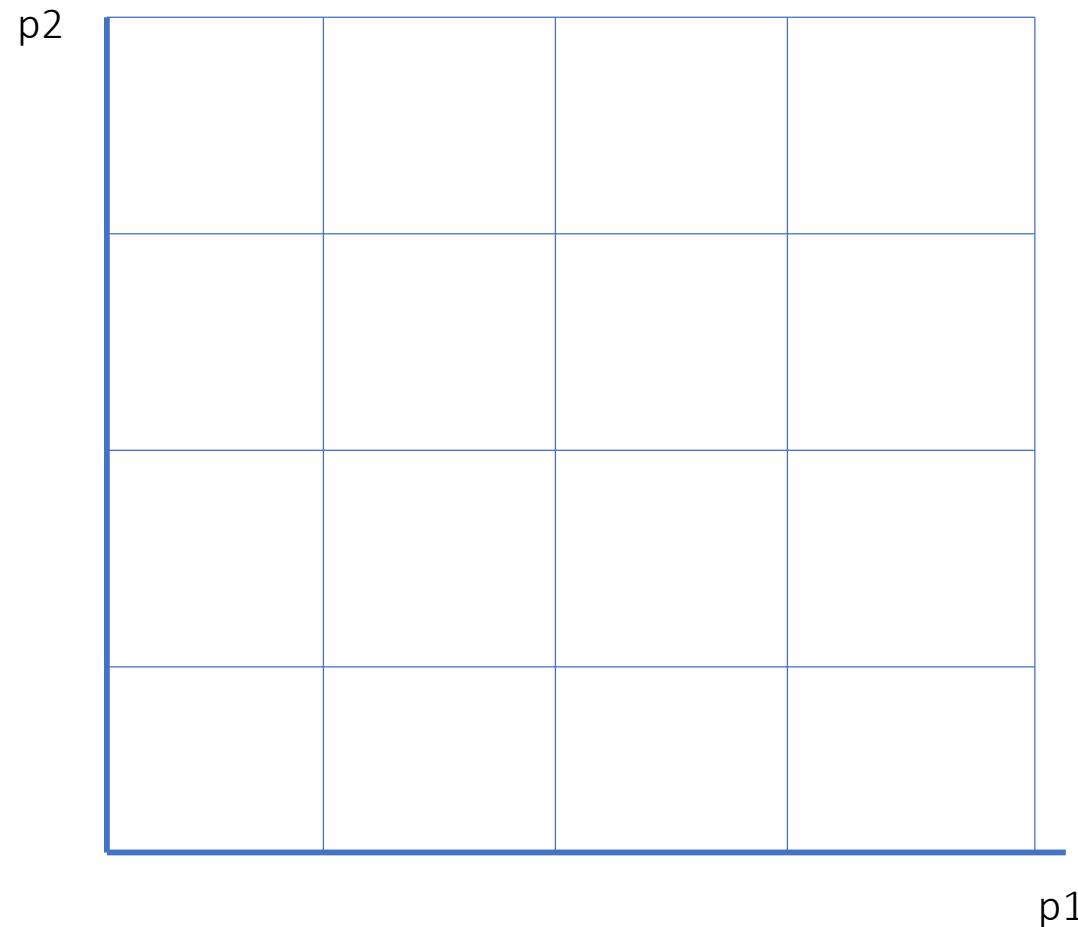
How many model runs?

- Consider a model with k parameters
- Assume we want to explore the k parameters across a range with a min and max
- Denote the number of levels explored as “ a ”
 - Mean (base case), Min, Max (in this case $a = 3$)
- $a * k$ is the number of runs $-(a - 1) * k$, since we did the base case analysis prior to doing sensitivity analyses
- If each model run takes 10 seconds, the total time is $10 * (a - 1) * k$ seconds
 - OWSA of a 180-parameter model in 1 hour

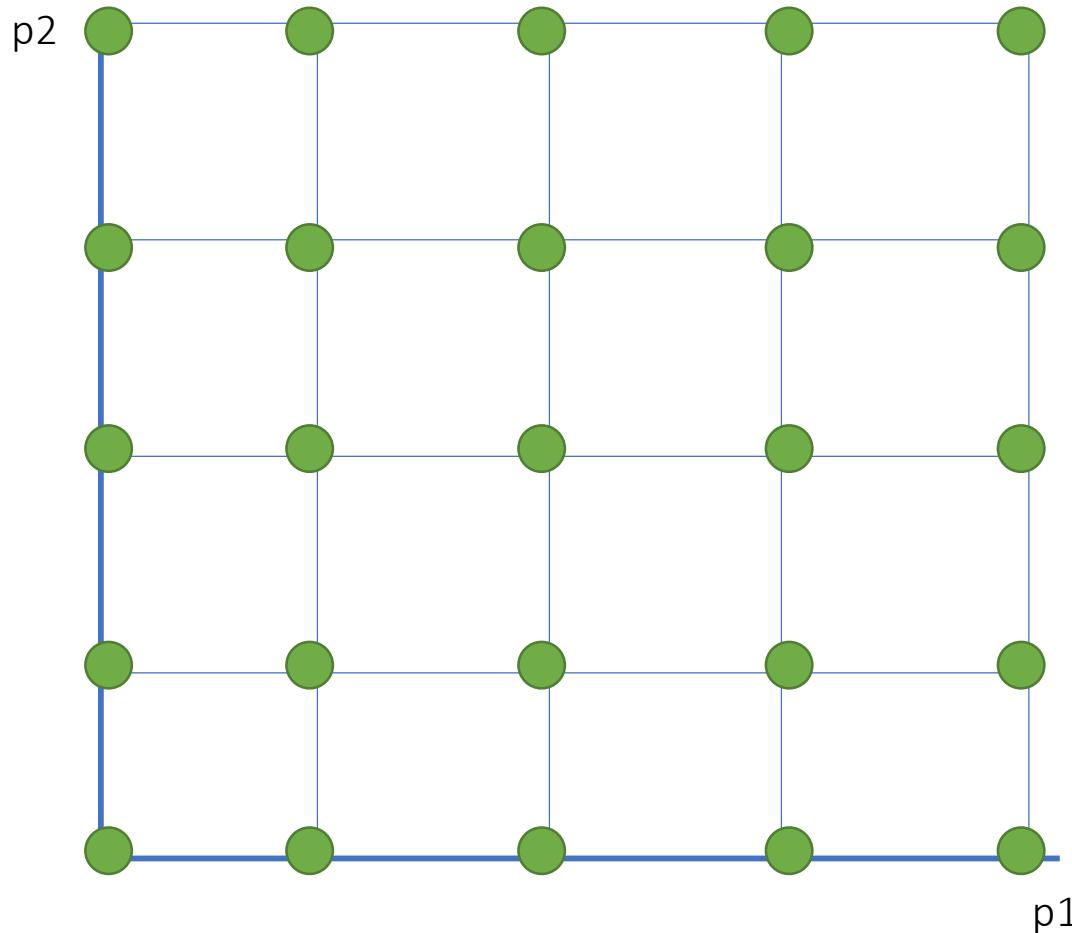
Two-Way Sensitivity Analysis (TWSA)



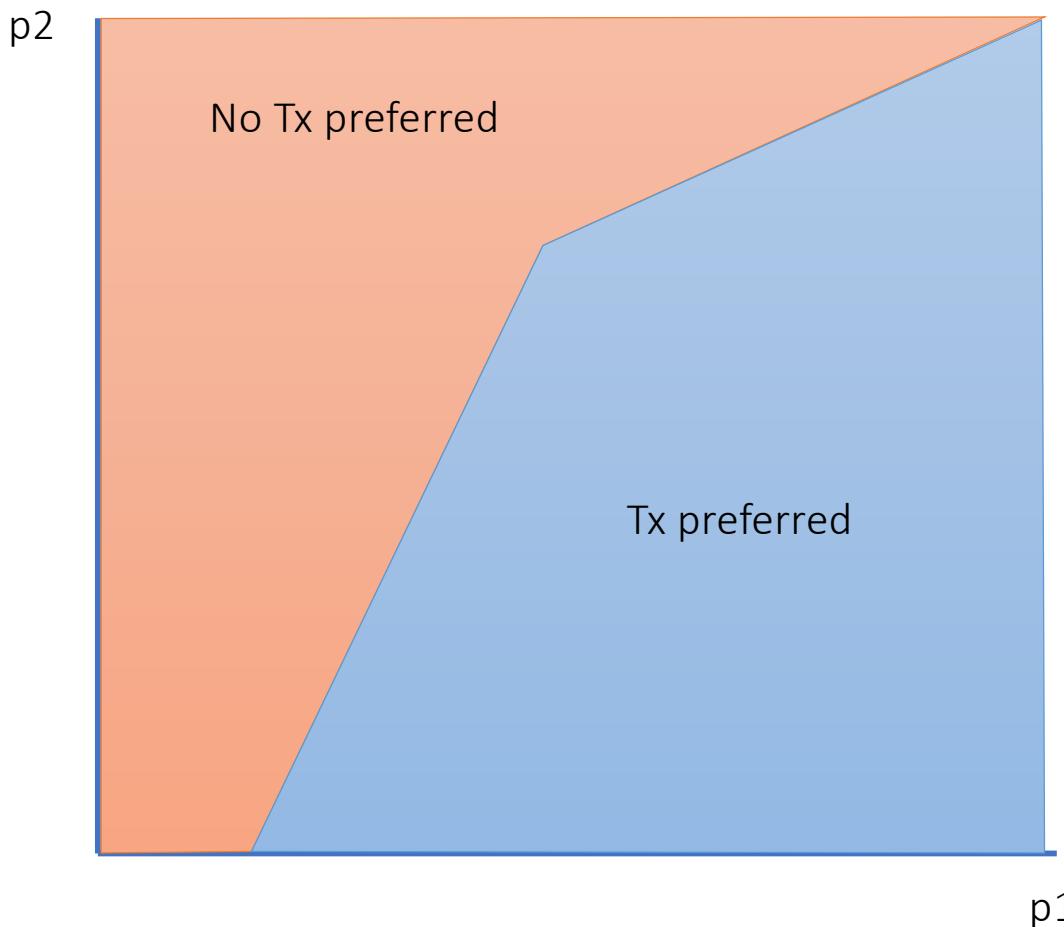
Two-Way Sensitivity Analysis (TWSA)



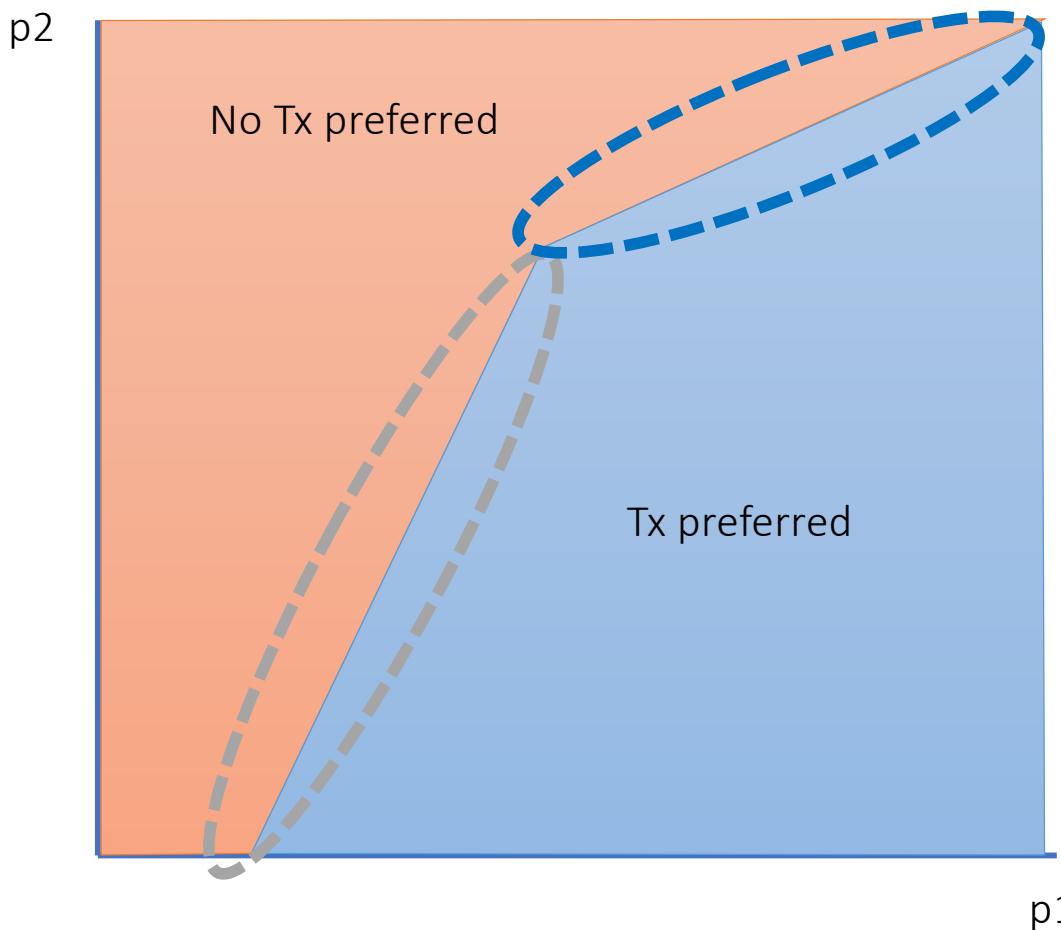
Two-Way Sensitivity Analysis (TWSA)



Two-Way Sensitivity Analysis (TWSA)



Two-Way Sensitivity Analysis (TWSA)



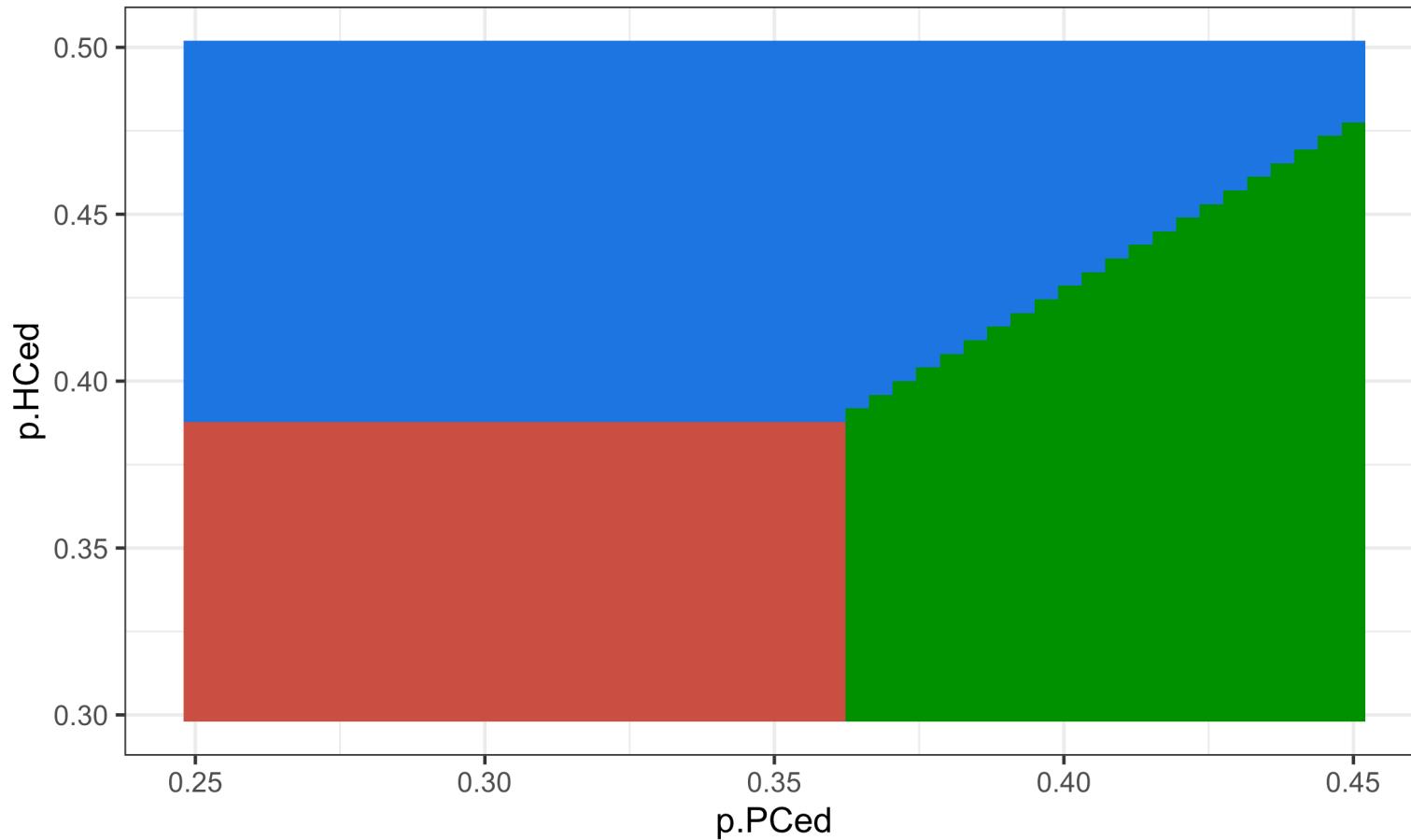
Two-Way Sensitivity Analysis (TWSA)

- Systematically vary *two* parameters over range of uncertainty, keeping all others fixed
 - p.PCed = 25%, p.HCed = 30%
 - p.PCed = 25%, p.HCed = 40%
 - p.PCed = 25%, p.HCed = 50%
 - p.PCed = 30%, p.HCed = 30%
 - p.PCed = 30%, p.HCed = 40%
 - etc...
- Particularly useful if one parameter influences the impact of the other on the optimal decision

Two-Way Sensitivity Analysis (TWSA)

Two-way sensitivity analysis

Net Monetary Benefit



Strategy: Routine Practice Primary Care Hospital Care

How many model runs?

- Consider a model with k parameters
- Assume we want to explore all pairs from the k parameters across a range with a min and max
- Denote # of levels of each parameter explored as “ a ”
 - When p_i is not one of the pairs, it is held at its mean value
 - Per parameter pair, the # of runs = $a^2 \Rightarrow$ total # for all parameters = $\binom{k}{2}a^2$
- If each model run takes 10 seconds, total time is 10*total # for all parameters (assume $a = 2$)
 - TWSA of a 14-parameter model in ~1 hour (compare to 180 for OWSA)

The question we are answering

- What is the marginal change in our outcome, due to a change in our parameter(s) (the ones being explored with the sensitivity analysis), if all others held at their base-case levels
- This does not say anything about what the marginal change would look like if our other parameters took on some other value

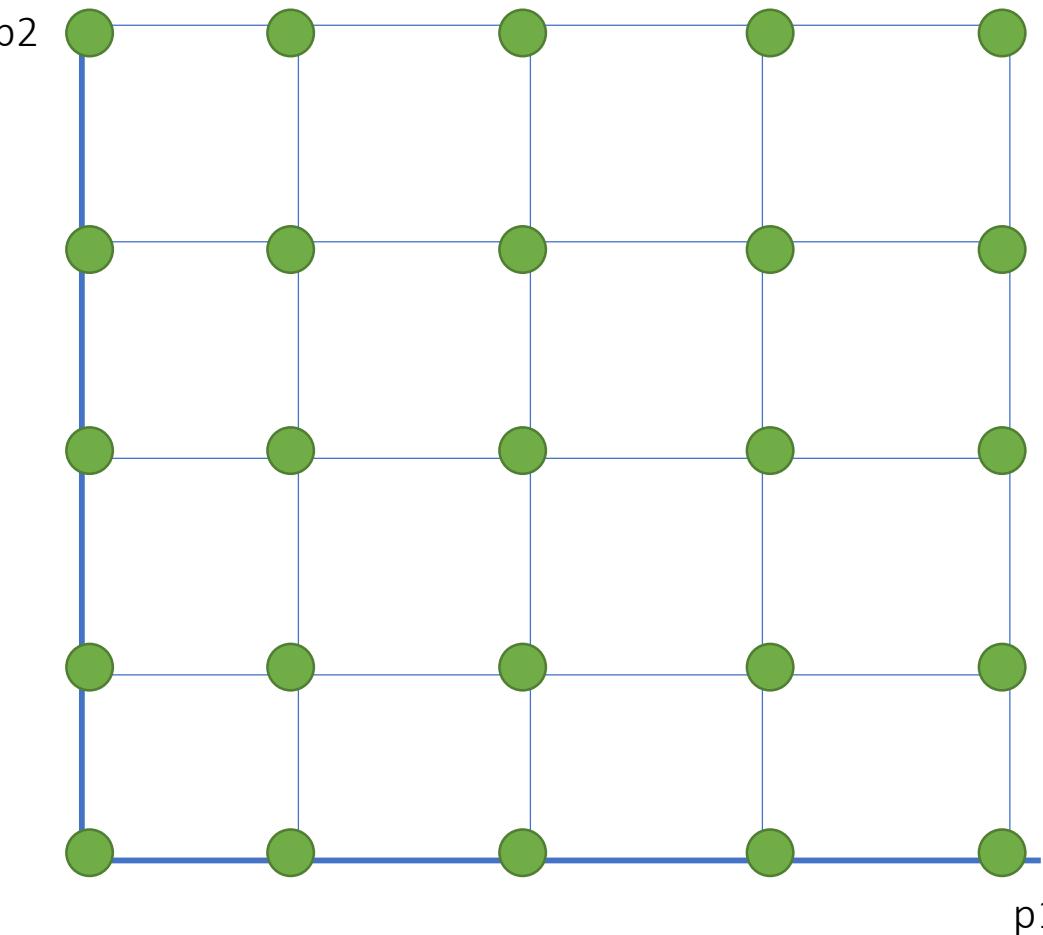
N-way sensitivity analysis

- More runs if more levels explored
- More runs if more parameters are simultaneously included in the sensitivity analysis
 - Per parameter n -tuples # of runs = $a^n \Rightarrow$ total # for all parameters = $\binom{k}{n}a^n$
- If 8 parameter model with 10 seconds per run
 - 2 non-dead states with 4 transitions, 2 costs, 2 QALY weights
 - 8-way sensitivity analysis with 2 levels is 0.7 hours
 - 8-way sensitivity analysis with 3 levels is 17 hours

More efficient ways to explore uncertainty...

- Design of experiments (fractional design) and Morris's method
 - R.J. Duintjer Tebbens et al.
- A k-way sensitivity analysis (k is the total # of parameters in the model) is a “design of experiments” or full factorial approach
 - The fractional design really means, that instead of doing all levels^k possible combinations of parameters, we sample at random X% of these combinations and simulate those
 - Random sampling gives us the general shape with some error due to sampling (which is hopefully small!)

Some parameter combinations more likely than others...



R session

Probabilistic Sensitivity Analysis

Definitions

- Stochastic uncertainty: random variability between identical individuals
- Parameter uncertainty: inadequate knowledge about a parameter value
- Heterogeneity: variability between individuals that can be attributed to individual characteristics
- Structural uncertainty: From model assumptions

Parameter Uncertainty

- Accounts for the likelihood of the values of each of the inputs and their effect on the model outputs
- Parameters have distributions
- Distributions of inputs reflect current knowledge of the parameters

Parameter Uncertainty

- Parameter Uncertainty
 - Rates
 - Probabilities
 - Effectiveness
 - Costs
- Model Structure and Process Uncertainty
 - Alternative Assumptions

Steps of a Probabilistic Sensitivity Analysis

1. Identify sources of parameter uncertainty
2. Characterize uncertain parameters as probability distributions
3. Define correlations as appropriate:
 - Patient-level data
 - Use of regression methods
4. Propagate uncertainty through model using second-order Monte Carlo simulation to describe uncertainty in the modeled outcomes

Which Distributions To Use?

- Beta (a, b)
 - values are between 0 and 1
 - shape is specified by two parameters, a and b
 - a = “number of successes” (or r)
 - $a + b$ = “number of trials” (or n)
- Lognormal (LN) (μ, σ)
 - values are greater than 0
 - values are positively skewed

Some Data

	Failure	Success	
Medicine	a = 15	b = 85	$n_1 = 100$
Surgery	c = 5	d = 95	$n_2 = 100$

One option (assumes independence):

$p_{\text{FailMed}} \sim \text{Beta}(a=15, b=85)$

$p_{\text{FailSurg}} \sim \text{Beta}(a=5, b=95)$

Some “Concerns”

- “Linked” probabilities
 - p_{FailMed} and p_{FailSurg} are not independent
 $p_{\text{FailMed}} = rr_{\text{FailMed}} * p_{\text{FailSurg}}$

Linking probabilities through RR

$$\widehat{RR} = \frac{0.15}{0.05} = 3.0$$

$$SD(\ln \widehat{RR}) = \sqrt{\frac{b}{a \cdot n_1} + \frac{d}{c \cdot n_2}} = \sqrt{\frac{85}{1500} + \frac{95}{500}} = 0.5$$

95% confidence interval for \widehat{RR} : [1.13, 7.94]

Derivation of SD assumes $\ln \widehat{RR} \sim \text{Normal}$

$\Rightarrow \widehat{RR}$ is distributed Lognormal

Distribution for rr_FailMed

- Goal: Find μ and σ of Lognormal distribution with correct mean (3.0) and 95% CI
- Problem: If mean = 3.0 then confidence interval is off (shifted left); if confidence interval is correct then mean is not (3.39)

Distributions in the Example

Variable	Distribution	Mean	S.D.
p_FailSurg	Beta (a=5, b=95)	0.05	0.02
* { p_FailMed Beta (a=15, b=85) 0.15 0.04			
rr_FailMed LN ($\mu=0.97$, $\sigma=0.50$) 3.0 1.60			
mu_Fail LN ($\mu = -3.95$, $\sigma = 0.33$) 0.02 0.007			

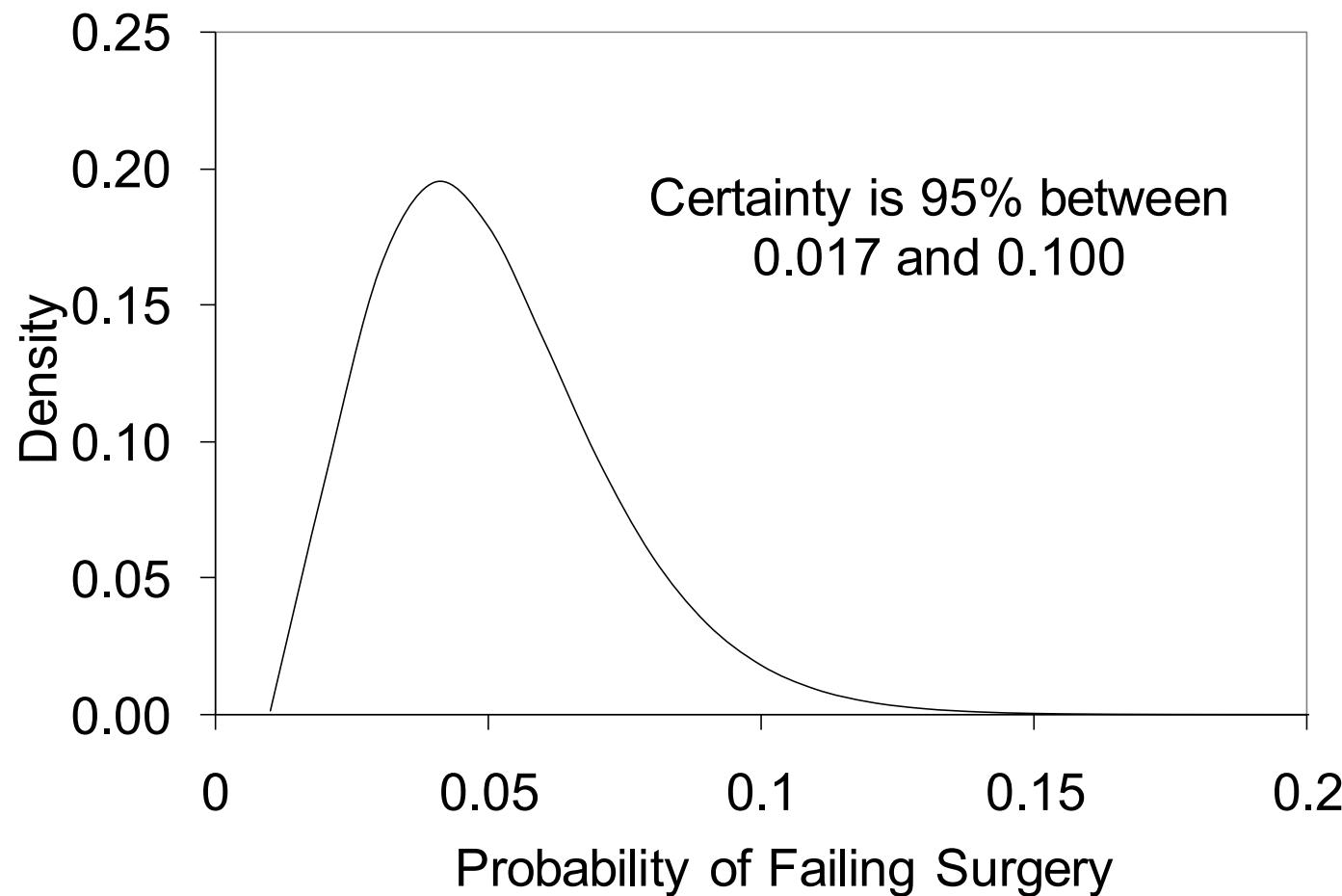
$$\text{Mean of Beta} = a / (a + b); \quad \text{S.D. of Beta} = \sqrt{ab / ((a + b)^2 (a + b + 1))}$$

$$\text{Mean of LN} = \exp(\mu + 0.5\sigma^2); \quad \text{S.D. of LN} = \sqrt{E(X)^2 (\exp(\sigma^2) - 1)}$$

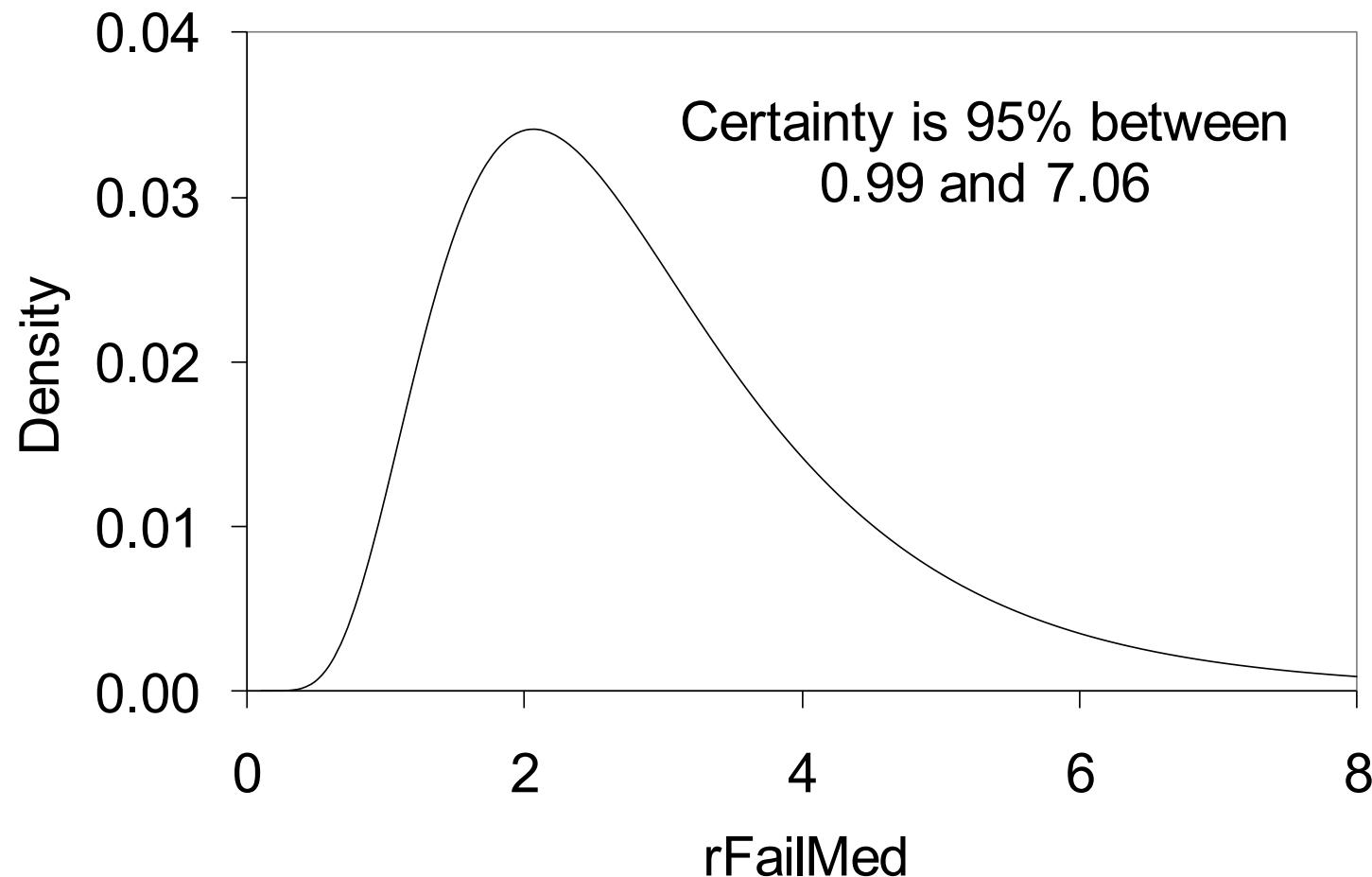
Method-of-Moments Fitting

- From the data, get the mean and standard error
- The mean and standard deviation of Beta distribution are a function of r and n (or a and b)
- Solve for r and n (or a and b)

Beta Density



Lognormal Density



Additional “Concerns”

- Multiple branches off of chance nodes or multiple states to transition to
 - Restructure tree
 - Rescale probabilities $p_i = \frac{q_i}{\sum_{j=1}^n q_j}$
 - Or use the Dirichlet distribution!

Briggs, A. H., Ades, A. E., & Price, M. J. (2003). Probabilistic Sensitivity Analysis for Decision Trees with Multiple Branches: Use of the Dirichlet Distribution in a Bayesian Framework. *Medical Decision Making*,

23(4), 341–350. <https://doi.org/10.1177/0272989X03255922>

Distributions

Distribution	Parameter modeled	Form	Comment
Uniform	Any	Range low-high	All values are equally likely.
Normal	A continuos parameter	Normal(μ, s^2)	
Triangular	Any	Minimum, maximum, likeliest	
Beta	Probability Quality of life weights (utility)	Beta (r, n); r = number of events and n = number of patients. For observed mean μ and standard error s : $r = \mu n; n = \left(\frac{\mu(1-\mu)}{s^2}\right) - 1;$ or Beta (α, β); $\alpha = \left(\frac{1-\mu}{\sigma^2} - \frac{1}{\mu}\right) \mu^2; \beta = \alpha \left(\frac{1}{\mu} - 1\right)$	Bounded between 0 and 1
Dirichlet	Probability in the context of multiple events	Dirichlet($\alpha_1, \alpha_2, \dots, \alpha_K$); α_k number of events/transitions in/to category/state $k = 1, \dots, K$	Extension of the beta distribution, for multiple events

Distributions II

Distribution	Parameter modeled	Form	Comment
Lognormal	Rates; Relative risk; Hazard ratio; Odds ratio; Costs	In(parameter) has a normal distribution with mean and standard error. For observed mean μ and variance σ^2 , the location, m , and scale, s , parameters are: $m = \ln\left(\frac{\mu}{\sqrt{1+\frac{\sigma^2}{\mu^2}}}\right); s = \sqrt{\ln\left(\sqrt{1 + \frac{\sigma^2}{\mu^2}}\right)}$	Values > 0, positively skewed
Gamma	Resource use; Costs	Gamma (α, β) For observed mean μ and standard error s : $\alpha = \frac{\mu^2}{s^2}$; $\beta = \frac{\mu}{s^2}$	
Truncated			Restricting the domain of some other probability distribution
Histogram	Any	non-parametric	Observed relative frequency per value or per interval
Bootstrap	Any	non-parametric	Simulated relative frequency per value

PSA in R

Common naming structure among (most) distributions in R

- “q”+ *dist.* (e.g. `qnorm()`): quantile function
- “d”+ *dist.*(e.g. `dnorm()`): density function
- “p”+ *dist.*(e.g. `pnorm()`): **c.d.f function**
- “r” + *dist.*(e.g. `rnorm()`): **random number generating function**

`sample()`: Random number sampling with(out) replacement and weights (e.g. for bootstrapping)

Resources for PSA in R: dampack package

dampack: Decision-Analytic Modeling Package

A suite of functions for analyzing and visualizing the health economic outputs of mathematical models. This package was developed with funding from the National Institutes of Allergy and Infectious Diseases of the National Institutes of Health under award no. R01AI138783. The content of this package is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The theoretical underpinnings of 'dampack's functionality are detailed in Hunink et al. (2014) <[doi:10.1017/CBO9781139506779](https://doi.org/10.1017/CBO9781139506779)>.

Version: 1.0.2.1000
Depends: R (\geq 3.5), [ggplot2](#) (\geq 3.3.0)
Imports: [ellipse](#), [dplyr](#), [scales](#), [stringr](#), [mgcv](#), [truncnorm](#), [triangle](#), [ggrepel](#), [tidyverse](#), [rlang](#)
Suggests: [testthat](#), [lintr](#), [knitr](#), [rmarkdown](#), [kableExtra](#)
Published: 2024-09-30
DOI: [10.32614/CRAN.package.dampack](https://doi.org/10.32614/CRAN.package.dampack)
Author: Fernando Alarid-Escudero  [aut], Greg Knowlton [aut], Caleb W. Easterly  [aut], David Garibay [ctb, cre], Eva Enns  [aut]
Maintainer: David Garibay <dgari039 at uottawa.ca>
BugReports: <https://github.com/DARTH-git/dampack/issues>
License: [GPL-3](#)
URL: <https://github.com/DARTH-git/dampack>

Install the release version from CRAN

```
install.packages ("dampack")
```

Install the development version from GitHub

```
devtools::install_github ("DARTH-git/dampack")
```

Mean of Ratios or Ratio of Means?

- For each simulation calculate $\Delta C / \Delta E$ and then average over all simulations (mean of ratios)
- Average ΔC and ΔE separately over all simulations and then create the $\Delta C / \Delta E$ ratio (ratio of means)

Stinnett & Paltiel 1997

Net Monetary Benefit (NMB)

- E_d : Health effect of strategy d
- C_d : Cost of strategy d
- λ : willingness-to-pay (WTP) or cost-effectiveness threshold

$$NMB_d = E_d\lambda - C_d$$

- Incremental NMB of d vs i

$$INMB_{d|i} = (E_d - E_i)\lambda - (C_d - C_i)$$

- If $INMB_{d|i} > 0$, d is cost-effective

Stinnett AA, Mullaly J. Net health benefits: a new framework for the analysis of uncertainty in cost-

Stanford | Freeman Spogli Institute
effectiveness analysis. Med Decis Making. 1998 Apr-Jun;18(2 Suppl):S68-80.

Stanford | Health Policy

Net Health Benefit (NHB)

- E_d : Health effect of strategy d
- C_d : Cost of strategy d
- λ : willingness-to-pay (WTP) or cost-effectiveness threshold

$$NHB_d = E_d - \frac{C_d}{\lambda}$$

- Incremental NMB of d vs i

$$INHB_{d|i} = (E_d - E_i) - \frac{(C_d - C_i)}{\lambda}$$

- If $INHB_{d|i} > 0$, d is cost-effective

Decision rule

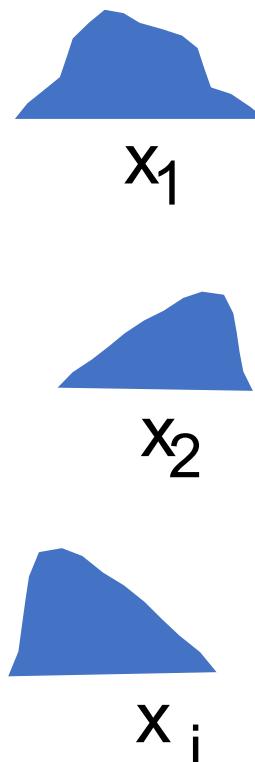
- For a given C/E threshold, the competing choice alternative with the greatest NHB (or NMB) is the most cost-effective option *at that budget constraint*.
- Comparing NHB (or NMB) at a fixed C/E threshold is equivalent to applying the rule of selecting the *largest* competing alternative whose *incremental* C/E ratio is below the C/E threshold.

Probabilistic Sensitivity Analysis (PSA) (2nd order Monte Carlo)

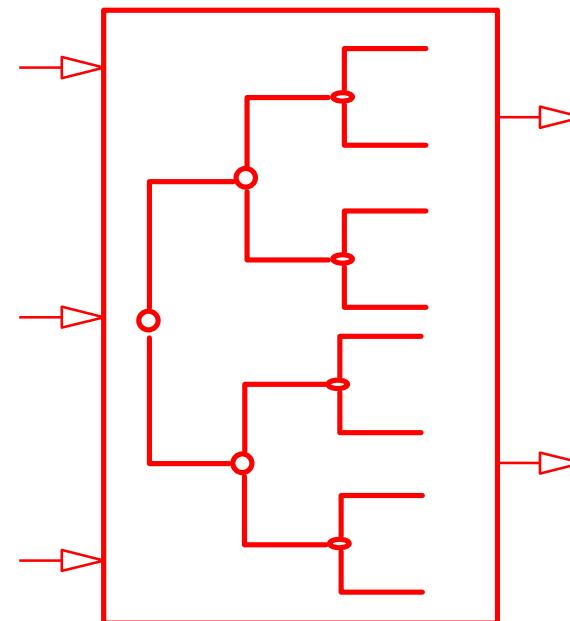
- Replace point estimates in decision model with distributions (mean, variance)
- Randomly draw from each distribution and analyze decision model
- Repeat many times
- Produce distribution of expected outcome
- Doublé et al. (1985)
- Results include means and standard deviations of the expected values of each strategy

Probabilistic Sensitivity Analysis (PSA)

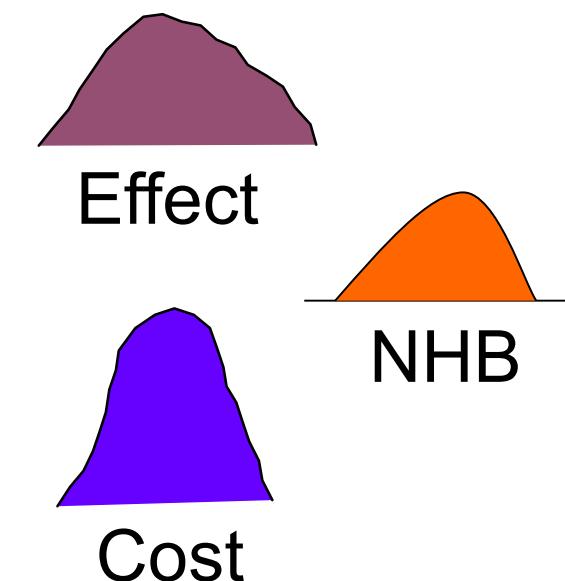
Inputs



Model



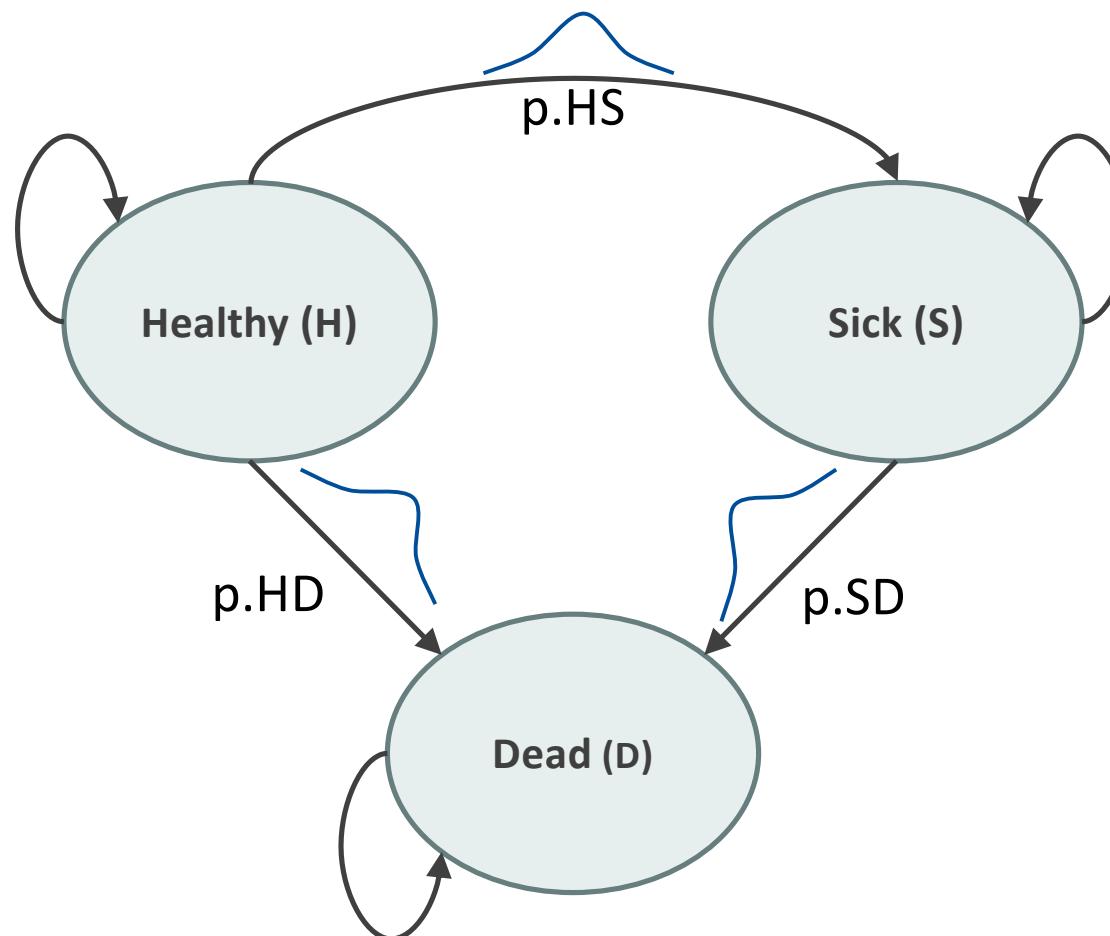
Outputs



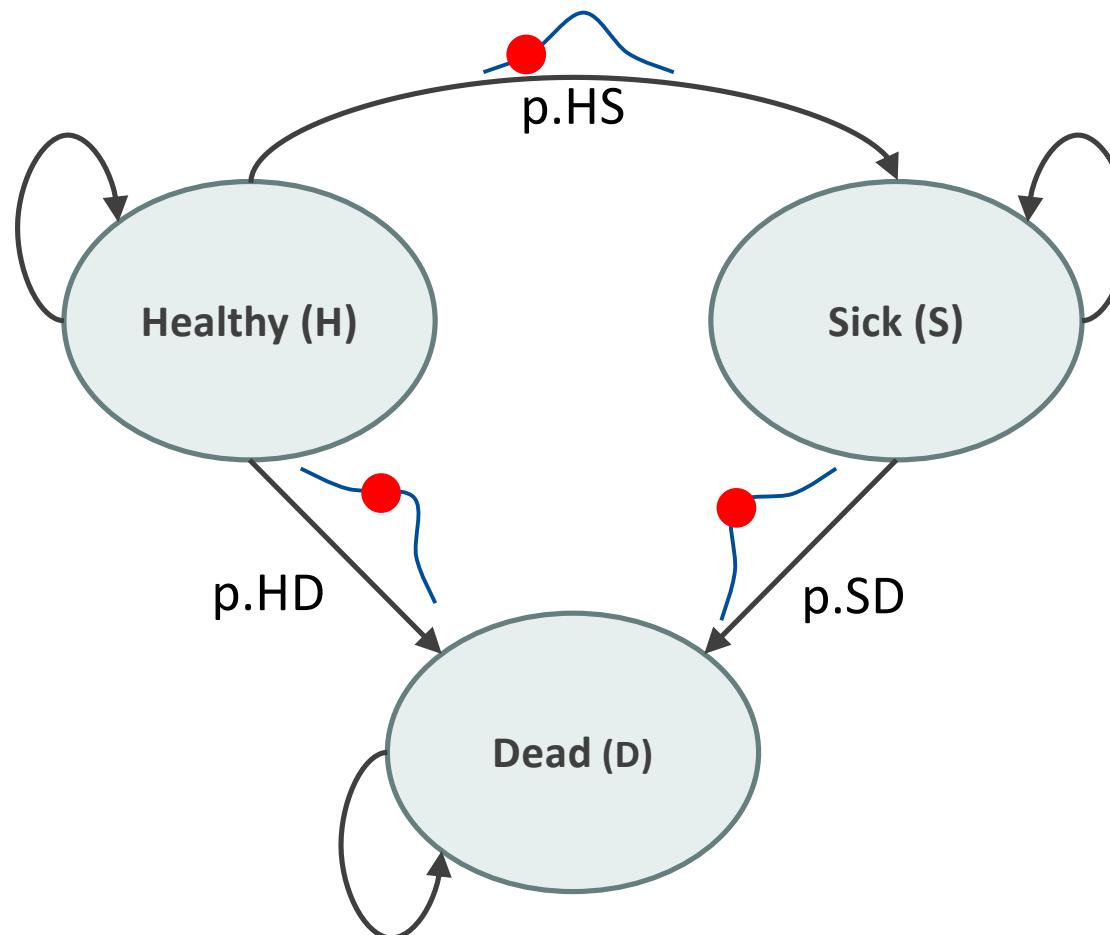
Decision rule accounting for parametric uncertainty

- For a given C/E threshold, the competing choice alternative with the **expected** greatest NHB (or NMB) is the most cost-effective option *at that budget constraint*.
- In other words, the strategy with the greatest **expected** NHB (or NMB) is the **optimal strategy**

Probabilistic Sensitivity Analysis (PSA)



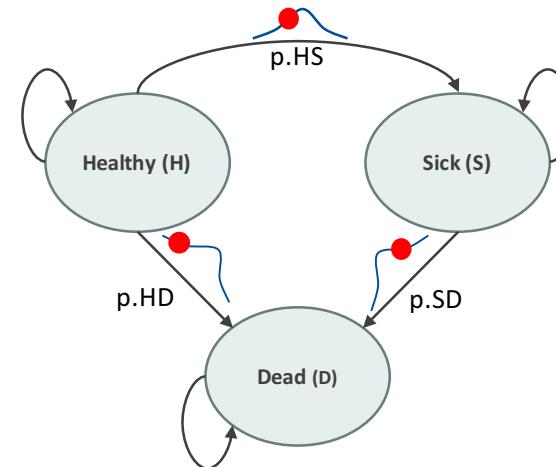
Probabilistic Sensitivity Analysis (PSA)



Matrix Implementation of the Markov Model

Transition probability matrix

$$P^1 = \begin{bmatrix} \mathbf{s} & \mathbf{p} & \mathbf{d} \\ 1 - p_{SP} - p_{SD} & p_{SP} & p_{SD} \\ 0 & 1 - p_{PD} & p_{PD} \\ 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} \mathbf{s} \\ \mathbf{p} \\ \mathbf{d} \end{bmatrix}$$



$$c^1 = \begin{bmatrix} c_S \\ c_P \\ 0 \end{bmatrix} \begin{bmatrix} \mathbf{s} \\ \mathbf{p} \\ \mathbf{d} \end{bmatrix} \quad e^1 = \begin{bmatrix} e_S \\ e_P \\ 0 \end{bmatrix} \begin{bmatrix} \mathbf{s} \\ \mathbf{p} \\ \mathbf{d} \end{bmatrix}$$

Calculating total costs & effects

Total effects (TE):

$$E^l = M e^l$$
$$TE^l = \boldsymbol{\iota}_T E^l$$

Total costs (TC):

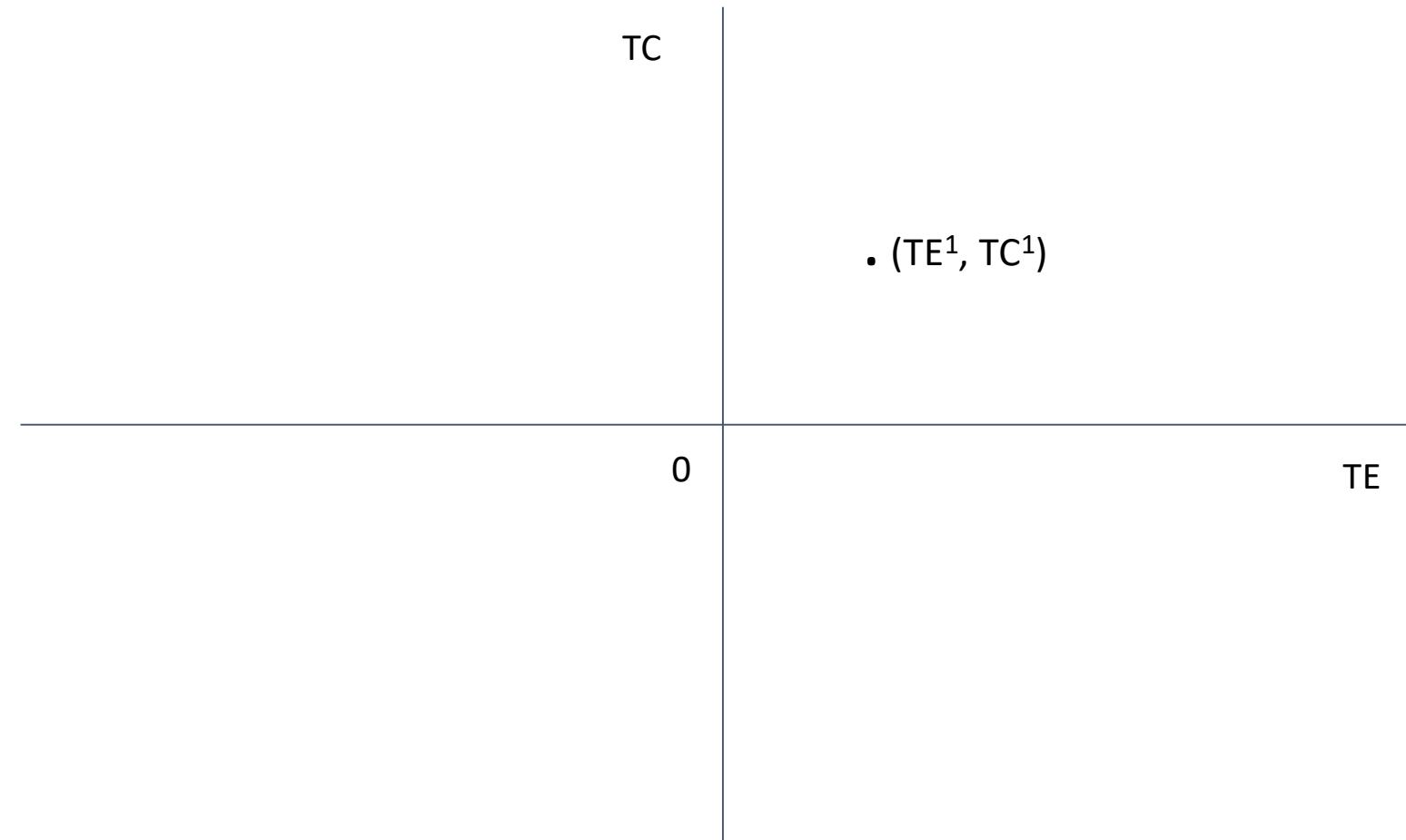
$$C^l = M c^l$$
$$TC^l = \boldsymbol{\iota}_T C^l$$

Net Monetary Benefit (NMB):

$$NMB^1 = TE^1 \lambda - TC^1$$

$\boldsymbol{\iota}_T$: $1 \times T$ vector of ones

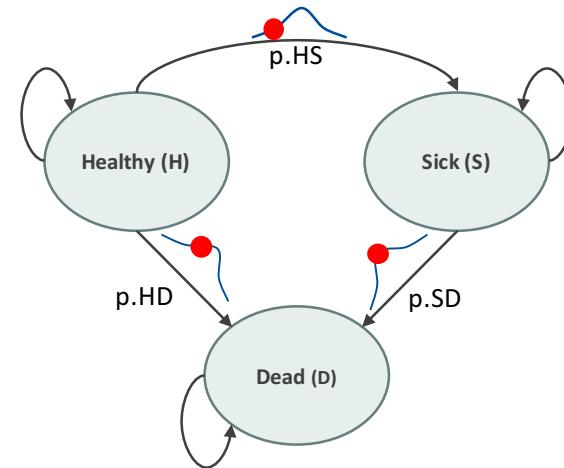
Presenting the PSA results



Matrix Implementation of the Markov Model

Transition probability matrix

$$P^2 = \begin{bmatrix} H & S & D & D \\ 1 - p_{SP} - p_{SD} & p_{SP} & p_{SD} & 0 \\ 0 & 1 - p_{PD} & p_{PD} & 0 \\ 0 & 0 & 1 & 0 \end{bmatrix}^2 \begin{matrix} S \\ P \\ D \end{matrix}$$



$$c^2 = \begin{bmatrix} c_S \\ c_P \\ 0 \end{bmatrix}^2 \quad e^2 = \begin{bmatrix} e_S \\ e_P \\ 0 \end{bmatrix}^2 \quad \text{comes}$$

Calculating total costs & effects

Total effects (TE):

$$E^2 = M^2 e^2$$
$$TE^2 = \boldsymbol{l}_T E^2$$

Total costs (TC):

$$C^2 = M^2 c^2$$
$$TC^2 = \boldsymbol{l}_T C^2$$

Net Monetary Benefit (NMB):

$$NMB^2 = TE^2 \lambda - TC^2$$

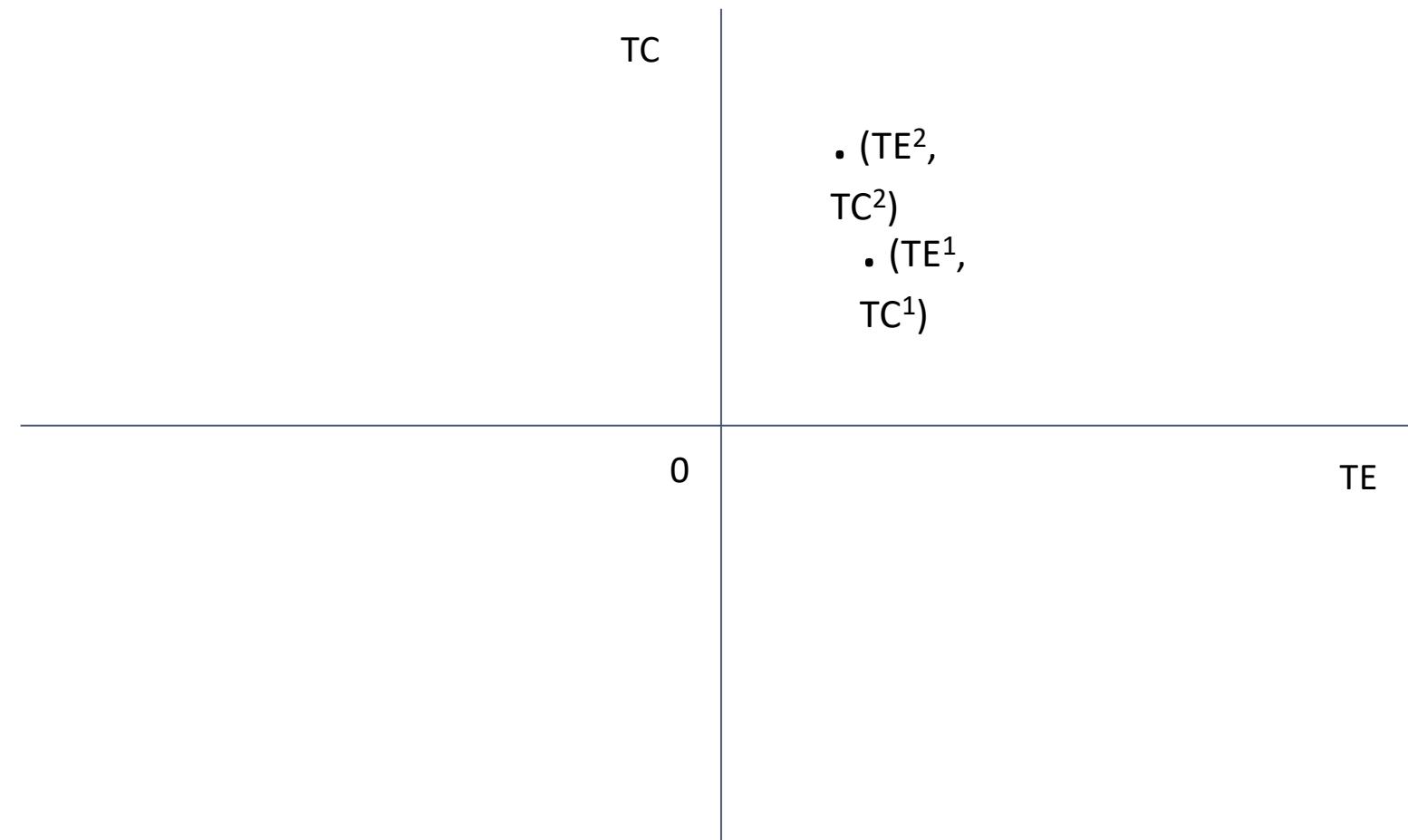
\boldsymbol{l}_T : $1 \times T$ vector of ones

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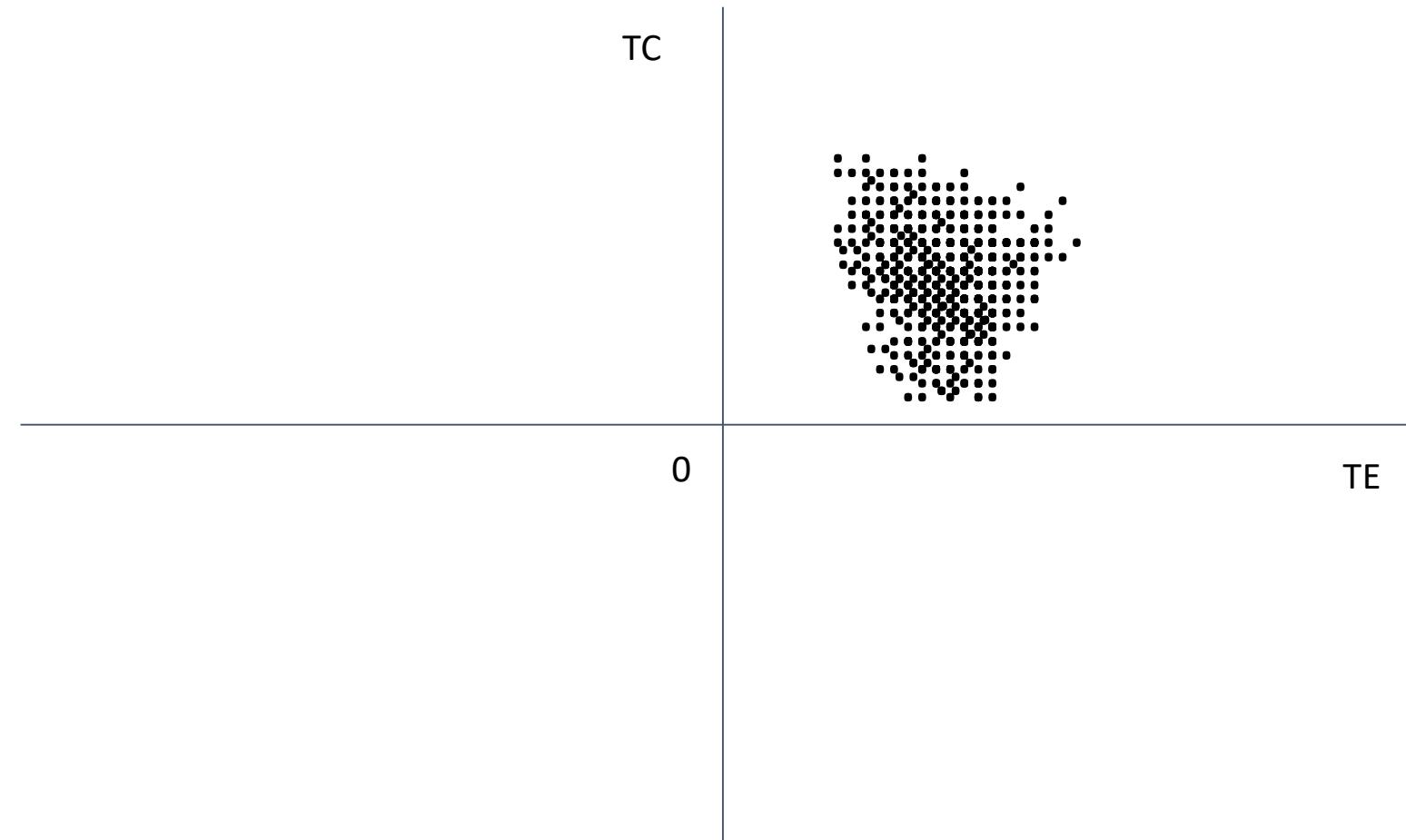
Willingness-to-pay or cost-effectiveness threshold

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Presenting the PSA results



Presenting the PSA results



Example of a PSA dataset

# Sim	Param 1	Param 2	Param 3	Param 4	NMB A	NMB B	NMB C
1	0.8878	1.5732	0.2263	0.4163	442531	446259	445305
2	1.1635	2.1315	0.1223	0.2879	443420	445029	445305
3	0.6734	1.6928	0.0587	0.3332	470225	448650	445305
4	0.6551	2.0667	0.0468	0.3559	475179	442967	445305
5	0.8546	2.5707	0.1000	0.3562	454703	436838	445305
6	0.5778	1.3295	0.3880	0.1979	440600	466317	445305
7	1.0599	1.9610	0.0522	0.2008	456628	453941	445305
8	0.5983	1.7325	0.1957	0.3190	449875	448901	445305
9	1.0920	1.4737	0.1201	0.3320	445512	451526	445305
10	0.9115	1.1154	0.2729	0.6097	440091	444312	445305

Decision Uncertainty

- The probability that a given strategy, d , is cost-effective

$$\Pr(CE)_d = \frac{N_d}{N}$$

- where N_d is the number of simulations in which strategy d has the maximum net benefit and N is the total number of PSA samples.

Cost-Effectiveness Acceptability Curves (CEAC)

- CEAC display the probability that each strategy is cost-effective given a certain willingness-to-pay (WTP) threshold
- The representation of $\Pr(CE)_d$ for all D strategies as a function of λ

Construction of CEAC

$N = 10$

$N_A = 5; N_B = 3; N_C = 2$

# Sim	Param 1	Param 2	Param 3	Param 4	NMB A	NMB B	NMB C	Best Strategy
1	0.8878	1.5732	0.2263	0.4163	442531	446259	445305	B
2	1.1635	2.1315	0.1223	0.2879	443420	445029	445305	C
3	0.6734	1.6928	0.0587	0.3332	470225	448650	445305	A
4	0.6551	2.0667	0.0468	0.3559	475179	442967	445305	A
5	0.8546	2.5707	0.1000	0.3562	454703	436838	445305	A
6	0.5778	1.3295	0.3880	0.1979	440600	466317	445305	B
7	1.0599	1.9610	0.0522	0.2008	456628	453941	445305	A
8	0.5983	1.7325	0.1957	0.3190	449875	448901	445305	A
9	1.0920	1.4737	0.1201	0.3320	445512	451526	445305	B
10	0.9115	1.1154	0.2729	0.6097	440091	444312	445305	C

$$\Pr(CE)_A = \frac{5}{10} = 0.5$$

$$\Pr(CE)_B = \frac{3}{10} = 0.3$$

$$\Pr(CE)_C = \frac{2}{10} = 0.2$$

Highest probability

Cost-Effectiveness Acceptability Frontier (CEAF)

- CEAF displays which strategy has highest expected net benefit given a certain WTP threshold
- Let $NMB_{i,d}$ be the NMB for the i -th simulation of the PSA data set for strategy d , and $\overline{NMB} = [\overline{NMB}_1 \overline{NMB}_2 \cdots \overline{NMB}_d \cdots \overline{NMB}_D]$ be the expected NMB of all D strategies averaged across all N simulations of a PSA, where the expected \overline{NMB}_d is defined as

$$\overline{NMB}_d = \frac{1}{N} \sum_{i=1}^N \overline{NMB}_{i,d} \quad \forall d \in [1, \dots, D]$$

- Then, the **optimal strategy** based on the **highest expected net benefit**, d^* , is defined as:

$$d^* = \operatorname{argmax}_{d \in [1, \dots, D]} \{\overline{NMB}_d\}$$

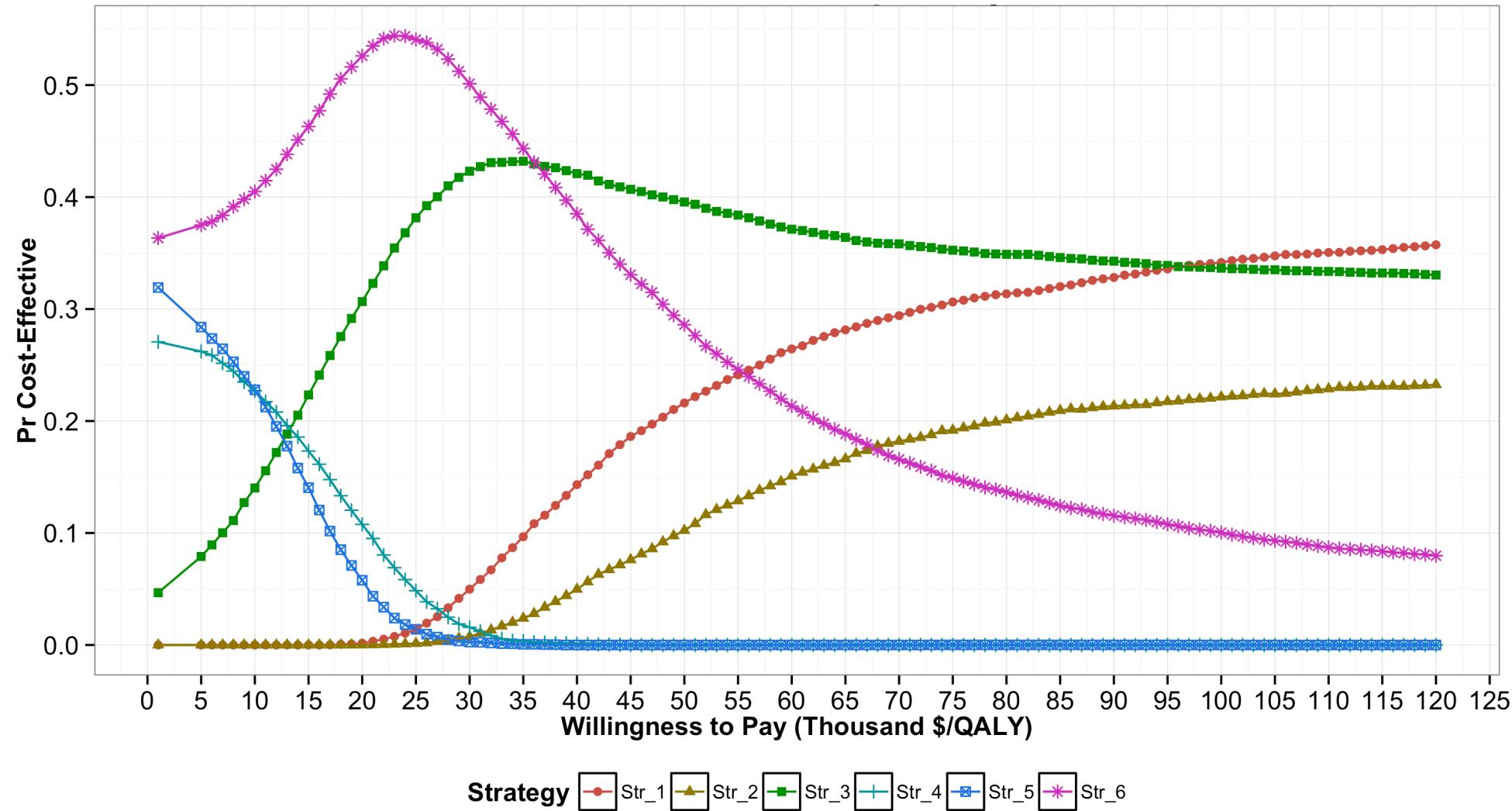
Construction of CEAF

# Sim	Param 1	Param 2	Param 3	Param 4	NMB A	NMB B	NMB C	Best Strategy
1	0.8878	1.5732	0.2263	0.4163	442531	446259	445305	B
2	1.1635	2.1315	0.1223	0.2879	443420	445029	445305	C
3	0.6734	1.6928	0.0587	0.3332	470225	448650	445305	A
4	0.6551	2.0667	0.0468	0.3559	475179	442967	445305	A
5	0.8546	2.5707	0.1000	0.3562	454703	436838	445305	A
6	0.5778	1.3295	0.3880	0.1979	440600	466317	445305	B
7	1.0599	1.9610	0.0522	0.2008	456628	453941	445305	A
8	0.5983	1.7325	0.1957	0.3190	449875	448901	445305	A
9	1.0920	1.4737	0.1201	0.3320	445512	451526	445305	B
10	0.9115	1.1154	0.2729	0.6097	440091	444312	445305	C
				Expectd NMB ->	451876	448474	445305	

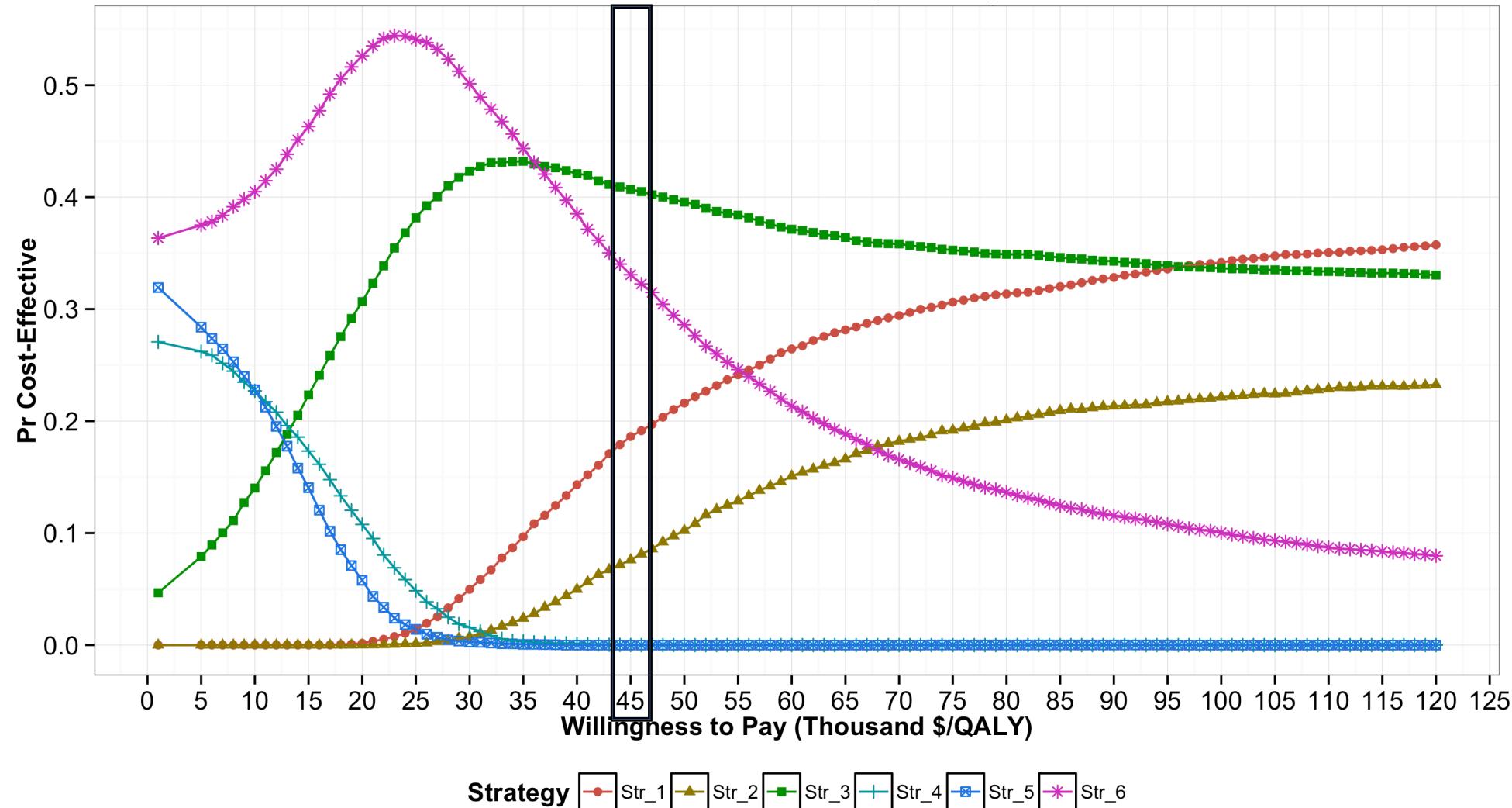


Highest expected net benefit = Optimal strategy

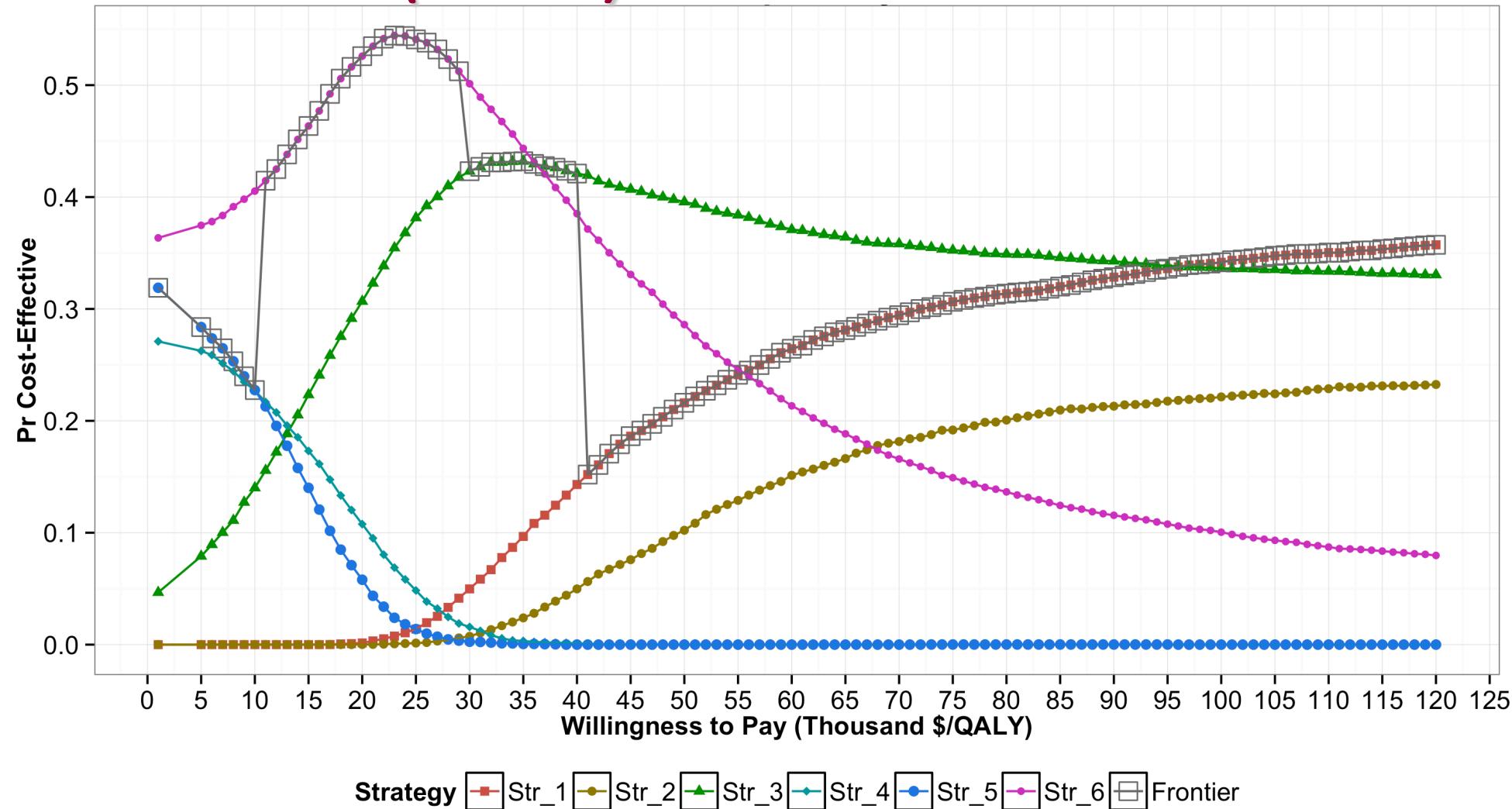
Cost-Effectiveness Acceptability Curves (CEACs)



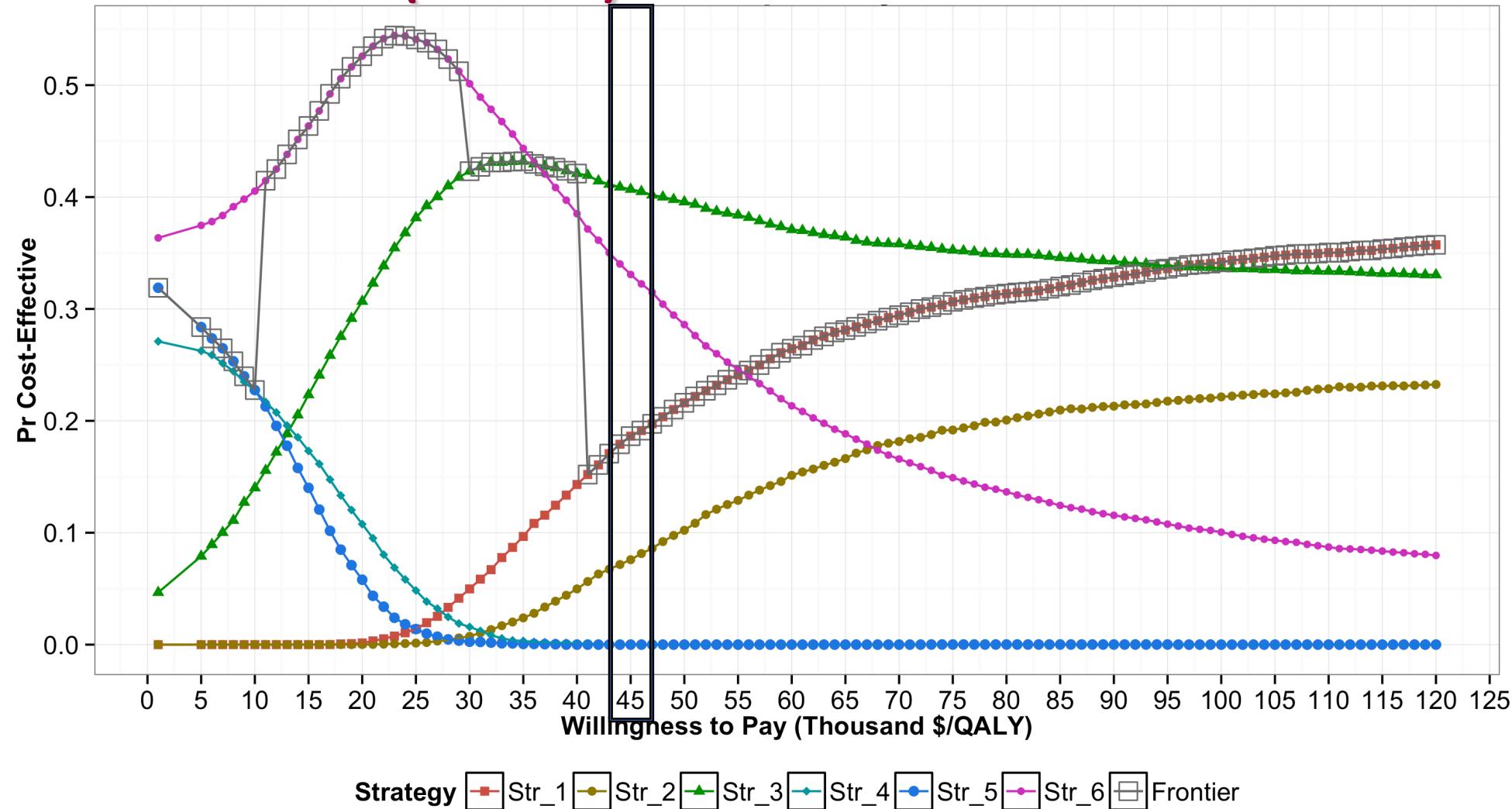
Cost-Effectiveness Acceptability Curves (CEACs)



Cost-Effectiveness Acceptability Curves (CEACs) and Frontier (CEAF)

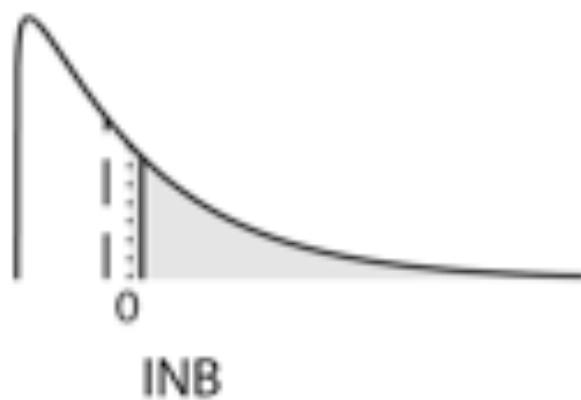


Cost-Effectiveness Acceptability Curves (CEACs) and Frontier (CEAF)

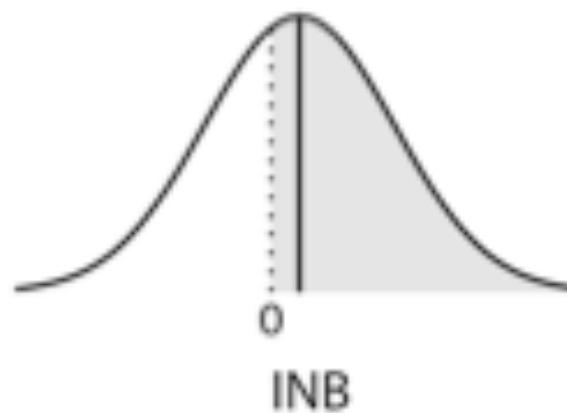


Distributions of Incremental NMB

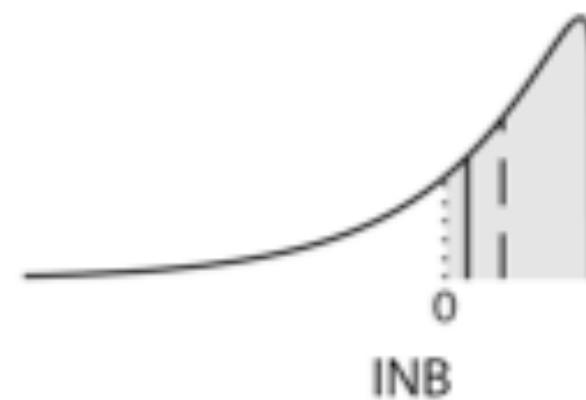
(A) Right skewed



(B) Symmetrical



(C) Left skewed



Limitations of CEACs and CEAF

- Only provide certain level of **comfort** in a decision but do not influence decision making
- Not actual **influence** on policy recommendation
- Could be **misleading** -> the strategy that is **most likely** to be cost-effective **should not** be conflated with the strategy that is **optimal** in expectation in the decision-making process

Limitations of CEACs

- Neither capture the magnitude of the **net benefit lost** in the proportion of PSA samples when chosen strategy is not cost-effective
- The **expected loss** in net benefits is truly the concern of the decision-maker because this represents the **foregone benefits** resulting from having chosen a given strategy
- Do not communicate the ordinal information in the ranking of the strategies by their expected benefits
 - Useful when implementing the optimal strategy is not feasible.

Value of Information

- How likely we are to make the wrong decision
- And how bad it is to make the wrong decision
- Cost of uncertainty (i.e., expected loss based on current information)
- Expected benefit of potential future research
- Can produce claims such as “**How likely AND how bad?**”

Expected Value of Perfect Information (EVPI)

- Value of **eliminating** all sources of **uncertainty** for all parameters (θ)
- **Maximum** willingness to pay to get perfect information on all parameters
- **No** future data collection effort **should exceed** EVPI

Overcoming limitations of CEACs and CEAF

- These limitations can be addressed by using **expected loss curves** (ELCs), previously proposed by others (Eckermann et al., 2008)
- ELCs present a **quantification of the consequences** of choosing a **suboptimal strategy** in terms of expected foregone benefits as a function of WTP threshold
- ELCs also display the **optimal strategy** (like CEAF), the **value of eliminating** current level of **decision uncertainty** through additional research (like EVPI), and the **ranking of strategies** in terms of expected losses

Definition of expected losses

Expected loss of strategy d , \bar{L}_d , averaged across all N simulations of a PSA

$$\bar{L}_d = \frac{1}{N} \sum_{i=1}^N [B_{i,d_i^*} - B_{i,d}]$$

where $B_{i,d_i^*} = \max_d (B_{i,d})$ is the net benefit of the optimal strategy for the i -th PSA sample, denoted d_i^*

Optimality criteria and VOI with expected losses

- Once the expected loss is calculated for all D strategies, it is possible to determine both the optimal strategy and the EVPI, because:
 1. For a risk-neutral decision maker, the optimal strategy is the strategy with the **highest expected benefit**, which is equivalent to the strategy with the **lowest expected loss**
 2. The **expected loss of the optimal strategy** equals the **EVPI**

Expected Loss Curves (ELCs)

- ELCs are a representation of the expected loss of all D strategies

$$L = [\bar{L}_1 \ \bar{L}_2 \ \cdots \ \bar{L}_d \ \cdots \ \bar{L}_D]$$

as a function of WTP

- The **lower envelope** of the ELCs is the expected loss of the **optimal strategy** and also the **EVPI**

- ELCs reveal by how much the optimal strategy is **better than** each of the other alternatives in terms of expected foregone benefits

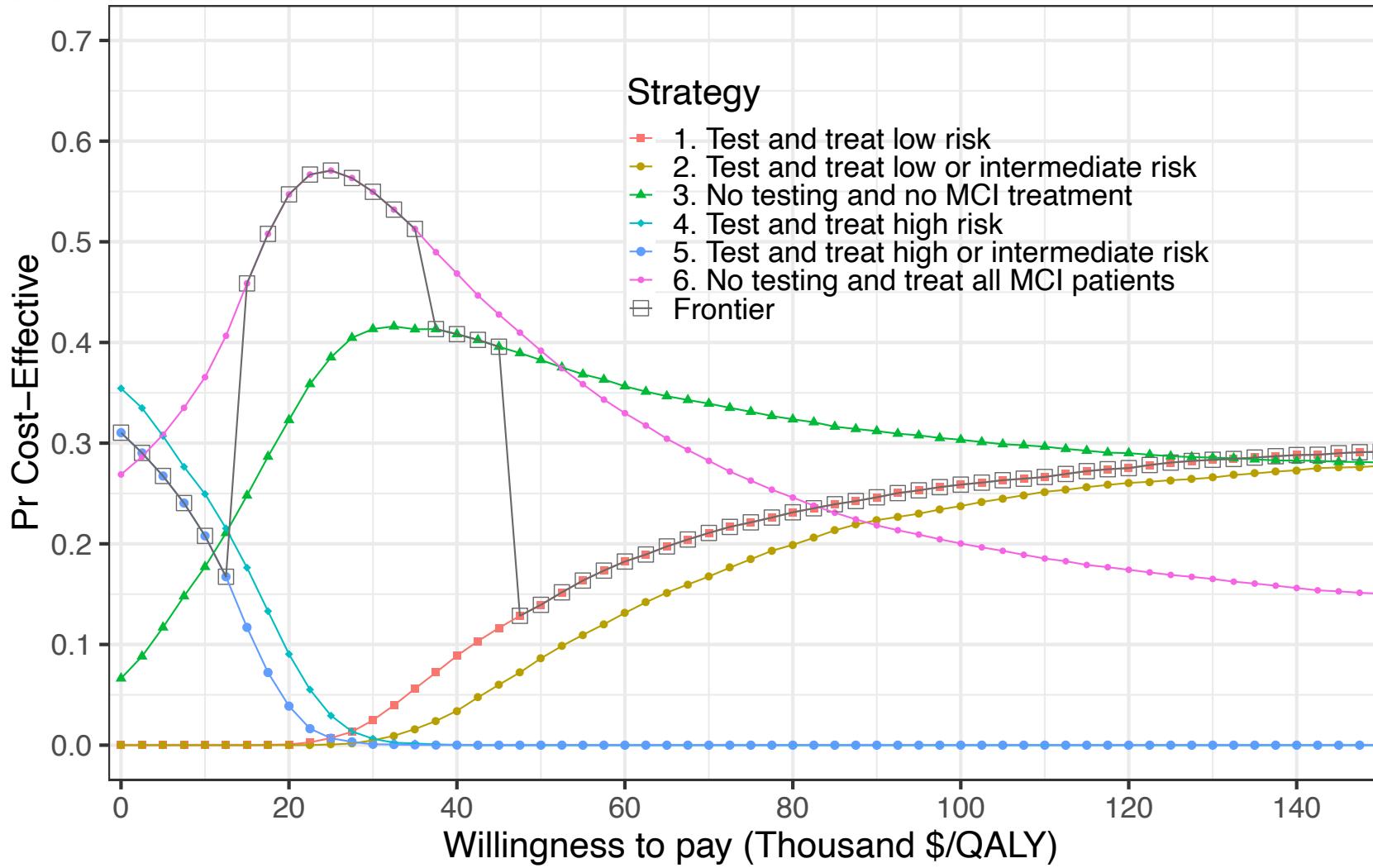
Alarid-Escudero F, Enns EA, Kuntz KM, Michaud TL, Jalal H. "Time Traveling Is Just Too Dangerous" But Some Methods Are Worth Revisiting: The Advantages of Expected Loss Curves Over Cost-Effectiveness Acceptability Curves and Frontier. *Value Health.* 2019;22(5):S11-S18.

Construction of ELCs

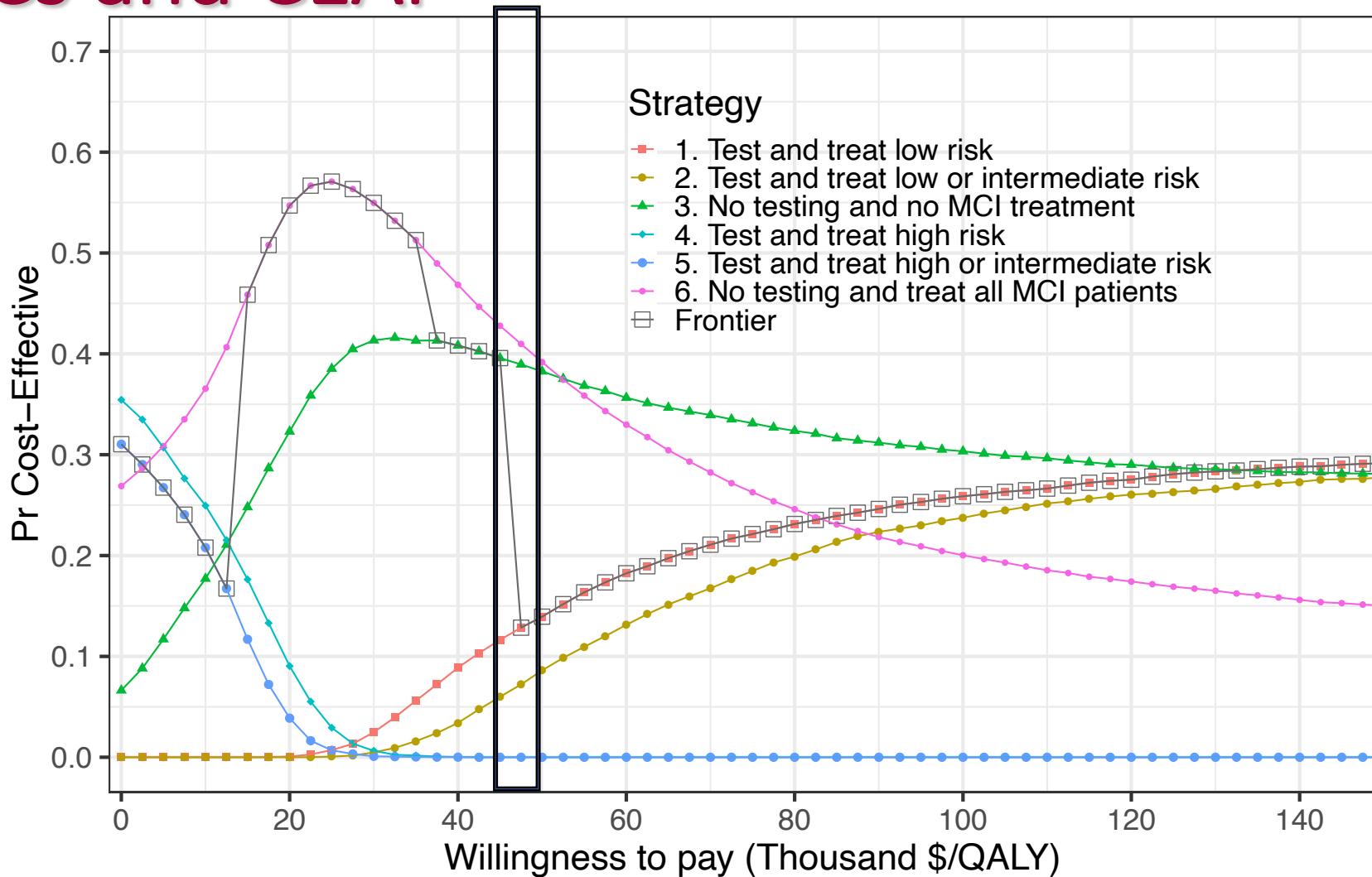
# Sim	NMB A	NMB B	NMB C	Best Strategy	Highest NMB	Loss A	Loss B	Loss C
1	442531	446259	445305	B	446259	3728	0	953
2	443420	445029	445305	C	445305	1885	277	0
3	470225	448650	445305	A	470225	0	21575	24920
4	475179	442967	445305	A	475179	0	32212	29874
5	454703	436838	445305	A	454703	0	17864	9398
6	440600	466317	445305	B	466317	25717	0	21012
7	456628	453941	445305	A	456628	0	2687	11323
8	449875	448901	445305	A	449875	0	974	4570
9	445512	451526	445305	B	451526	6014	0	6221
10	440091	444312	445305	C	445305	5214	993	0
					Expected Loss ->	4256	7658	10827

Lowest expected loss = Optimal strategy

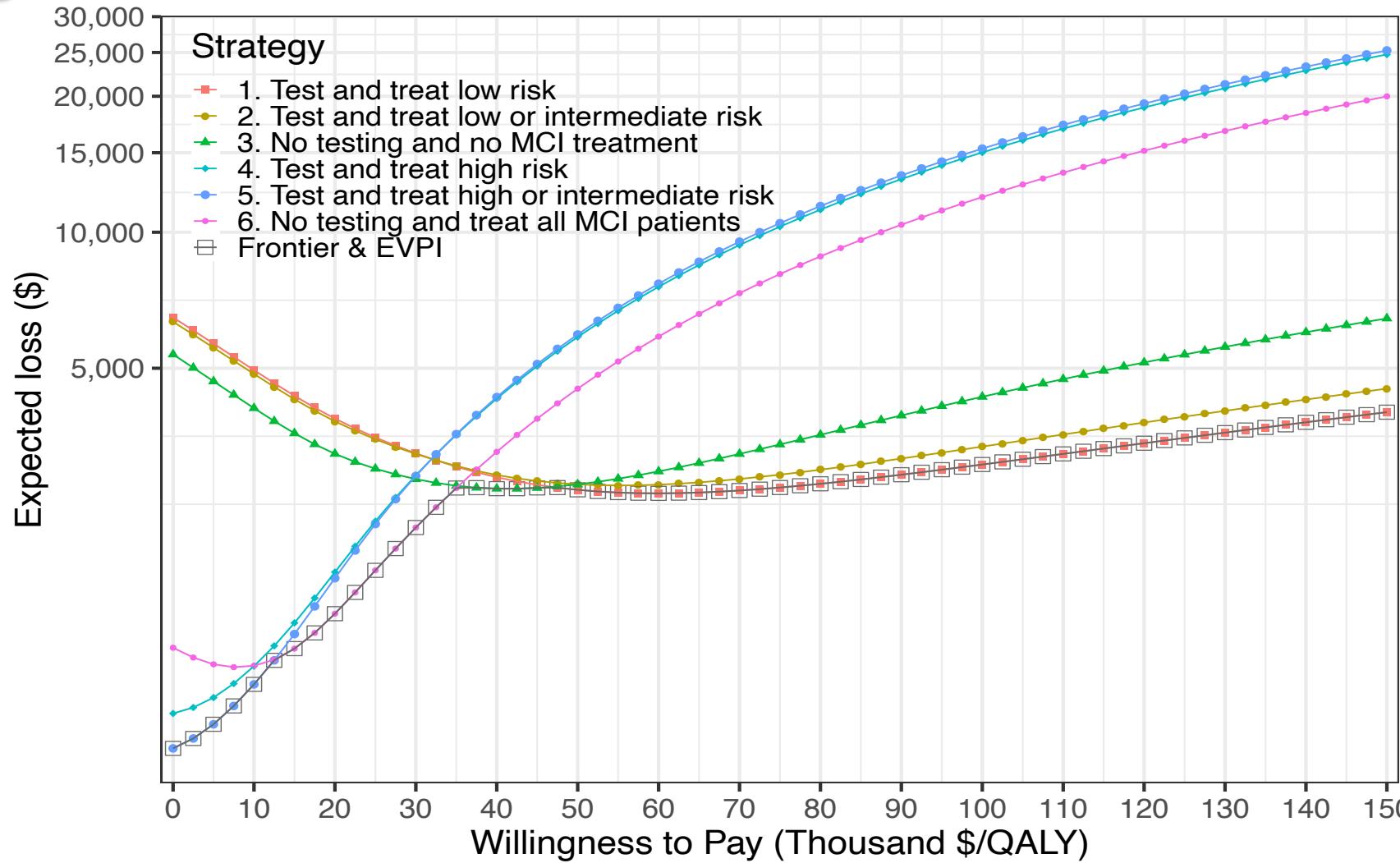
CEACs and CEAF



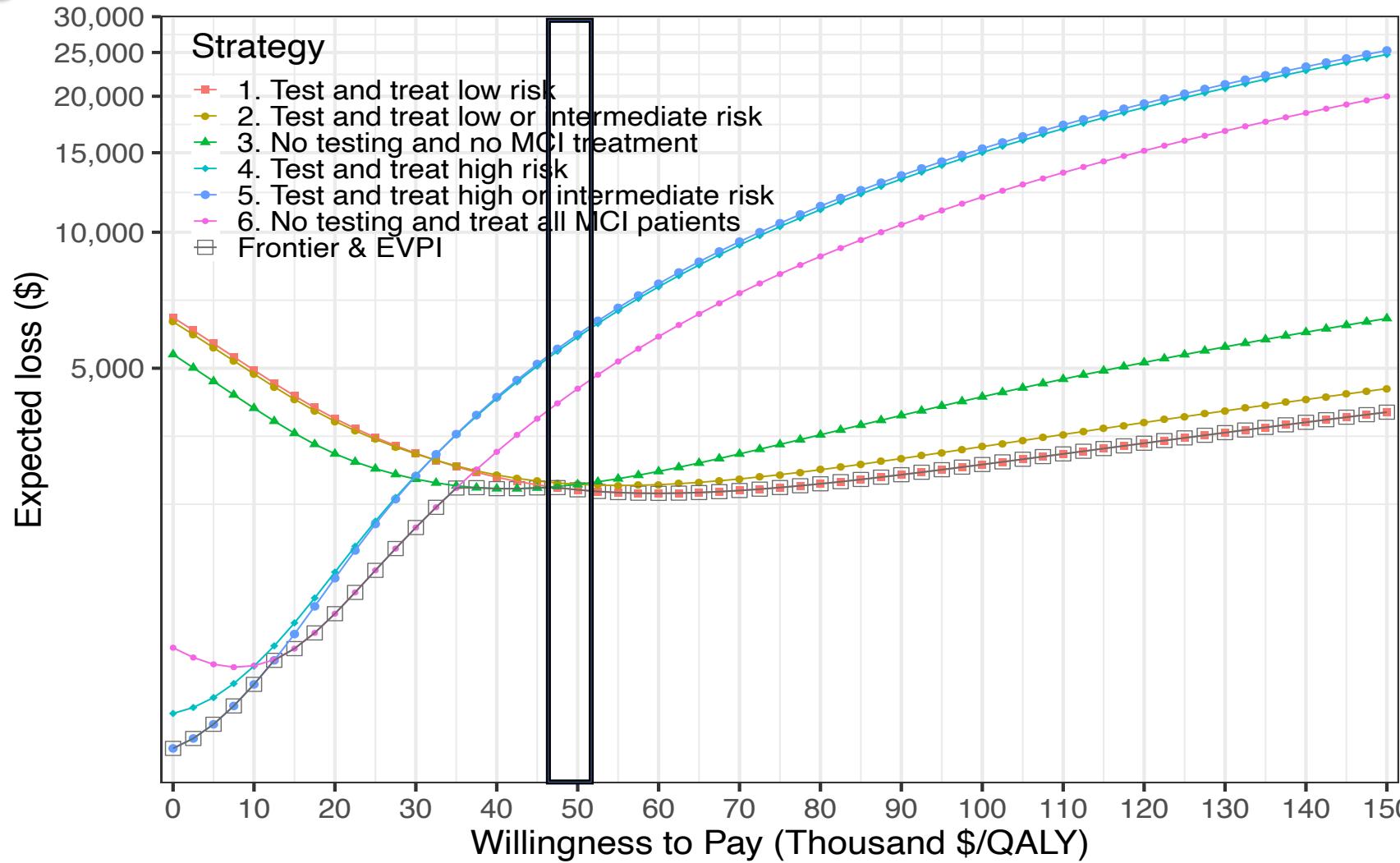
CEACs and CEAF



ELCs



ELCs



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“Time Traveling Is Just Too Dangerous” but Some Methods Are Worth Revisiting: The Advantages of Expected Loss Curves Over Cost-Effectiveness Acceptability Curves and Frontier

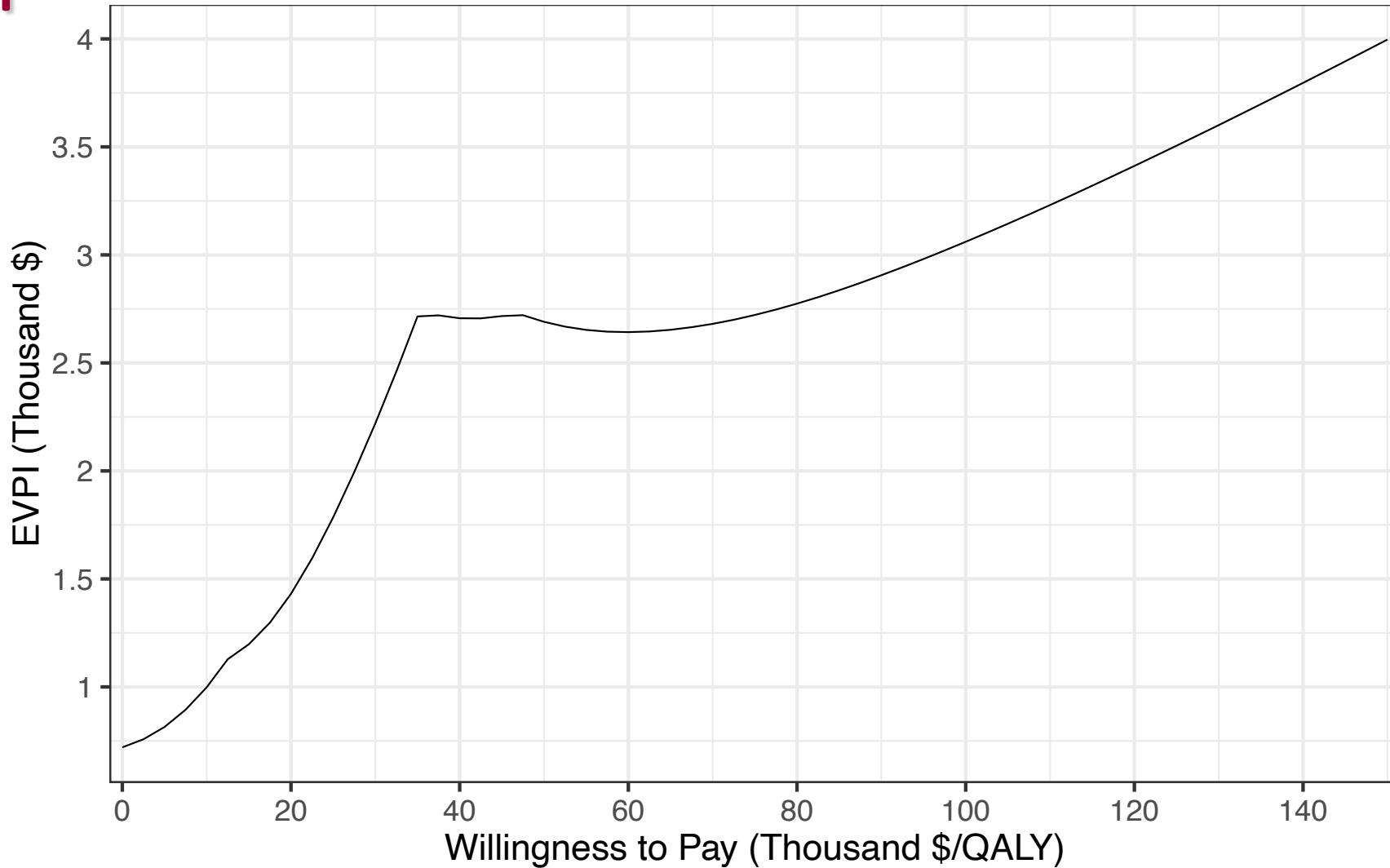
Fernando Alarid-Escudero, PhD¹  · Eva A. Enns, PhD² · Karen M. Kuntz, ScD² · Tzeyu L. Michaud, PhD³ · Hawre Jalal, MD, PhD⁴

Affiliations & Notes ▾ Article Info ▾

<https://pubmed.ncbi.nlm.nih.gov/31104743/>

<https://www.valueinhealthjournal.com/article/S1098-3015%2819%2930133-0/fulltext?>

EVPI



Which should I do?

- Do OWSA/Thresholds to learn how your model responds (and to debug) for **all** parameters
- Do a few MWSA to see how things interact (pick things that are influential/near influential on OWSA)
- Do PSA b/c some journals require, b/c n-way deterministic analyses are impossible, to start to get at uncertainty (important caveats we have discussed)
- Do Scenario Analyses: Clinically/Policy driven combinations of alternative parameters to ask what-if questions that are relevant – no claim about capturing uncertainty but easier to work into a narrative describing your analyses results in a way relevant to decision makers

How do I describe these?

- **Model-centric**: “We varied model parameter p_complex_thing between 0.037 and 0.078 and found the ICER to fall from \$68,224.4456 to \$12,307.2380, showing that the model’s conclusions were sensitive to this value”
- **Policy-centric**: “There is controversy about the true effectiveness of the intervention given that RCTs have found values as low as 0.037 and as high as 0.078. We assessed whether our main findings were sensitive to this range of values, finding that when effectiveness was high, the intervention’s cost per QALY gained fell from approximately \$68,000 to just over \$12,000, which is below conventionally used willingness to pay values for health, demonstrating that conclusions are sensitive to this value.”

Sage advice we have heard

- Explore sensitivity/uncertainty in your model. It is as at least as important (if not more so) than the base case analysis

R session

Value of Information Analysis

- What information?
- Example of value of information:
 - Value of collecting information from 100 people is \$5000?
 - How did we know that?
- Or rather “Cost of uncertainty” ?
 - Same concept

Using Value of Information Analysis to Prioritise Health Research

Some Lessons from Recent UK Experience

Karl P. Claxton^{1,2} and Mark J. Sculpher¹

¹ Centre for Health Economics, University of York, York, England

² Department of Economics and Related Studies, University of York, York, England

Abstract

Decisions to adopt, reimburse or issue guidance on the use of health technologies are increasingly being informed by explicit cost-effectiveness analyses of the alternative interventions. Healthcare systems also invest heavily in research and development to support these decisions. However, the increasing transparency of adoption and reimbursement decisions, based on formal analysis, contrasts sharply with research prioritisation and commissioning. This is despite the fact that formal measures of the value of evidence generated by research are readily available.

The results of two recent opportunities to apply value of information analysis to directly inform policy decisions about research priorities in the UK are presented. These include a pilot study for the UK National Co-ordinating Centre for Health Technology Assessment (NCCHTA) and a pilot study for the National Institute for Health and Clinical Excellence (NICE). We demonstrate how these results can be used to address a series of policy questions, including: is further research required to support the use of a technology and, if so, what type of research would be most valuable? We also show how the results can be used to address other questions such as, which patient subgroups should be included in subsequent research, which comparators and endpoints should be included, and what length of follow up would be most valuable.

Viewpoint

A rational framework for decision making by the National Institute For Clinical Excellence (NICE)

Karl Claxton, Mark Sculpher, Michael Drummond

Regulatory and reimbursement authorities face uncertain choices when considering the adoption of health-care technologies. In this Viewpoint, we present an analytic framework that separates the issue of whether a technology should be adopted on the basis of existing evidence from whether more research should be demanded to support future decisions. We show the application of this framework to the assessment of health-care technologies using a published analysis of a new drug treatment for Alzheimer's disease. The results of the analysis show that the amount and type of evidence required to support the adoption of a health technology will differ substantially between technologies with different characteristics. Additionally, the analysis can be used to aid the efficient design of research. We discuss the implications of adoption of this new framework for regulatory and reimbursement decisions.

Many countries now request that manufacturers of health-care technologies provide evidence for their cost-effectiveness to support applications for funding by the health-care system. This approach was first used in Australia¹ and Ontario, Canada² in making decisions about funding new medicines, and has also been used by several managed care groups in the USA.³ Since then, in the UK, the National Institute for Clinical Excellence (NICE) has done technology appraisals that include analysis of the cost-effectiveness of interventions

Administration in the USA ask manufacturers to show safety and efficacy in experimental studies. In some instances, these studies can also provide data for costs. Data from these phase III registration trials have restrictions, however, for making decisions about reimbursement.⁵ First, decisions on cost-effectiveness should be based on the comparison of a new intervention with current practice, rather than with a placebo, as is usually the case in these trials. Second, phase III trials tend to be explanatory (rather than

VOI

- Uncertainty in every decision
- There's a **probability** of making the **wrong decision**
- Are there consequences for making the wrong decision?
 - Costs?
 - Foregone benefit?
 - Size of the population being affected by the decision?

VOI in essence....

- How likely we are to make the wrong decision and how bad it is to make the wrong decision
- Cost of uncertainty (i.e., expected loss based on current information)
- Expected benefit of research

Warm up exercise

Let's take it to the Matrix...

A Warm-up Exercise

- 100 patients have the Flu, but we don't know what type of flu they have
 - Blue flu, or
 - Red flu
- Neo is the policy-maker who **must** decide between two drugs to save the most lives
 - Red pill *cures* Red flu patients, but **kills** Blue flu patients
 - Blue pill *cures* Blue flu patients, but **kills** Red flu patients
- Neo asks 10 experts to inform the number of patients with either type

Expert Beliefs

		Number of people	
ID	Expert	Red Flu	Blue Flu
1	Ethna	20	80
2	Hilary	70	30
3	Kine	50	50
4	John	80	20
5	Joseph	55	45
6	Shi-Yi	90	10
7	Su-Hsin	30	70
8	Wei	75	25
9	Fernando	35	65
10	Hawre	40	60

Red pill → Red Flu
Blue pill → Blue Flu

Which pill should Neo choose?



Expert Beliefs

		Number of people	
ID	Expert	Red Flu	Blue Flu
1	Ethna	20	80
2	Hilary	70	30
3	Kine	50	50
4	John	80	20
5	Joseph	55	45
6	Shi-Yi	90	10
7	Su-Hsin	30	70
8	Wei	75	25
9	Fernando	35	65
10	Hawre	40	60
	Expected value	54.5	45.5

What is Neo risking?



Expert Beliefs

		Number of people		Opportunity loss
ID	Expert	Red Flu	Blue Flu	
1	Ethna	20	80	60
2	Hilary	70	30	0
3	Kine	50	50	
4	John	80	20	
5	Joseph	55	45	
6	Shi-Yi	90	10	
7	Su-Hsin	30	70	
8	Wei	75	25	
9	Fernando	35	65	
10	Hawre	40	60	
	Expected value	54.5	45.5	



Expert Beliefs

ID	Expert	Number of people		Opportunity loss
		Red Flu	Blue Flu	
1	Ethna	20	80	60
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3	Kine	50	50	0
4	John	80	20	0
5	Joseph	55	45	0
6	Shi-Yi	90	10	0
7	Su-Hsin	30	70	40
8	Wei	75	25	0
9	Fernando	35	65	30
10	Hawre	40	60	20
	Expected value	54.5	45.5	15

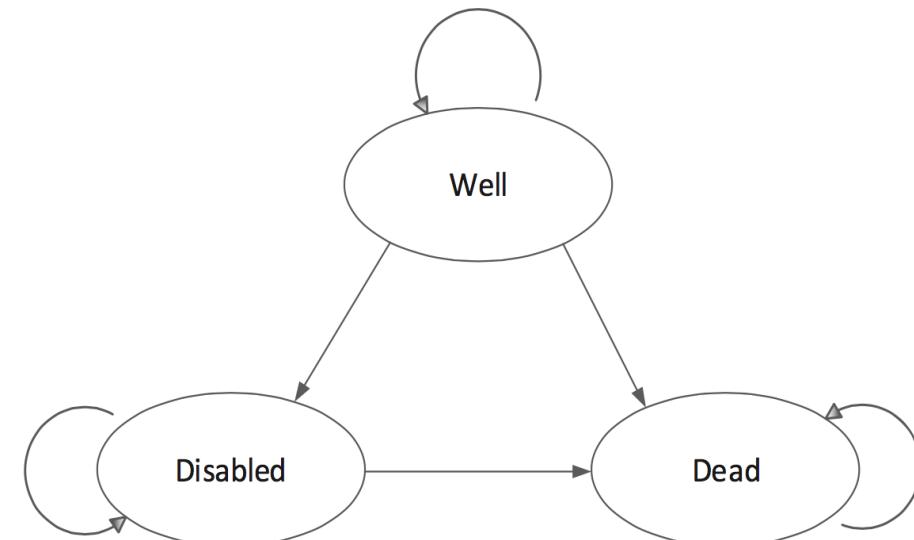
EVPI

Expected Value of Perfect Information (EVPI)

- Eliminating all sources of uncertainty for all parameters (θ)
- Maximum willingness to pay to get perfect information on all parameters
- No future data collection effort should exceed EVPI

Case Study

- Markov Model
- Syndrome X
 - Occasional flare-ups
 - → hospitalization
 - → disability
 - Higher mortality rates
- Three treatment interventions
 - A, B and C
 - A and B are new interventions
 - C is the standard of care
- There is uncertainty in some of the model parameters
 - Distributions based on prior information
 - Probabilistic sensitivity analysis (PSA)



Model parameters

Table 2: Model parameter descriptions

Parameter	Distribution	Mean	Shape	Scale
Number of hospital visits (intervention A)	Gamma	1	10	0.1
Number of hospital visits (intervention B)	Gamma	2	20	0.1
Number of hospital visits (intervention C)	Constant	2.8		
Annual probability of failing A	Beta	0.2	2	8
Annual probability of failing B	Beta	0.3	3	7
Annual probability of failing C	Constant	0.2		
QoL weight while disabled	Constant	0.8		
Annual mortality rate of well	Constant	0.005		
Annual mortality rate of disabled	Constant	0.01		
Annual cost of intervention A	Constant	\$10,000		
Annual cost of intervention B	Constant	\$2000		
Annual cost of intervention C	Constant	\$100		
Annual cost of disabled	Constant	\$5000		
Cost per hospital visit	Constant	\$5000		

Results

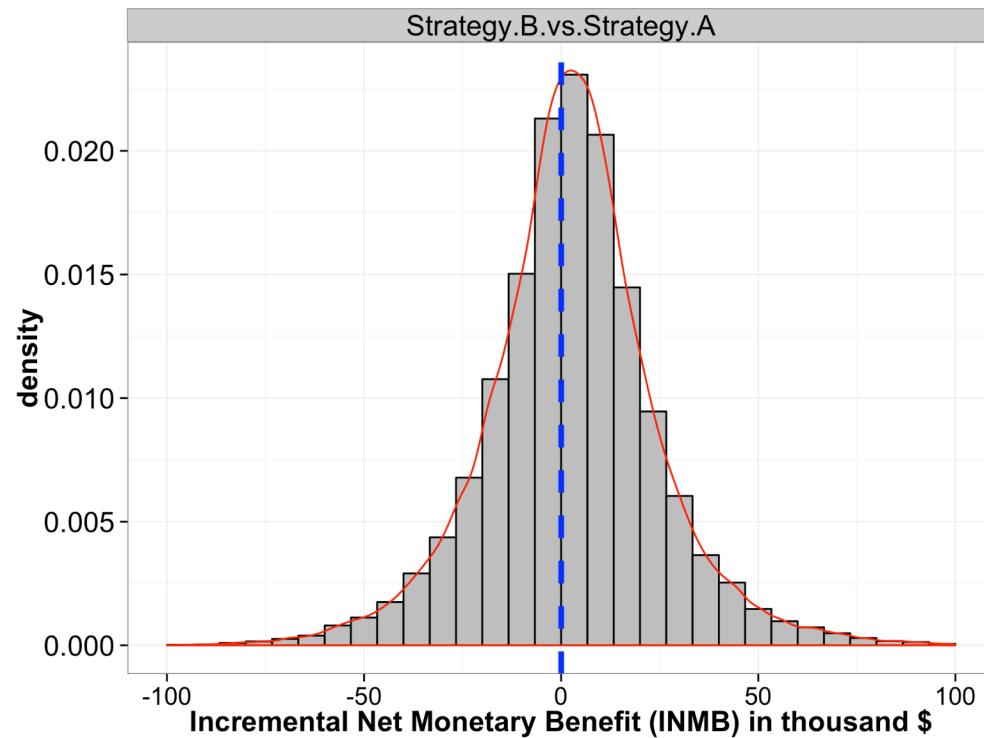
intervention	Simulations	Percent	Mean NMB
A	16,052	32.10%	\$563,410
B	19,815	39.63%	\$566,120
C	14,133	28.27%	\$562,250
Total	50,000	100%	

NMB: Net monetary benefit.

- Net Monetary Benefit (NMB)
 - $NMB = WTP * Effectiveness - Cost$
- If you were a rational decision maker, which strategy would you choose?
 - (Not a trick question!)
- Is B always the correct choice?
 - Of course, not (only 40%)
 - In some scenarios/states of the world → A or C is the best (60%).

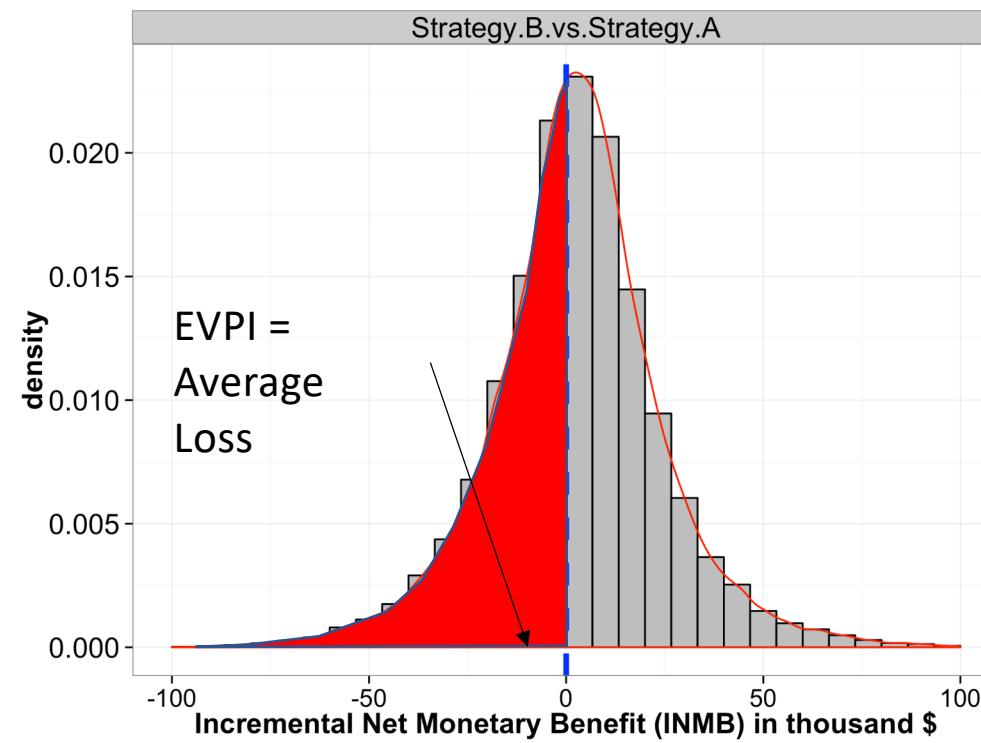
Incremental NMB (B vs. A)

- Distribution of INMB
- Where is the opportunity loss?



Incremental NMB (B vs. A)

- Distribution of INMB
- Where is the opportunity loss?
- The loss is the negative INMB
- The expected loss is \$8,350.
- EVPI = \$8,350!



PSA Dataset

# Sim	No. Visits(A)	No. Visits(B)	Prob. Fail A	Prob. Fail B	NMB A	NMB B	NMB C	Best Strategy
1	0.88783	1.57320	0.22631	0.41629	442531	446259	445305	B
2	1.16348	2.13149	0.12228	0.28788	443420	445029	445305	C
3	0.67341	1.69278	0.05871	0.33316	470225	448650	445305	A
4	0.65508	2.06674	0.04684	0.35586	475179	442967	445305	A
5	0.85459	2.57065	0.09996	0.35624	454703	436838	445305	A
6	0.57783	1.32949	0.38804	0.19791	440600	466317	445305	B

PSA Dataset

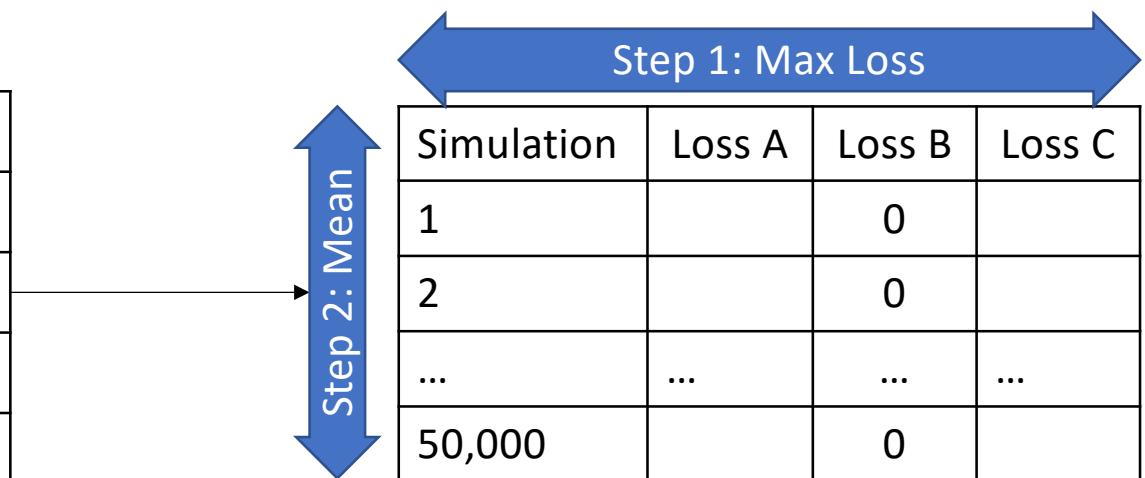
# Sim	NMB A	NMB B	NMB C	Best Strategy	Loss A	Loss B	Loss C
1	442531	446259	445305	B	-3728	0	-953
2	443420	445029	445305	C	-1608	0	277
3	470225	448650	445305	A	21575	0	-3345
4	475179	442967	445305	A	32212	0	2338
5	454703	436838	445305	A	17864	0	8467
6	440600	466317	445305	B	-25717	0	-21012

Math of EVPI

- Trace back our steps of how we calculated EVPI for Neo
- Calculate NMB for each strategy
- Determine the optimal strategy (highest expected benefit) = B
- Calculate the Loss matrix
- Calculate the losses.

Simulation	θ	NMB A	NMB B	NMB C
1				
2				
...				
50,000				

$$L(d, \theta^{(i)}) = B(d, \theta^{(i)}) - B(d^*, \theta^{(i)})$$



$$\text{EVPI} = \mathbb{E} \left[\max_d \{ L(d, \theta^{(i)}) \} \right]$$

Expected Value of *Partial* Perfect Information (EV_{PPI})

- Value of *eliminating* uncertainty on a *subset* of one or more parameters of interest (θ_I)
- Maximum willingness to pay for one or more parameters
- No future data collection effort should exceed this limit for a parameter

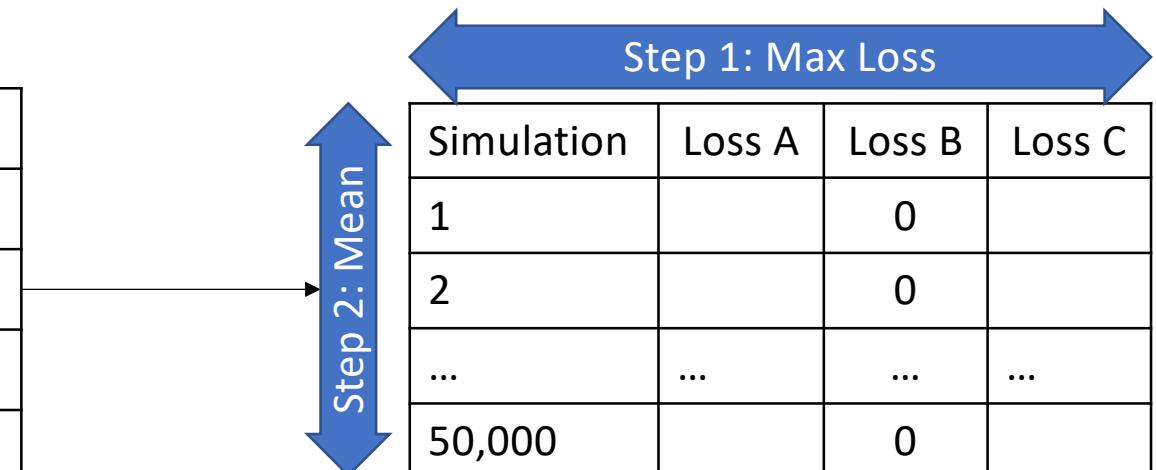
How to calculate EVPPI?

- EVPI = average of maximum losses for each value of θ
- EVPPI = average of maximum losses for each value of θ_I

Recall math of EVPI

- Trace back our steps of how we calculated EVPI
- Calculate NMB for each strategy
- Determine the optimal strategy (highest expected benefit) = B
- Calculate the loss matrix
- Calculate the losses

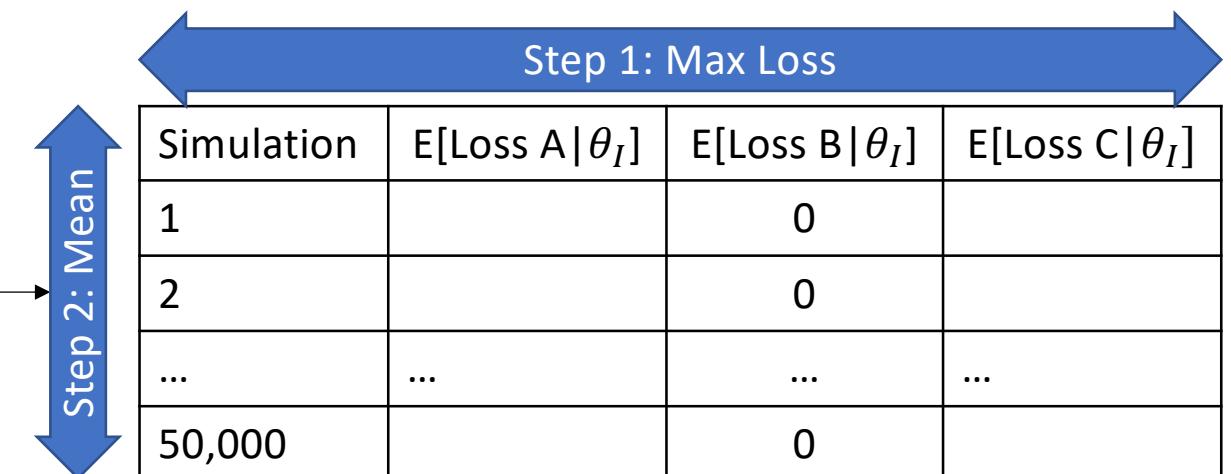
Simulation	θ	NMB A	NMB B	NMB C
1				
2				
...				
50,000				



Math of EVPPI

- We know how to calculate EVPI
- EVPPI is the same except that we need to calculate the **conditional loss** for each strategy given the parameters of interest (θ_I).

Simulation	θ_I	θ_C	NMB A	NMB B	NMB C
1					
2					
...					
50,000					



$$\text{EVPPI}_{\theta_I} = \mathbb{E}_{\theta_I} \left[\max_d \{ \mathbb{E}_{\theta_C} [L(d, \theta_I, \theta_C) | \theta_I] \} \right]$$

Computing this is hard!

Linear regression metamodel method for EVPPI

Steps

1. Compute the opportunity loss $L(d, \theta)$.
2. Estimate a linear metamodel for $L(d, \theta)$ for each strategy d , by regressing them on the spline basis functions of θ_I .
3. Compute EVPPI using the estimated losses for each d strategy, $\hat{L}(d, \theta)$, and

Calculate the Conditional Loss

- Loss explained by θ_I , but not θ_C
- Regression metamodeling
 - Isolate the effect of θ_I on the Loss

$$L(d, \theta_I, \theta_C) | \theta_I = \alpha + \beta \theta_I + e$$

- The conditional loss is simply the expected predicted loss given θ_I

$$\mathbb{E}[L(d, \theta_I, \theta_C) | \theta_I] = \hat{\alpha} + \hat{\beta} \theta_I$$

EVPI with Regression Metamodeling Overview

$$\text{EVPI}_{\theta_I} = \mathbb{E}_{\theta_I} \left[\max_d \left\{ \mathbb{E}_{\theta_C} [L(d, \theta_I, \theta_C) | \theta_I] \right\} \right]$$

Expected loss of strategy d conditional on θ_I

Maximum expected loss for all strategies conditional on θ_I

Expected maximum loss over all θ_I

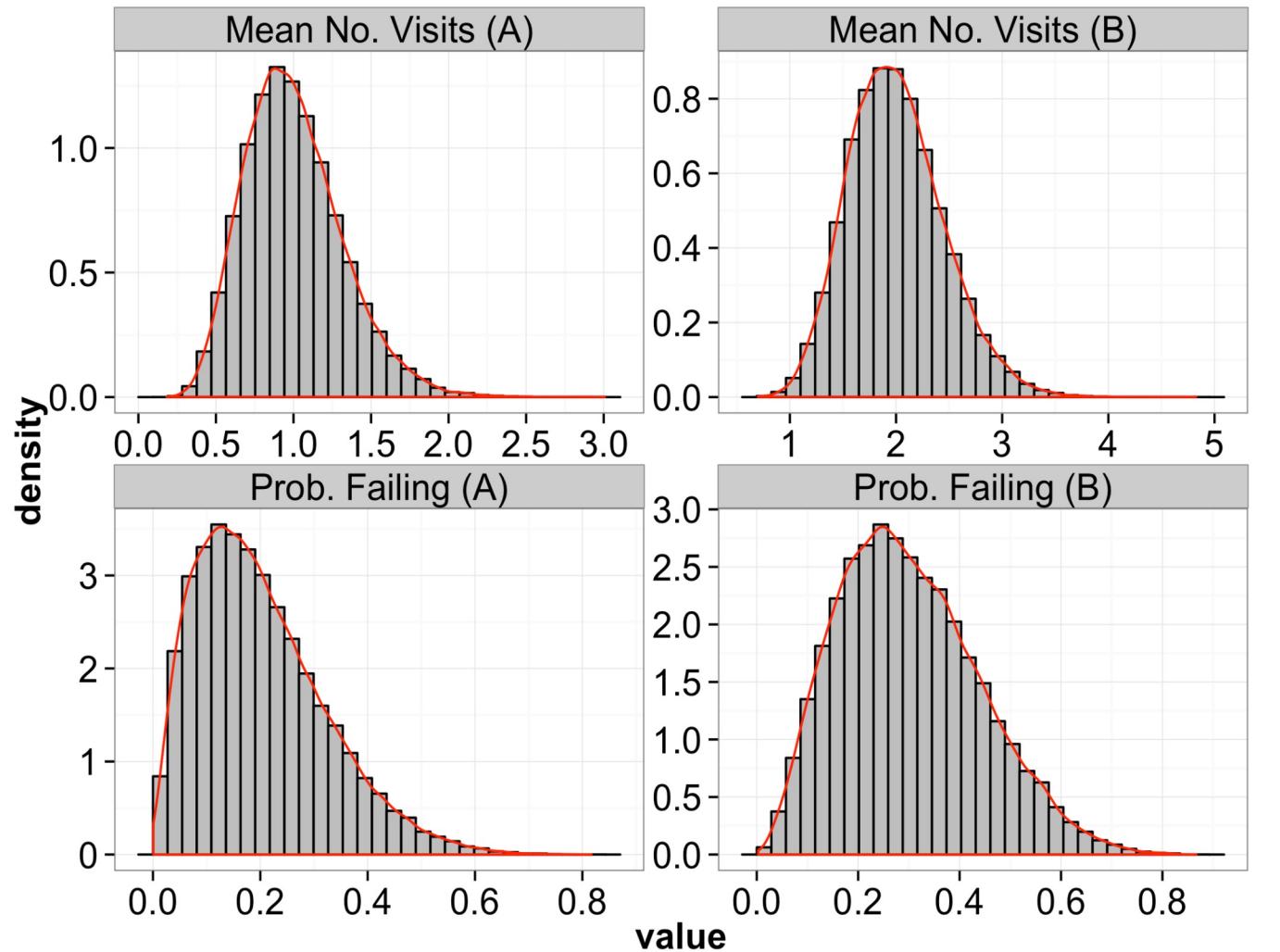
$$\begin{aligned} \mathbb{E}_{\theta_C} [L(d, \theta_I, \theta_C) | \theta_I] &= \mathbb{E}_{\theta_C} [\delta_d + \beta_d f(\theta_I) + \gamma_d g(\theta_C)] \\ &= \hat{\delta}_d + \hat{\beta}_d f(\theta_I) + \gamma_d \mathbb{E}_{\theta_C} [g(\theta_C)] \\ &= \hat{\alpha}_d + \hat{\beta}_d f(\theta_I) \end{aligned}$$

Single expectation
= computationally
inexpensive

$$\text{EVPI}_{\theta_I} = \mathbb{E}_{\theta_I} \left[\max_d \{ \hat{\alpha}_d + \hat{\beta}_d f(\theta_I) \} \right]$$

Case study

- Parameters
 - Mean No. Visits (A)
 - Mean No. Visits (B)
 - Prob. Failing (A)
 - Prob. Failing (B)



EVPPI Example

