Sensitivity Analysis

Brief note NMB in CEA

- Consider a CEA that compares D strategies in terms of their effectiveness, E, and costs, C.

- The net benefit of a given strategy is often considered in monetary terms and referred to as Net Monetary Benefit (NMB).

- The **NMB** for strategy d is defined as

$$NMB_d = E_d\lambda - C_d$$

- λ is the willingness-to-pay (WTP) or cost-effectiveness threshold

Types of uncertainty

Term	Concept	Other terms	Model/method
Heterogeneity	Variability between patients that can be attributed to characteristics of those patients		Microsimulation

Summarized from: Briggs AH, Weinstein MC, Fenwick EAL, Karnon J, Sculpher MJ, Paltiel AD, ISPOR-SMDM Modeling Good Research Practices Task Force. Model parameter estimation and uncertainty analysis: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group-6. *Med Decis Making*. 2012; 32(5):722–732.

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Parameter Uncertainty

- We have imperfect data about the input parameters and are therefore uncertain about the true parameter value

- Accounts for the likelihood of the values of each of the inputs and their effect on the model outputs

- We use distributions of inputs to reflect current knowledge on the parameters

Distributions

Distribution	Parameter modeled	Form	Comment
Uniform	Any	Range low-high	All values are equally likely. Uninformative distribution
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: $r = \mu n$ $n = (\mu(1-\mu)/s^2) - 1$	Bounded between 0 and 1
Dirichlet	Probability in the context of multiple events		Extension of the beta distribution, for multiple events

Hunink MGM, Weinstein MC, Wittenberg E, Drummond MF, Pliskin JS, Wong JB, Glasziou PP. Decision Making in Health and Medicine: Integrating Evidence and Values. Cambridge University Press, Cambridge, UK, 2014. ISBN 978-1-107-69047-9. Table 12.2, page 371

Distributions (2)

Distribution	Parameter modeled	Form	Comment
Lognormal	Rate Relative risk Hazard rate ratio Odds ratio Costs	ln(parameter) has a normal distribution with mean and standard error	Values >0, positively skewed
Gamma	Resource use Costs	Gamma (α,β) For observed mean μ and standard error s: $\alpha = \mu^2/s^2$ $\beta = \mu/s^2$	Values >0, positively skewed
Truncated			Restricting the domain of some other probability distribution
Histogram	Any	non-parametric	Based on trial data: observed relative frequency per value or per interval
Bootstrap	Any	non-parametric	Based on trial data: simulated relative frequency per value

Sensitivity Analysis

- Vary input parameters within plausible ranges
- For which values is each strategy optimal?

- 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)
  - 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

Deterministic Sensitivity Analysis

One-Way Sensitivity Analysis

- Systematically vary **one single** parameter over range of values, keeping all others fixed

p_PCed $= 30\%;\ = 40\%;\ = 50\%$, *etc...*

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

One-Way Sensitivity Analysis

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

One-Way Sensitivity Analysis

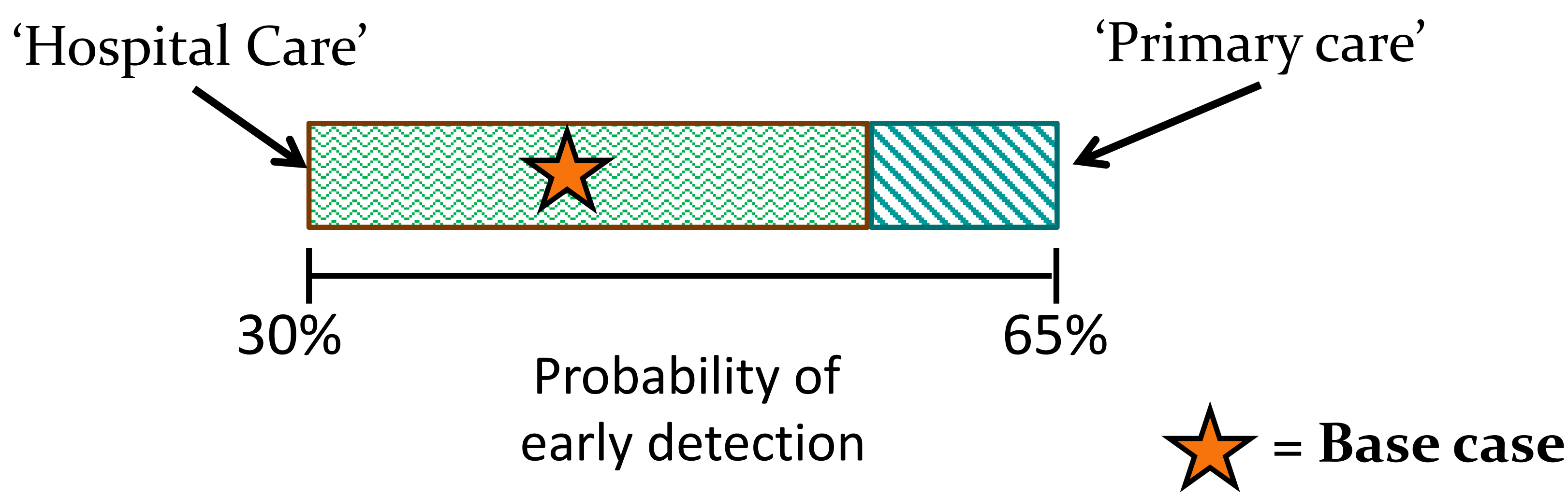
Probability of early detection (Primary care)	Life Expectancy		
	Routine practice	Primary Care	Hospital Care
30%			
35%			
40%			
45%			
50%			
55%			
60%			
65%			

One-Way Sensitivity Analysis

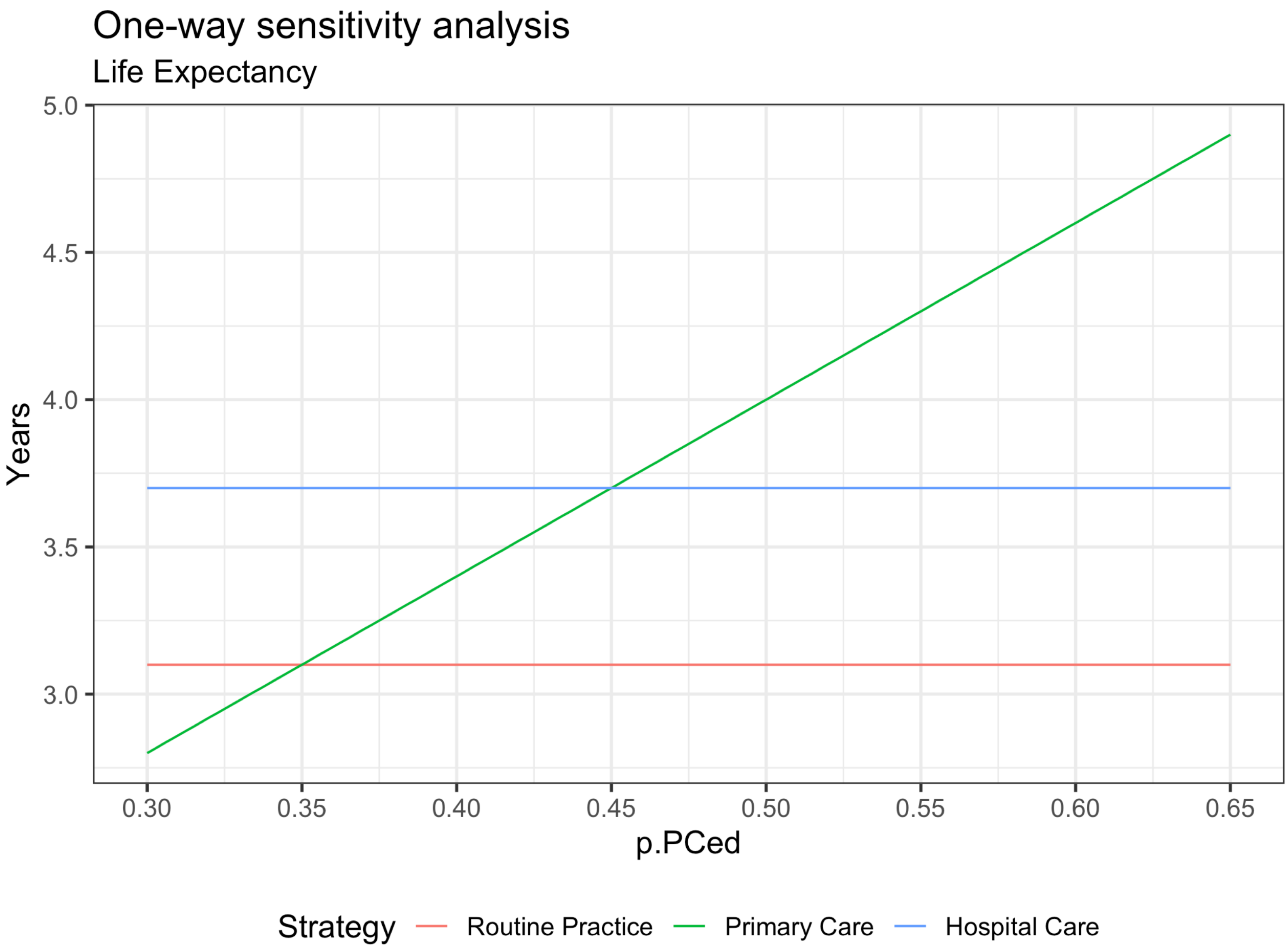
Probability of early detection (Primary care)	Life Expectancy		
	Routine practice	Primary Care	Hospital Care
30%	3.1	2.8	3.7
35%	3.1	3.1	3.7
40%	3.1	3.4	3.7
45%	3.1	3.7	3.7
50%	3.1	4.0	3.7
55%	3.1	4.3	3.7
60%	3.1	4.6	3.7
65%	3.1	4.9	3.7

One-Way Sensitivity Analysis

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



One-Way Sensitivity Analysis



Two-Way Sensitivity Analysis

- Systematically vary *two* parameters over range of uncertainty, keeping all others fixed

  p_PCed $= 25\%$, p_HCed $= 30\%$

  p_PCed $= 25\%$, p_HCed $= 40\%$

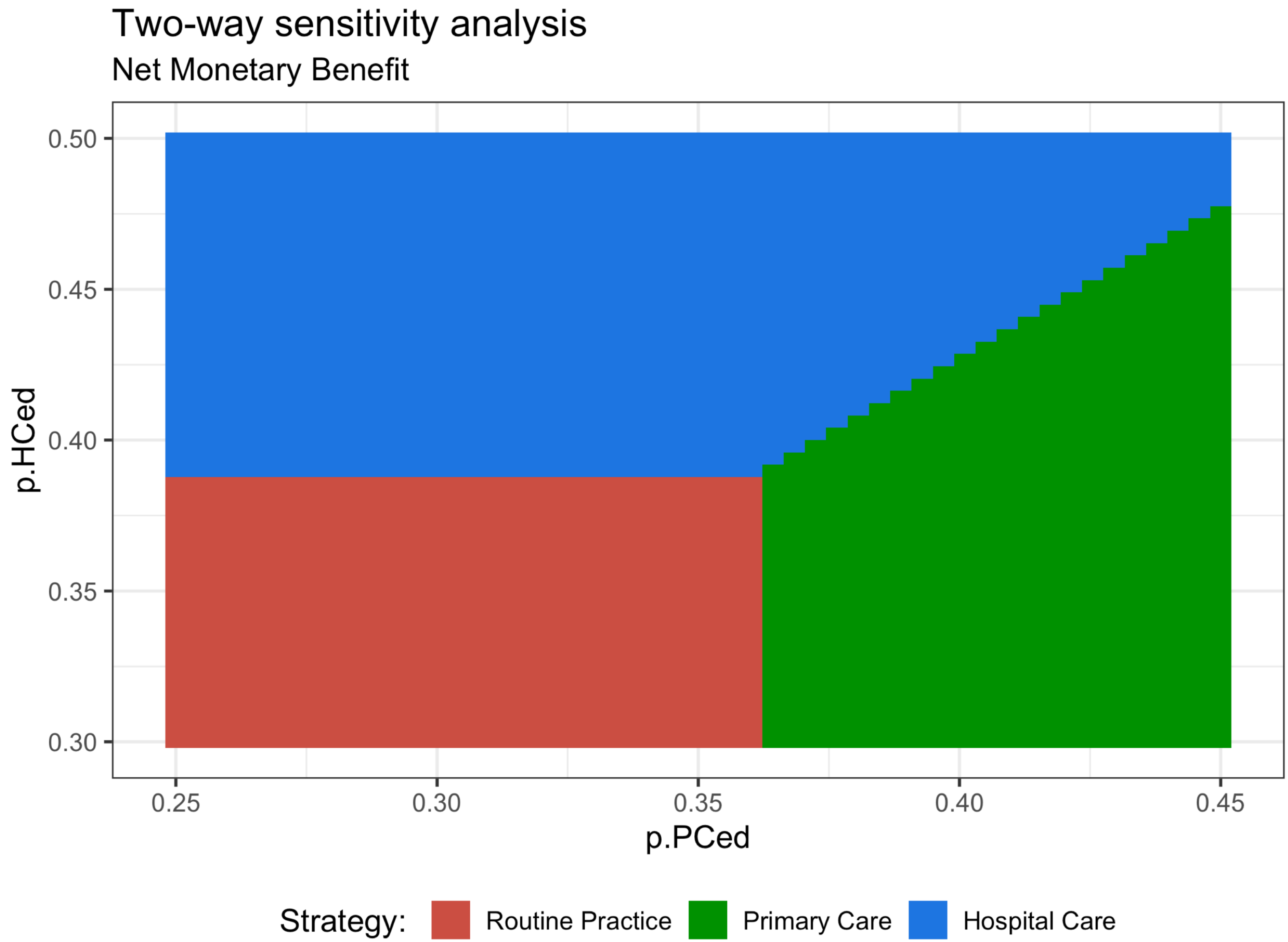
  p_PCed $= 25\%$, p_HCed $= 50\%$

  p_PCed $= 30\%$, p_HCed $= 30\%$

  p_PCed $= 30\%$, p_HCed $= 40\%$

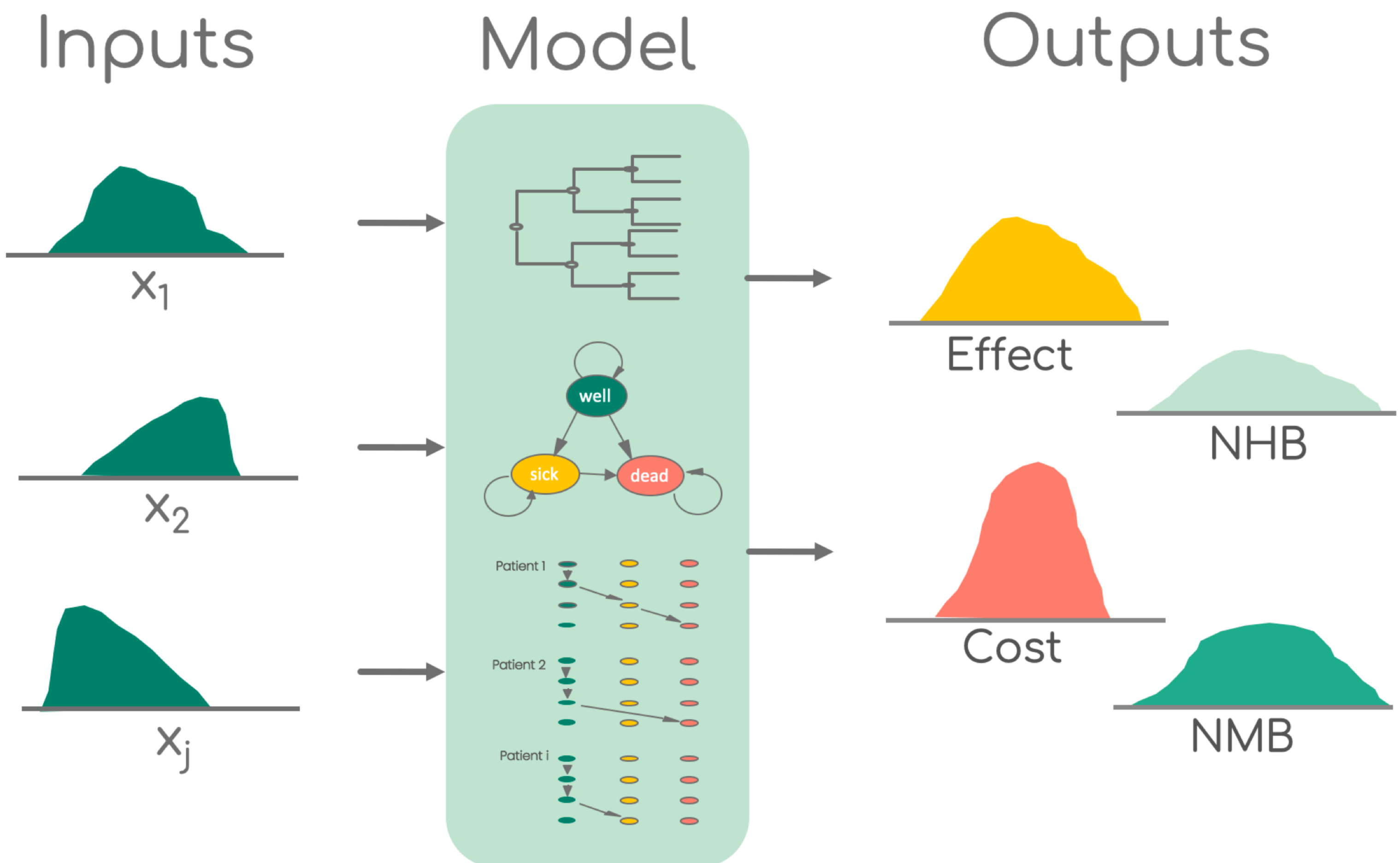
  etc…
- Particularly useful if one parameter influences the impact of the other on the optimal decision

Two-Way Sensitivity Analysis



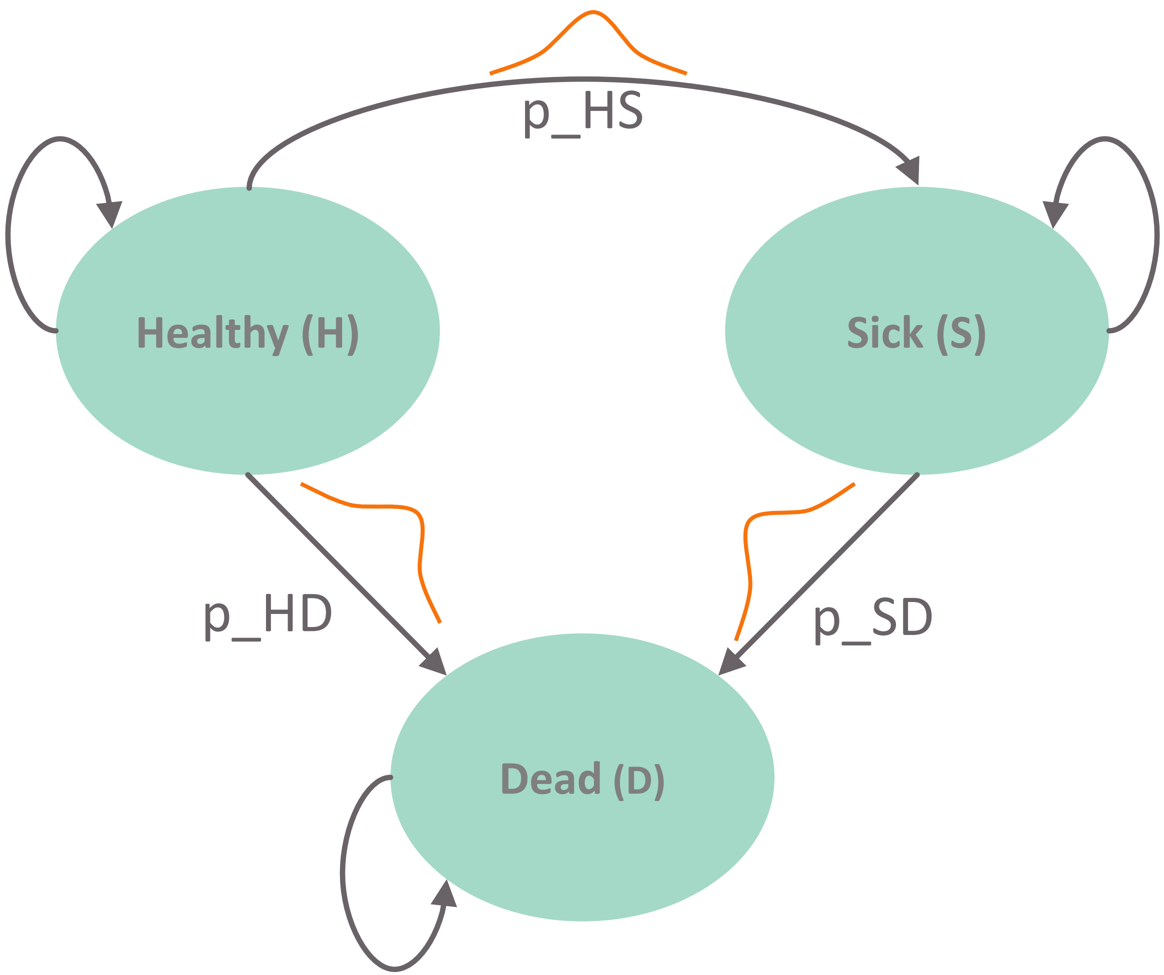
Probabilistic Sensitivity Analysis (PSA)

Probabilistic Sensitivity Analysis

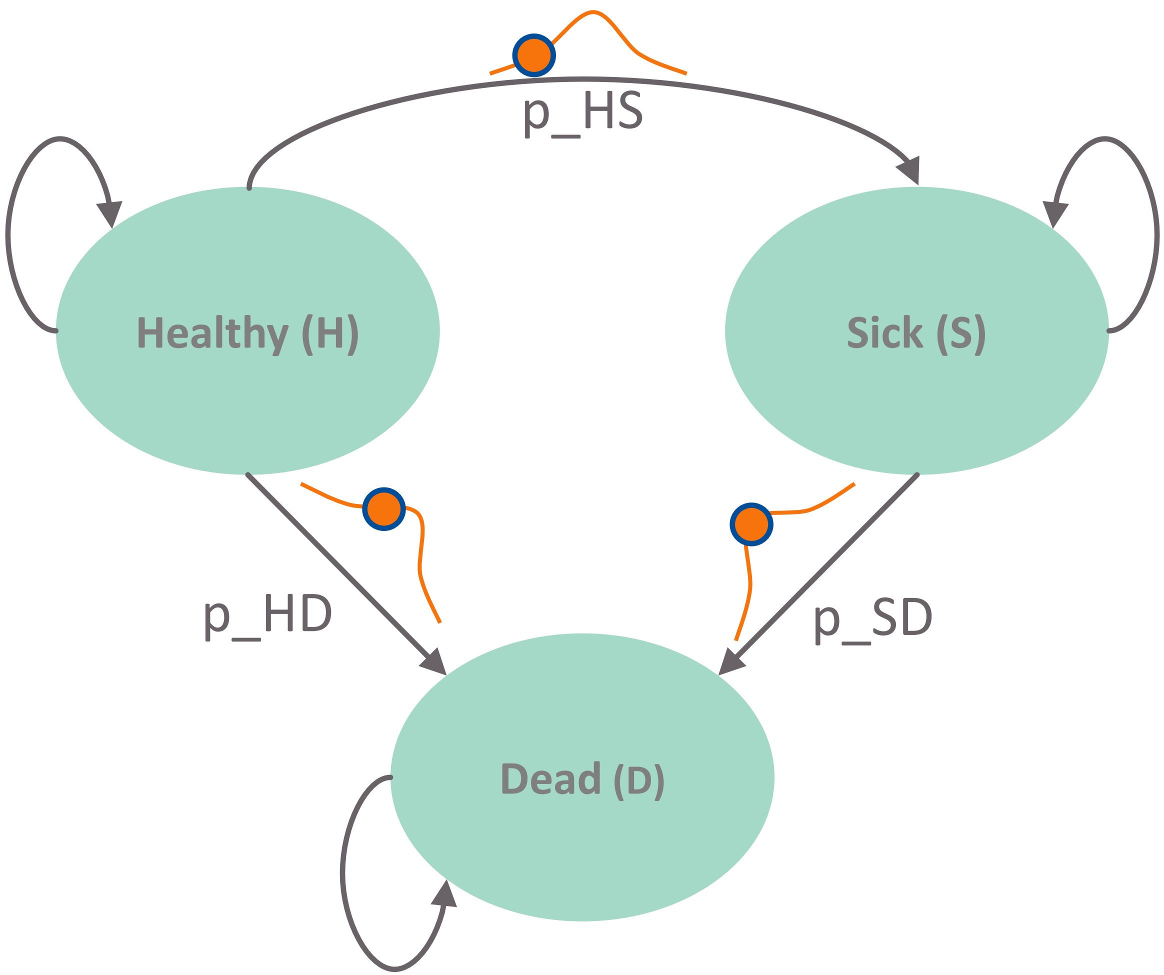


NHB: Net health benefit ; NMB: Net monetary benefit

Probabilistic Sensitivity Analysis (PSA)



Probabilistic Sensitivity Analysis (PSA)



Remember!

Transition Matrix Calculations

- Transition probabilities as a matrix

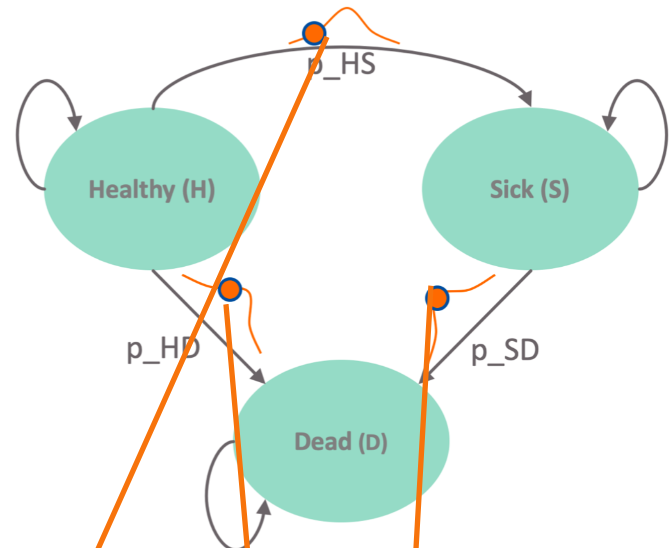
		To: Healthy	Sick	Dead
From:	Healthy	0.75	0.20	0.05
	Sick	0	0.85	0.15
	Dead	0	0	1.0

= P

- Calculated cohort distribution

$$\underset{x_1}{\begin{bmatrix} 0.75 & 0.20 & 0.05 \end{bmatrix}} = \underset{x_0}{\begin{bmatrix} 1.0 & 0.0 & 0.0 \end{bmatrix}} \underset{P}{\begin{bmatrix} 0.75 & 0.20 & 0.05 \\ 0 & 0.85 & 0.15 \\ 0 & 0 & 1.0 \end{bmatrix}}$$

Update matrix structures for PSA iteration



Transition probability matrix **P**

$$
P_1 = \text{From:}\;
\begin{array}{l|ccc|}
 & \text{To: Healthy} & \text{Sick} & \text{Dead} \\
\text{Healthy} & 1 - p\_HS - p\_HD & p\_HS & p\_HD \\
\text{Sick} & 0 & 1 - p\_SD & p\_SD \\
\text{Dead} & 0 & 0 & 1
\end{array}
$$

Indicate P is not time dependent = 1 means first PSA iteration

Update matrix structures for PSA iteration (2)

Markov Trace **M**

$$\mathbf{M_1} = \begin{array}{c|ccc} & \text{Healthy} & \text{Sick} & \text{Dead} \\ \hline \text{Cycle 0} & 1 & 0 & 0 \\ \text{Cycle 1} & 0.97 & 0.02 & 0.01 \\ \vdots & \vdots & \vdots & \vdots \\ \text{Cycle n} & 0 & 0 & 1.0 \end{array}$$

Vector of cycle's cost/outcomes

$$\mathbf{c_1} = \begin{bmatrix} c_H \\ c_S \\ 0 \end{bmatrix} \qquad \mathbf{e_1} = \begin{bmatrix} e_H \\ e_S \\ 0 \end{bmatrix}$$

Calculating total costs & effects

Total effects (TE):

$$\mathrm{E}_1 \quad = \mathbf{M}_1\, \mathrm{e}_1$$
$$\mathrm{TE}_1 = \iota_T E_1$$

Total costs (TC):

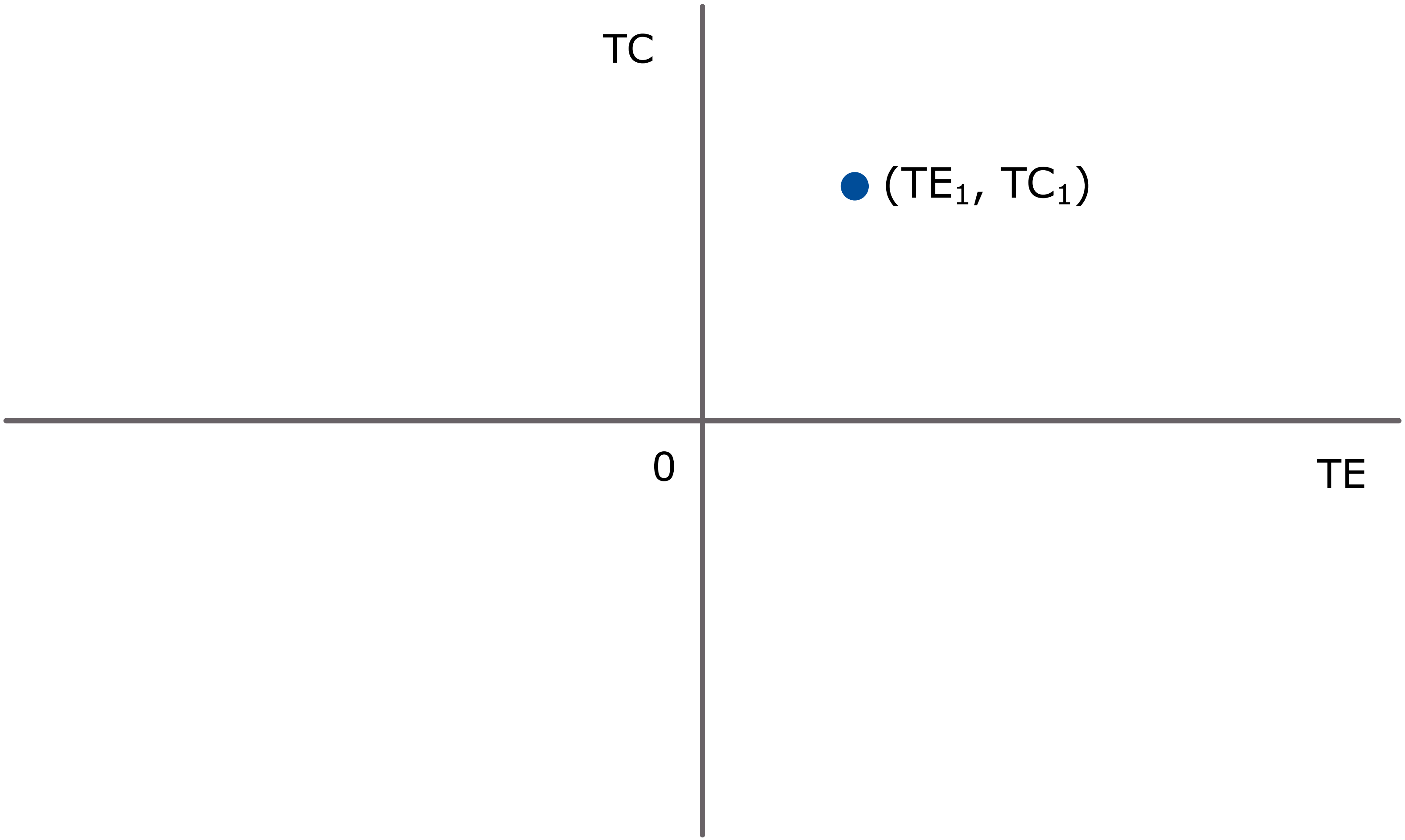
$$\mathrm{C}_1 \quad = \mathbf{M}_1\, \mathrm{e}_1$$
$$\mathrm{TC}_1 = \iota_T C_1$$

Monetary Benefit (NMB): $\mathrm{NBM}_1 = \mathrm{TE}_1\, \lambda - \mathrm{TC}_1$

ι_T: $1 \times T$ vector of ones

λ: Willingness-to-pay or cost-effectiveness threshold

Presenting the PSA results



Calculating total costs & effects (2)

Total effects (TE):

$$\mathrm{E}_2 \quad = \mathbf{M_2}\, \mathrm{e}_2$$
$$\mathrm{TE}_2 = \iota_T E_2$$

Total costs (TC):

$$\mathrm{C}_2 \quad = \mathbf{M_2}\, \mathrm{e}_2$$
$$\mathrm{TC}_2 = \iota_T C_2$$

Monetary Benefit (NMB): $\mathrm{NBM}_2 = \mathrm{TE}_2\, \lambda - \mathrm{TC}_2$

ι_T: $1 \times T$ vector of ones

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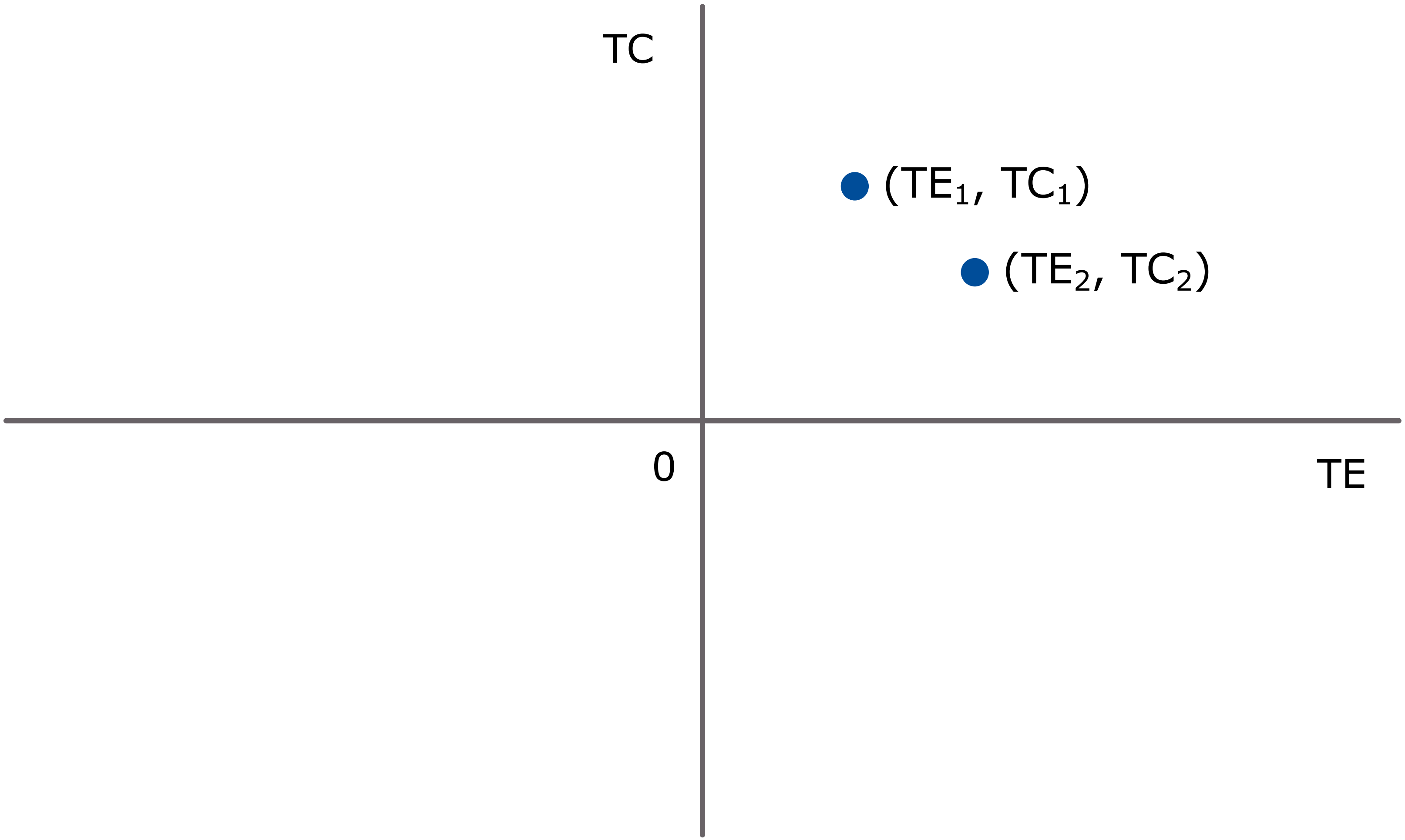
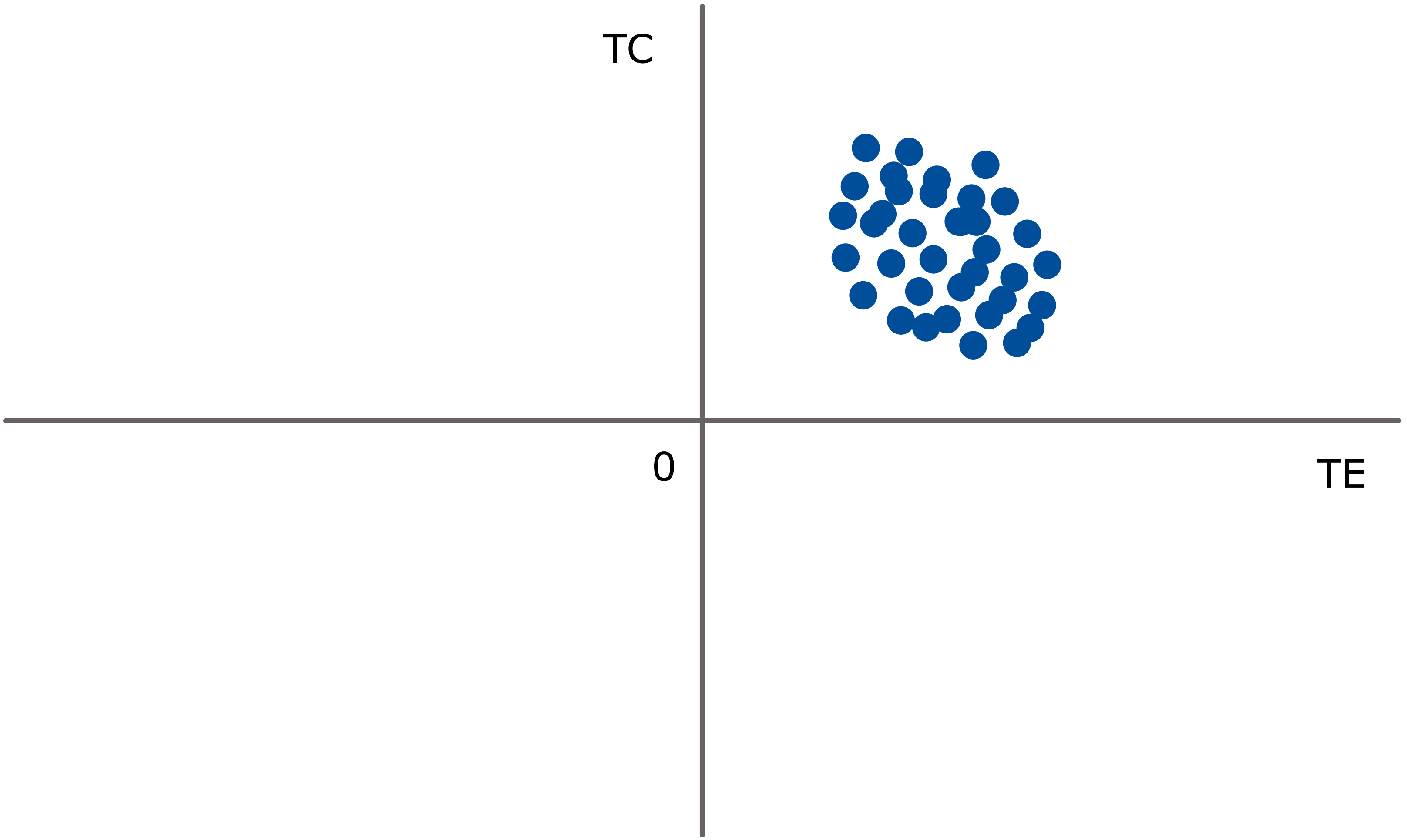
Presenting the PSA results (2)



Presenting the PSA results (3)



Example of 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

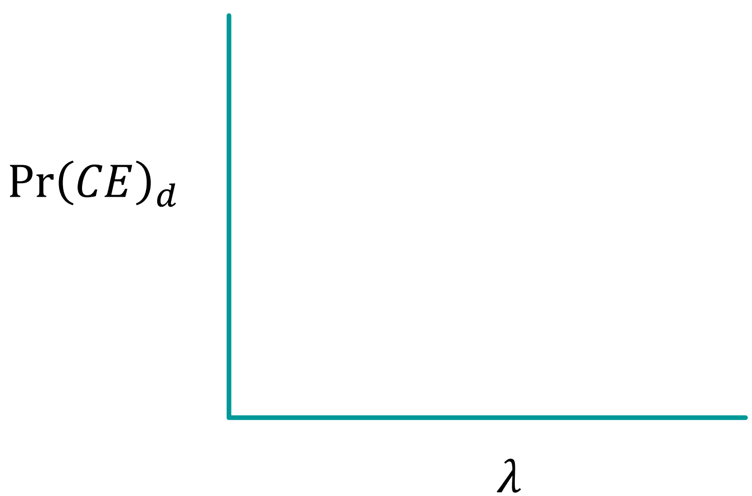
$$\Pr(CE)_d = \frac{N_d}{N}$$

- 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 <u>probability</u> 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

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

$N = 10$

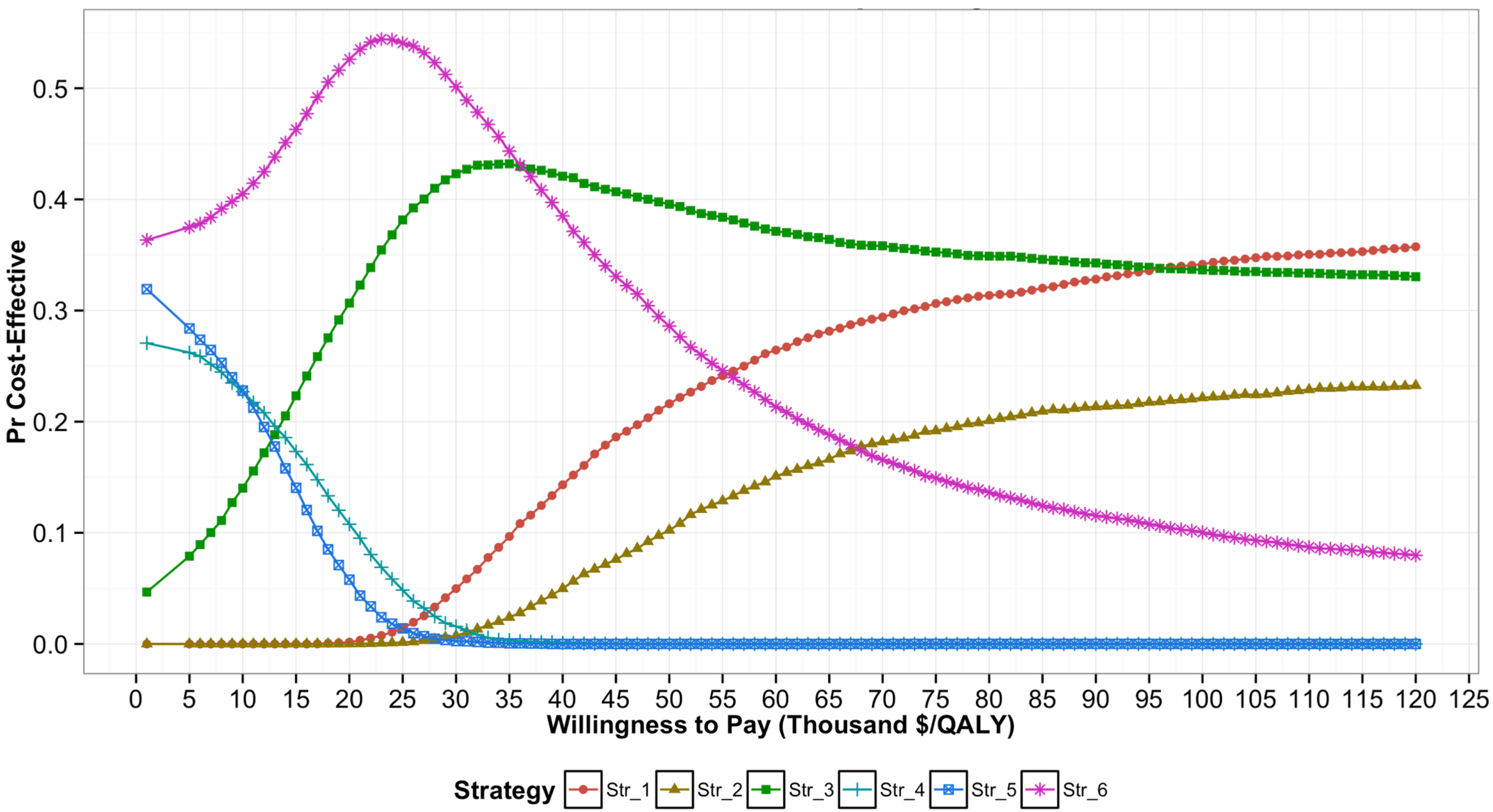
# Sim	Param 1	Param 2	Param 3	Param 4	NMB A	NMB B	NMB C	Best Strategy
1	0.8878	1.5732	0.2263	0.4163	442531	**446259**	445305	B
2	1.1635	2.1315	0.1223	0.2879	443420	445029	**445305**	C
3	0.6734	1.6928	0.0587	0.3332	**470225**	448650	445305	A
4	0.6551	2.0667	0.0468	0.3559	**475179**	442967	445305	A
5	0.8546	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

$\boxed{\Pr(CE)_A = \frac{5}{10} = 0.5}$ $\Pr(CE)_B = \frac{3}{10} = 0.3$ $\Pr(CE)_B = \frac{2}{10} = 0.2$

Highest probability

for this given λ used in the NMB calculation

Cost-effectiveness acceptability curves (CEACs)



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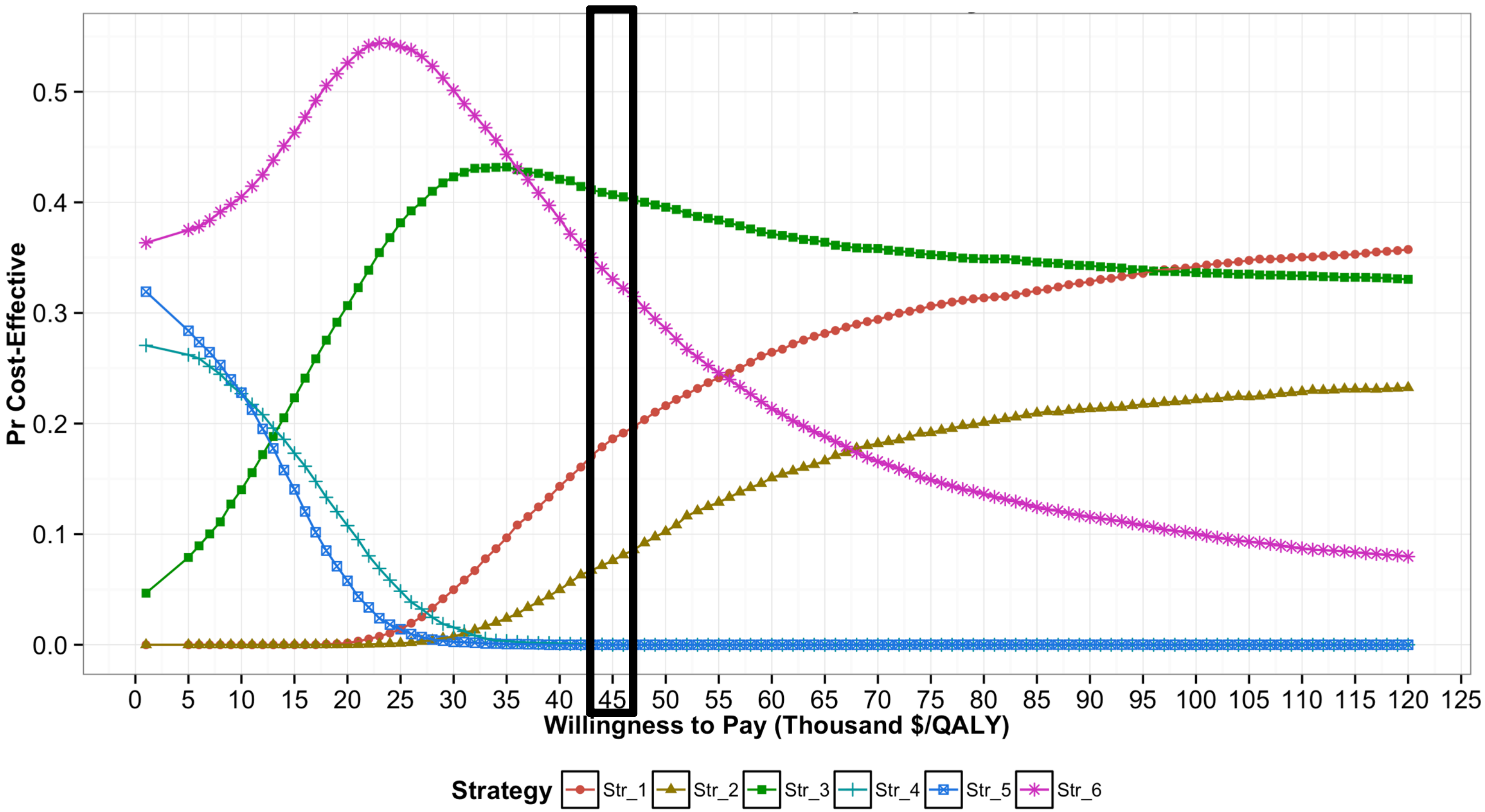

Cost-Effectiveness Acceptability **Frontier** (CEAF)

- 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 $\overline{NMB}_d$ 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

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

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

$$d^* = \max_{d\in[1,\ldots,D]}\{\overline{NMB}_d\}$$

Construction of CEAF

# Sim	Param 1	Param 2	Param 3	Param 4	NMB A	NMB B	NMB C	Best Strategy
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2	1.1635	2.1315	0.1223	0.2879	443420	445029	**445305**	C
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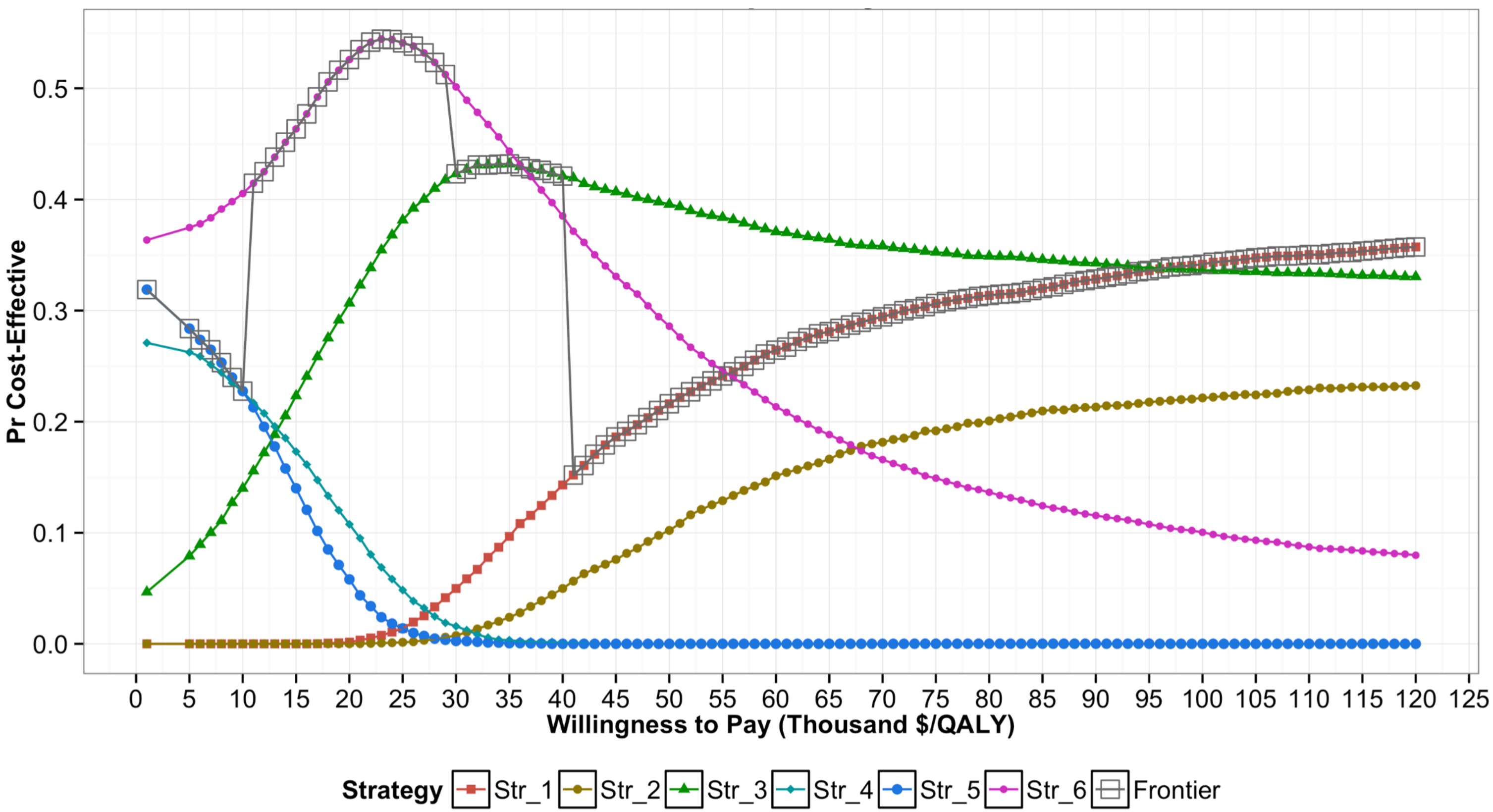
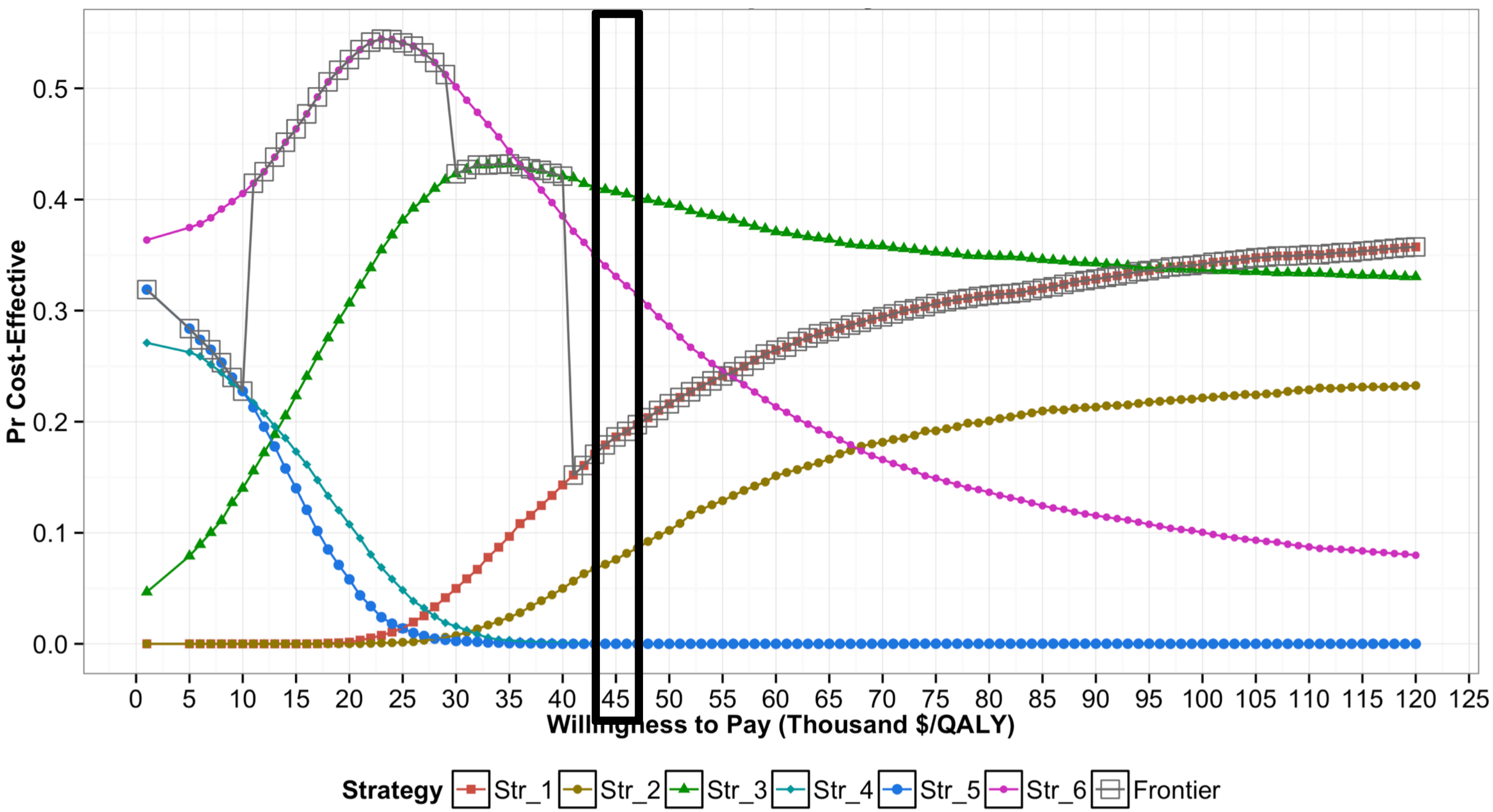
8	0.5983	1.7325	0.1957	0.3190	**449875**	448901	445305	A
9	1.0920	1.4737	0.1201	0.3320	445512	**451526**	445305	B
10	0.9115	1.1154	0.2729	0.6097	440091	444312	**445305**	C
				Expectd NMB ->	**451876**	**448474**	**445305**	

Highest expected net benefit = Optimal strategy

Cost-effectiveness acceptability curves (CEACs) and frontier (CEAF)



Cost-effectiveness acceptability curves (CEACs) and frontier (CEAF)



Limitations of CEACs

- 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 and CEAF

- 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.

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