Sensitivity Analysis in R

Brief note on 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

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

Parameter Uncertainty

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

- It is often conducted in a similar approach than PSA but distributions of inputs reflect current knowledge on the parameters

Deterministic Sensitivity Analysis

One-Way Sensitivity Analysis

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

$$\text{p\_PCed} = 30\%, \ \text{p\_PCed} = 40\%, \ \text{p\_PCed} = 50\%, \text{ etc...}$$

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

One-Way Sensitivity Analysis

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%			

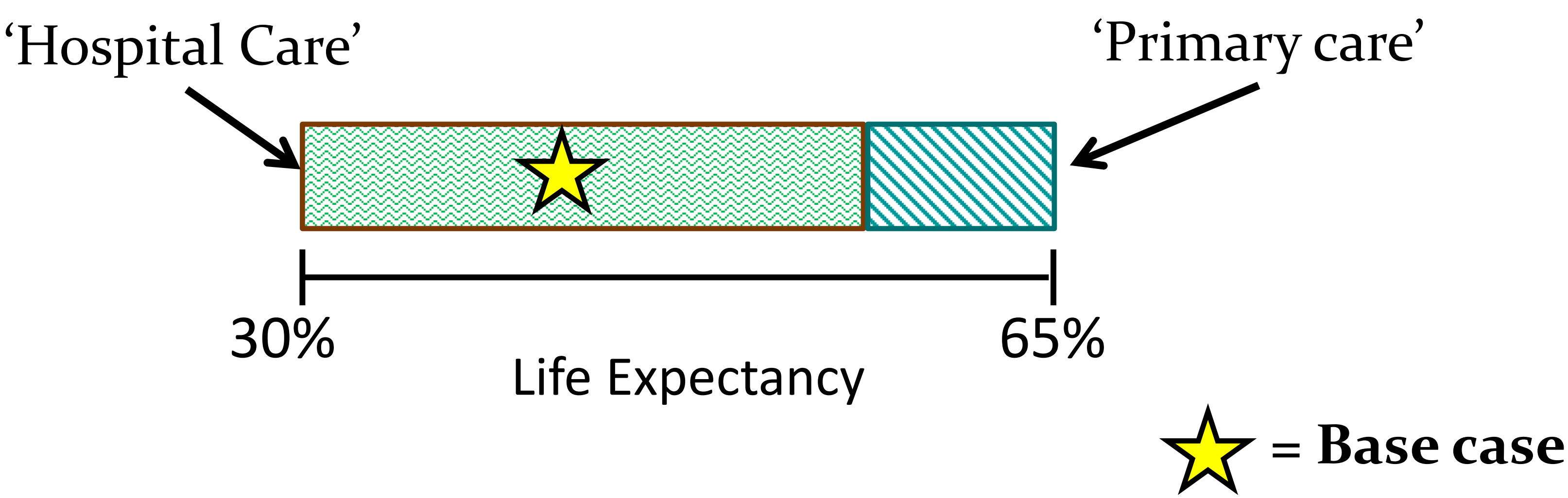
One-Way Sensitivity Analysis

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

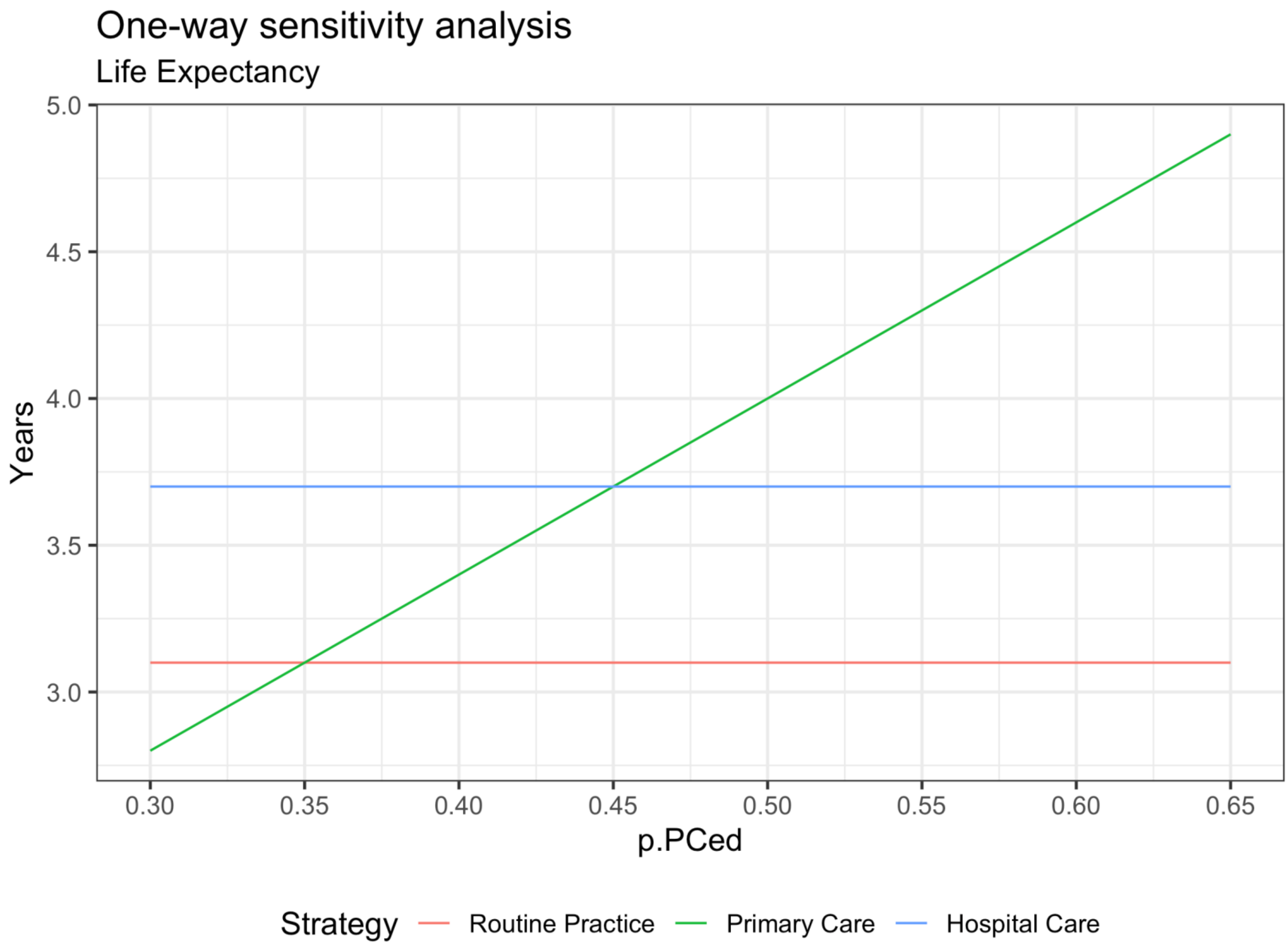
One-Way Sensitivity Analysis

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

  p.PCed = 30%, p.PCed = 40%, p.PCed = 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

$$\text{p.PCed} = 25\%, \text{p.HCed} = 30\%$$

$$\text{p.PCed} = 25\%, \text{p.HCed} = 40\%$$

$$\text{p.PCed} = 25\%, \text{p.HCed} = 50\%$$

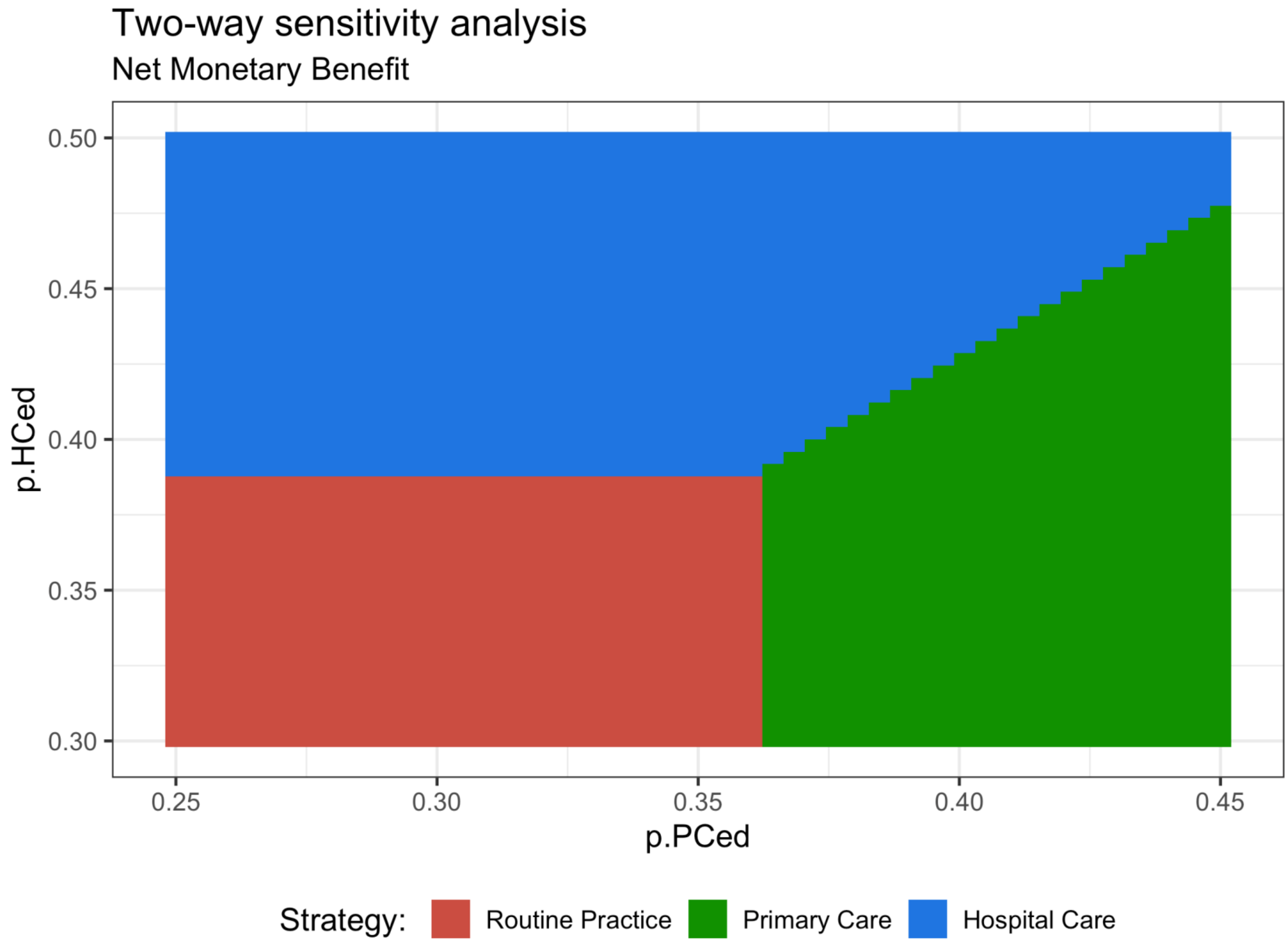
$$\text{p.PCed} = 30\%, \text{p.HCed} = 30\%$$

$$\text{p.PCed} = 30\%, \text{p.HCed} = 40\%$$

etc…

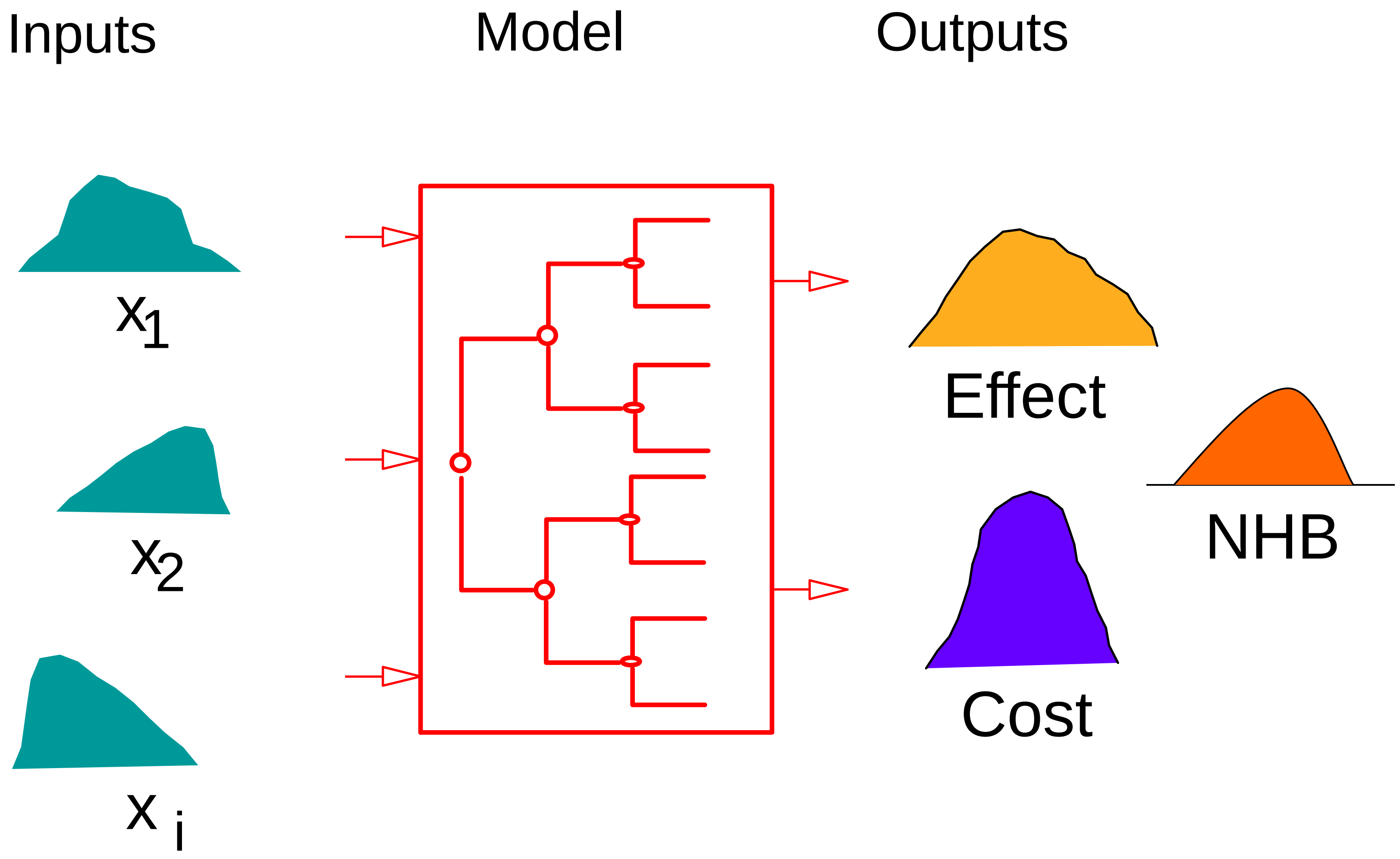
- Particularly useful if one parameter influences the impact of the other on the optimal decision

Two-Way Sensitivity Analysis

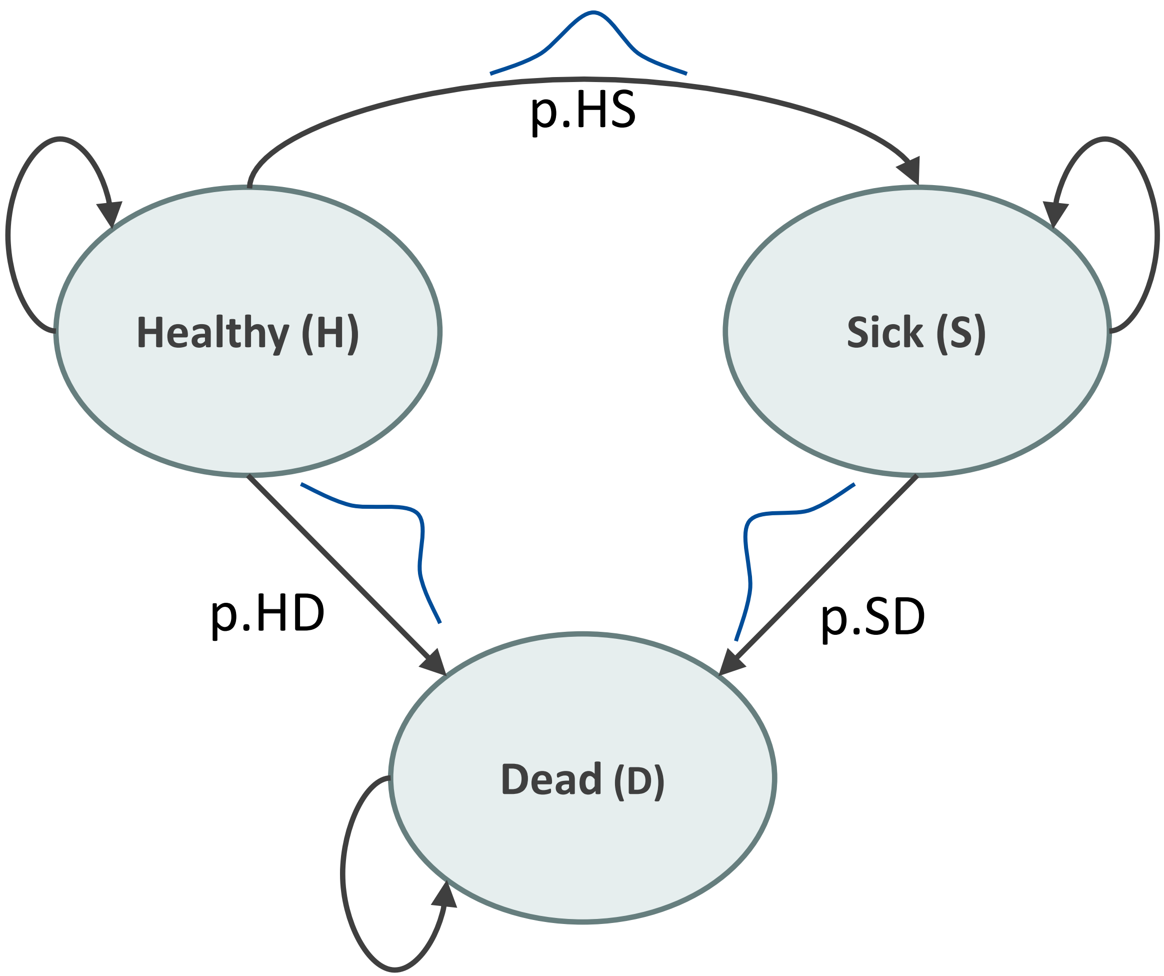


Probabilistic Sensitivity Analysis (PSA)

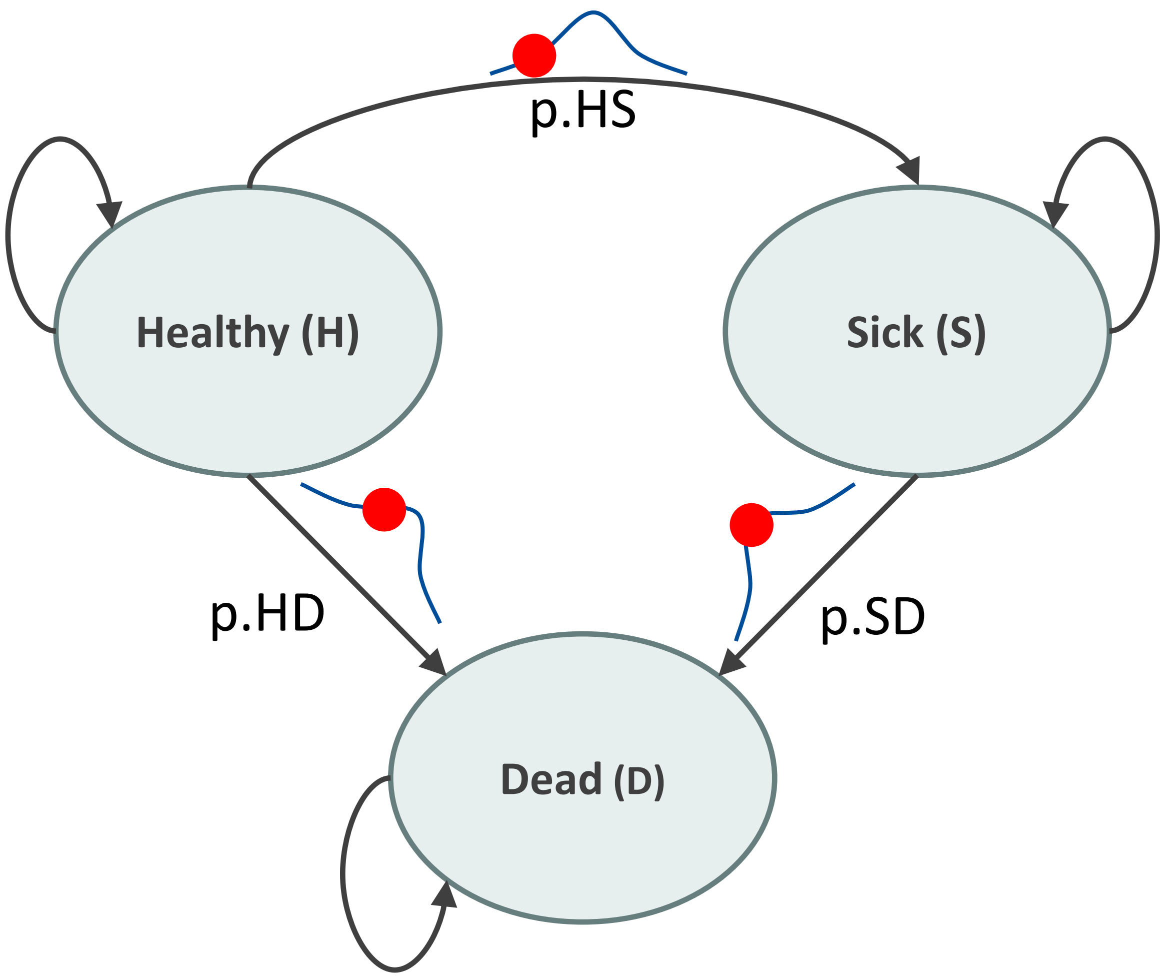
Probabilistic Sensitivity Analysis (PSA)



Probabilistic Sensitivity Analysis (PSA)



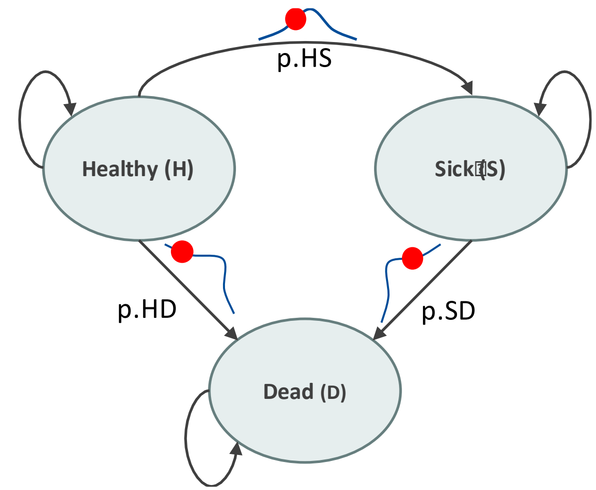
Probabilistic Sensitivity Analysis (PSA)



Matrix Implementation of the Markov Model

Transition probability matrix

$$
P^1 = \begin{array}{c c}
\begin{array}{ccc} \mathbf{S} & \mathbf{P} & \mathbf{D} \end{array} & \\
\begin{bmatrix} 1 - p_{SP} - p_{SD} & p_{SP} & p_{SD} \\ 0 & 1 - p_{PD} & p_{PD} \\ 0 & 0 & 1 \end{bmatrix}^1 & \begin{array}{c} \mathbf{S} \\ \mathbf{P} \\ \mathbf{D} \end{array}
\end{array}
$$



Vector of cycle’s cost/outcomes

$$
c^1 = \begin{bmatrix} c_S \\ c_P \\ 0 \end{bmatrix}^1 \begin{array}{c} \mathbf{S} \\ \mathbf{P} \\ \mathbf{D} \end{array} \qquad e^1 = \begin{bmatrix} e_S \\ e_P \\ 0 \end{bmatrix}^1 \begin{array}{c} \mathbf{S} \\ \mathbf{P} \\ \mathbf{D} \end{array}
$$

Calculating total costs & effects

Total effects (TE):

$$E^1 = M e^1$$

$$TE^1 = \iota_T E^1$$

Total costs (TC):

$$C^1 = M c^1$$

$$TC^1 = \iota_T C^1$$

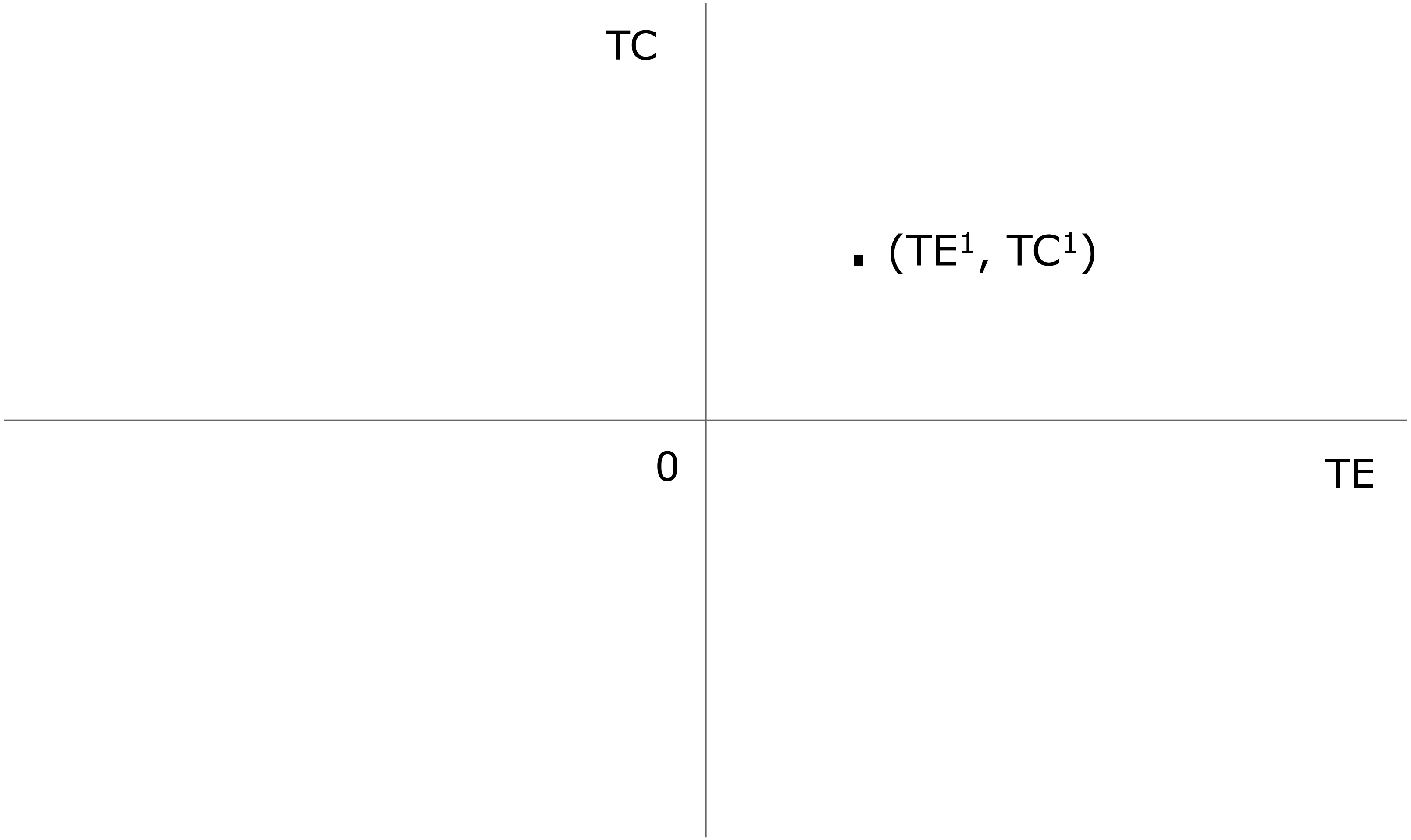
Net Monetary Benefit (NMB):

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

$\iota_T : 1 \times T$ vector of ones

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

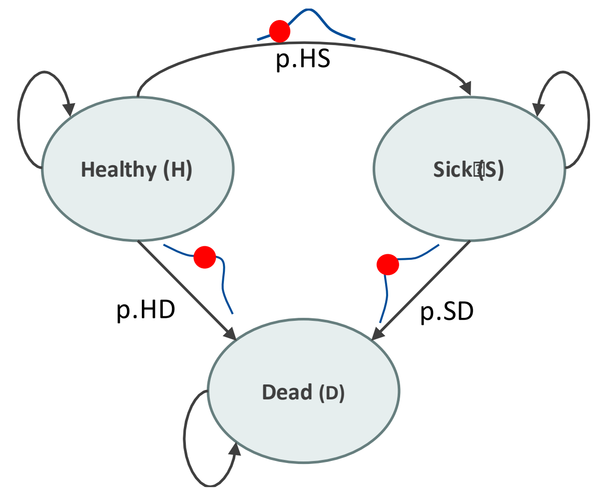
Presenting the PSA results



Matrix Implementation of the Markov Model

Transition probability matrix

$$P^2 = \begin{array}{cc} \begin{array}{ccc} \mathbf{H} & \mathbf{S} & \mathbf{D} \end{array} & \\ \begin{bmatrix} 1-p_{SP}-p_{SD} & p_{SP} & p_{SD} \\ 0 & 1-p_{PD} & p_{PD} \\ 0 & 0 & 1 \end{bmatrix}^2 & \begin{array}{c} \mathbf{S} \\ \mathbf{P} \\ \mathbf{D} \end{array} \end{array}$$



Vector of cycle's cost/outcomes

$$c^2 = \begin{bmatrix} c_S \\ c_P \\ 0 \end{bmatrix}^2 \begin{array}{c} \mathbf{H} \\ \mathbf{S} \\ \mathbf{D} \end{array} \qquad e^2 = \begin{bmatrix} e_S \\ e_P \\ 0 \end{bmatrix}^2 \begin{array}{c} \mathbf{H} \\ \mathbf{S} \\ \mathbf{D} \end{array}$$

Calculating total costs & effects

Total effects (TE):

$$E^2 = M^2 e^2$$

$$TE^2 = \iota_T E^2$$

Total costs (TC):

$$C^2 = M^2 c^2$$

$$TC^2 = \iota_T C^2$$

Net Monetary Benefit (NMB):

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

$\iota_T : 1 \times T$ vector of ones

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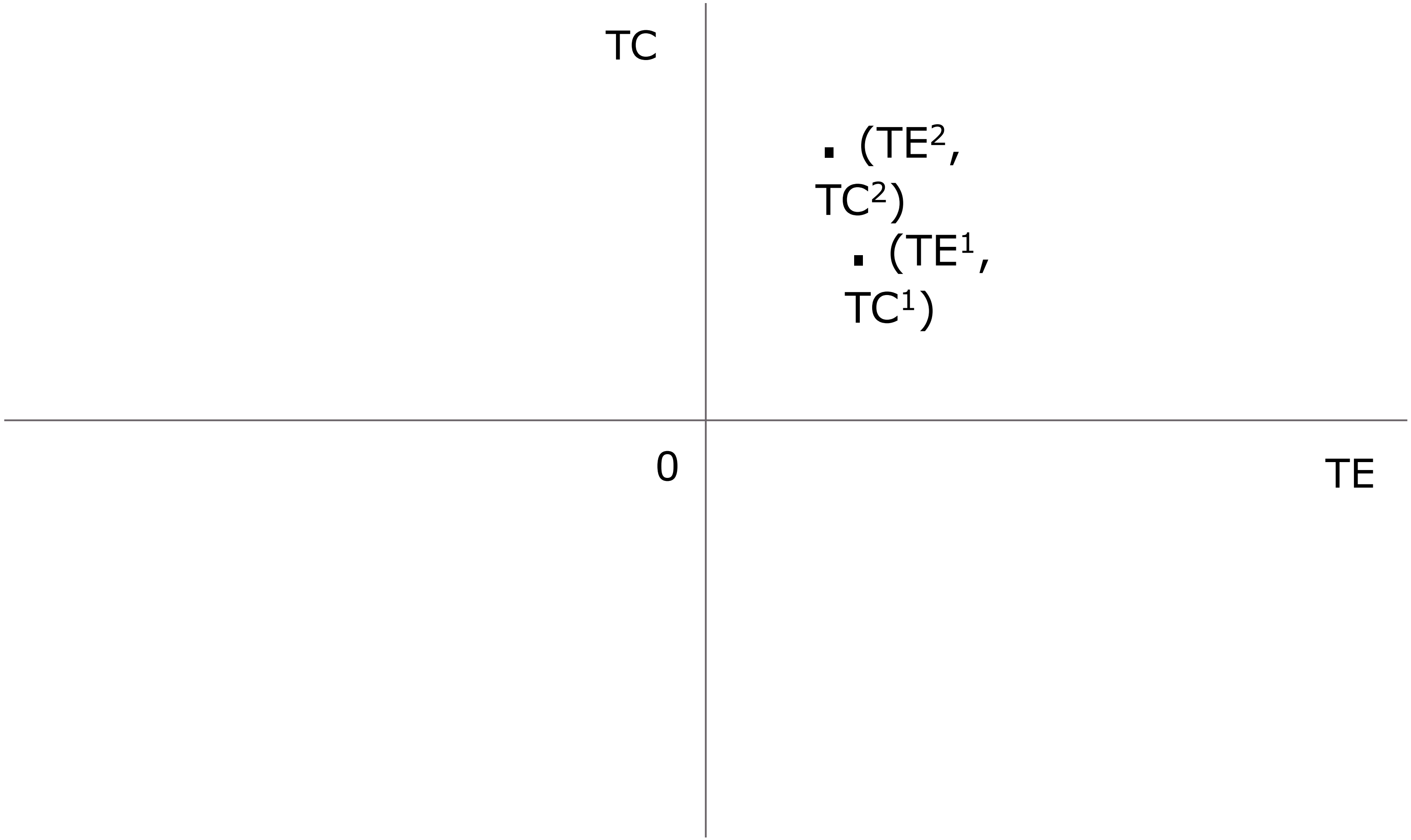
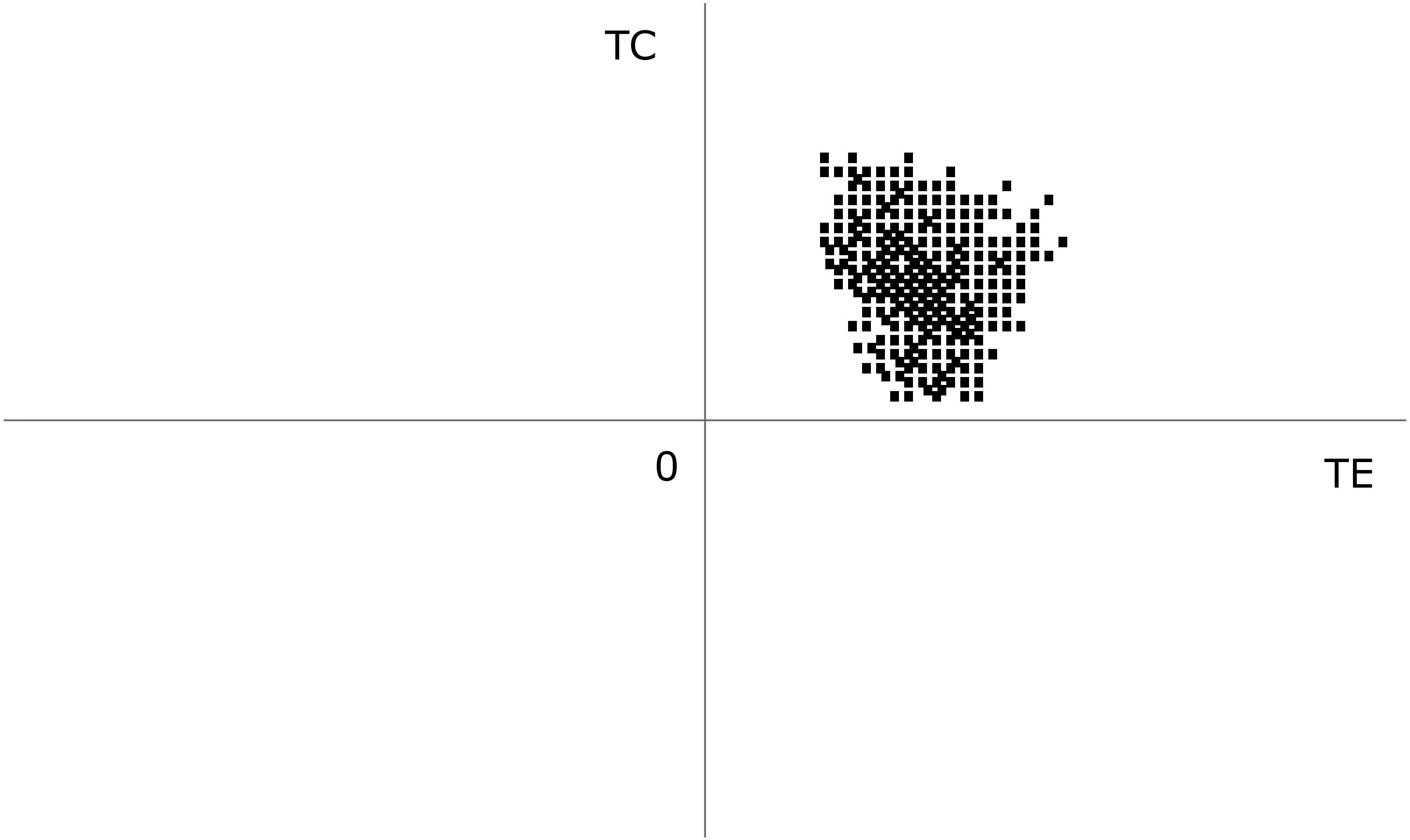
Presenting the PSA results



Presenting the PSA results



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

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 $r = \mu n$ $n = (\mu(1-\mu)/s^2) - 1$	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 II

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

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)

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

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

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

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

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

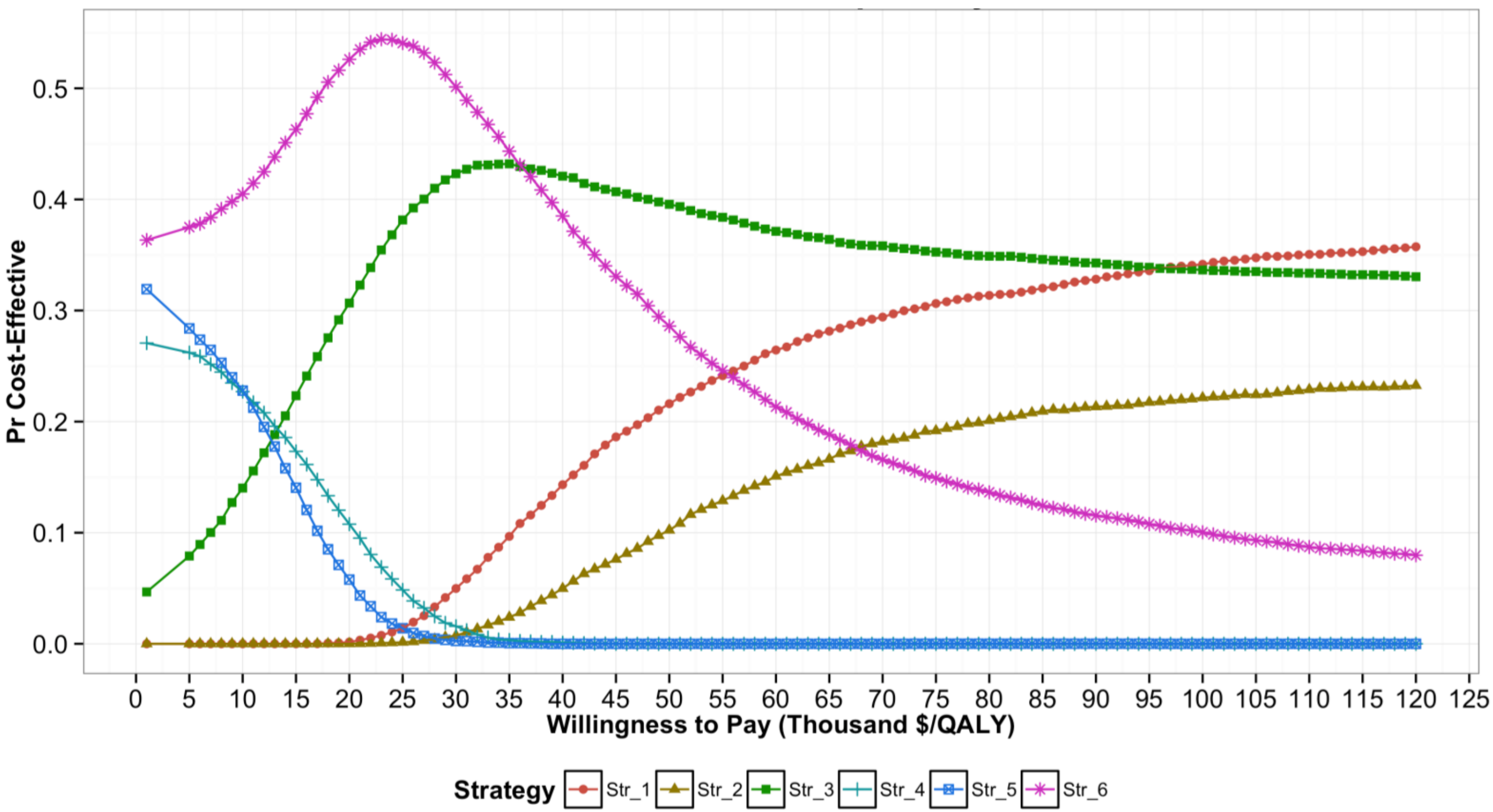
$$d^* = \text{argmax}_{d\in[1,\ldots,D]}\{\overline{NMB}_d\}$$

Construction of CEAF

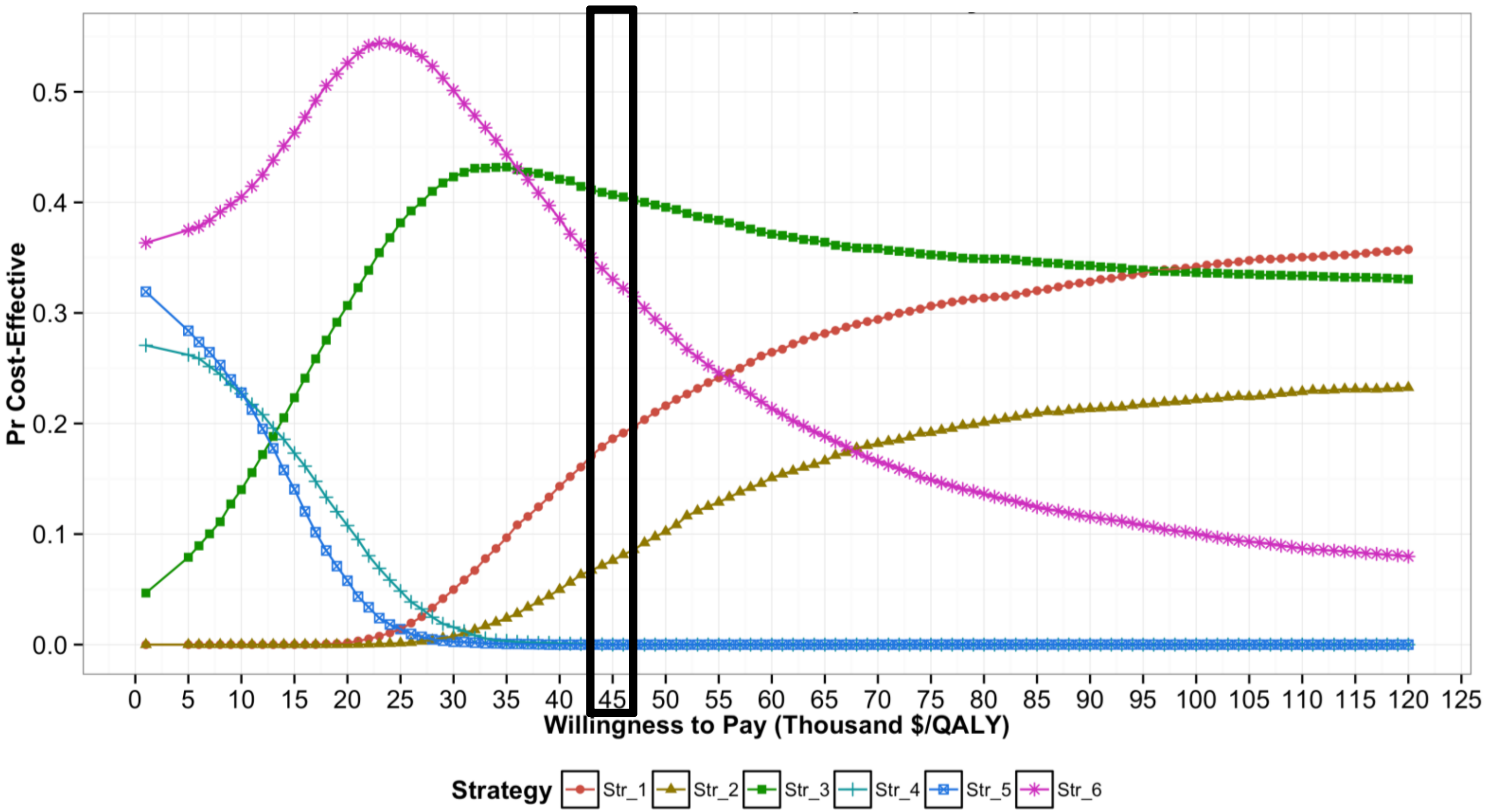
# Sim	Param 1	Param 2	Param 3	Param 4	NMB A	NMB B	NMB C	Best Strategy
1	0.8878	1.5732	0.2263	0.4163	442531	**446259**	445305	B
2	1.1635	2.1315	0.1223	0.2879	443420	445029	**445305**	C
3	0.6734	1.6928	0.0587	0.3332	**470225**	448650	445305	A
4	0.6551	2.0667	0.0468	0.3559	**475179**	442967	445305	A
5	0.8546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

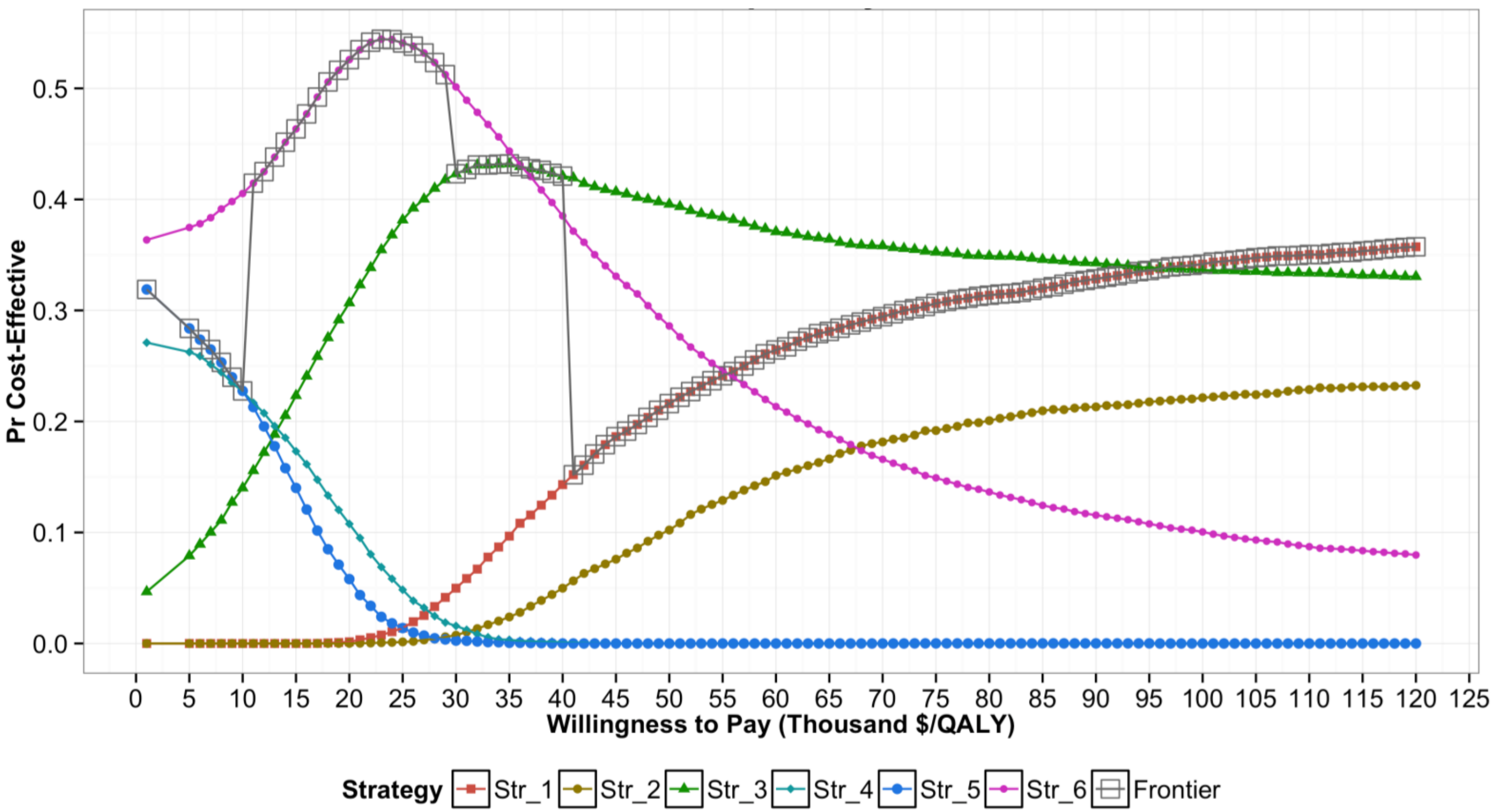
Cost-effectiveness acceptability curves (CEACs)



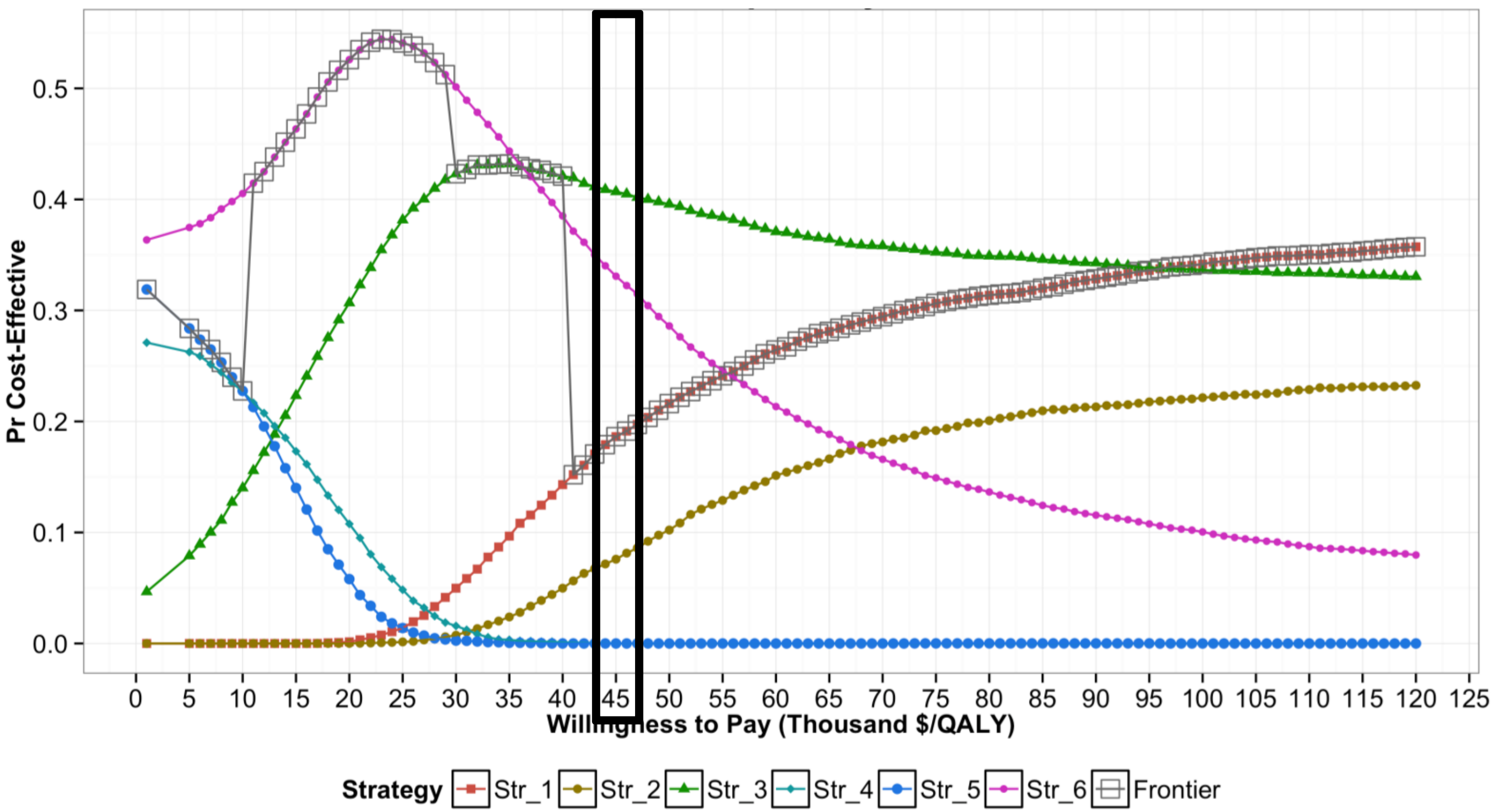
Cost-effectiveness acceptability curves (CEACs)



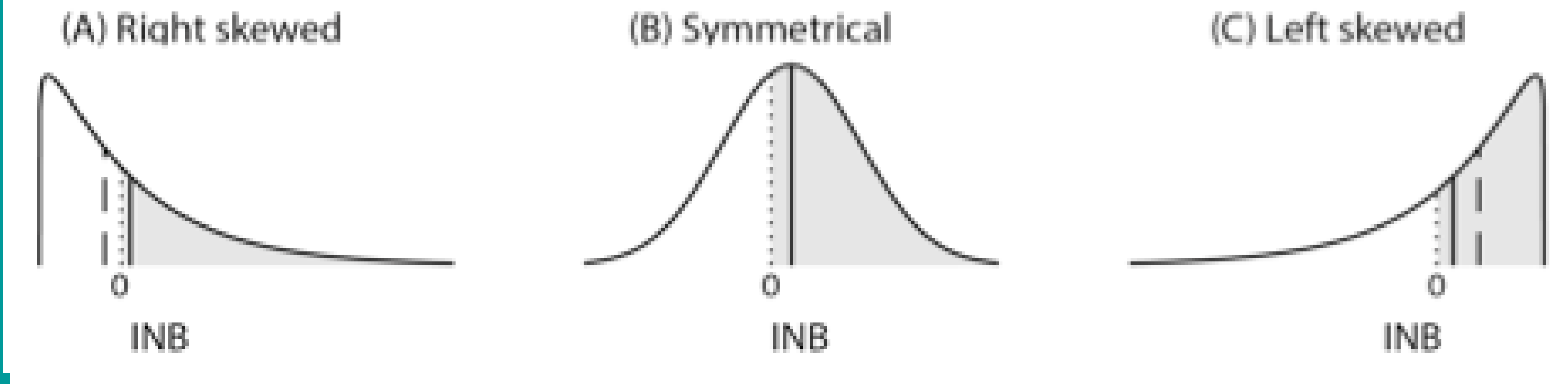
Cost-effectiveness acceptability curves (CEACs) and frontier (CEAF)



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



Distributions of Incremental NMB



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.

Value of Information

- How likely we are to make the wrong decision
- <u>And</u> 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

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

where $B_{i,d_i^*} = max_d\left(B_{i,d}\right)$ 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

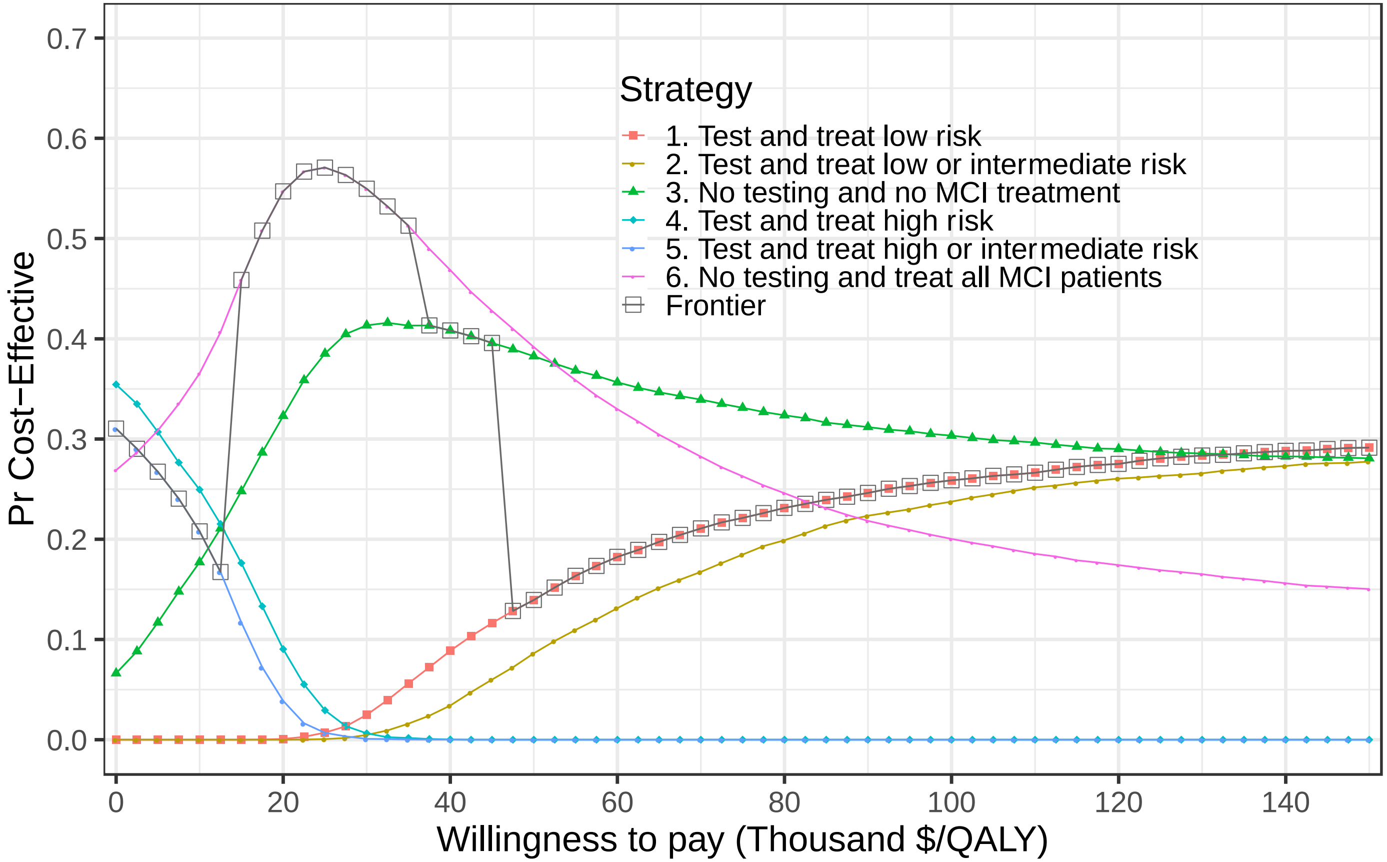
Alarid-Escudero F, Enns EA, Kuntz KM, Michaud TL, Jalal H. "Time Traveling Is Just Too Dangerous" But Some Methods Are Worth Revisiting: The Advantages of Expected Loss Curves Over Cost-Effectiveness Acceptability Curves and Frontier. *Value Health*. 2019;In Press.

Construction of ELCs

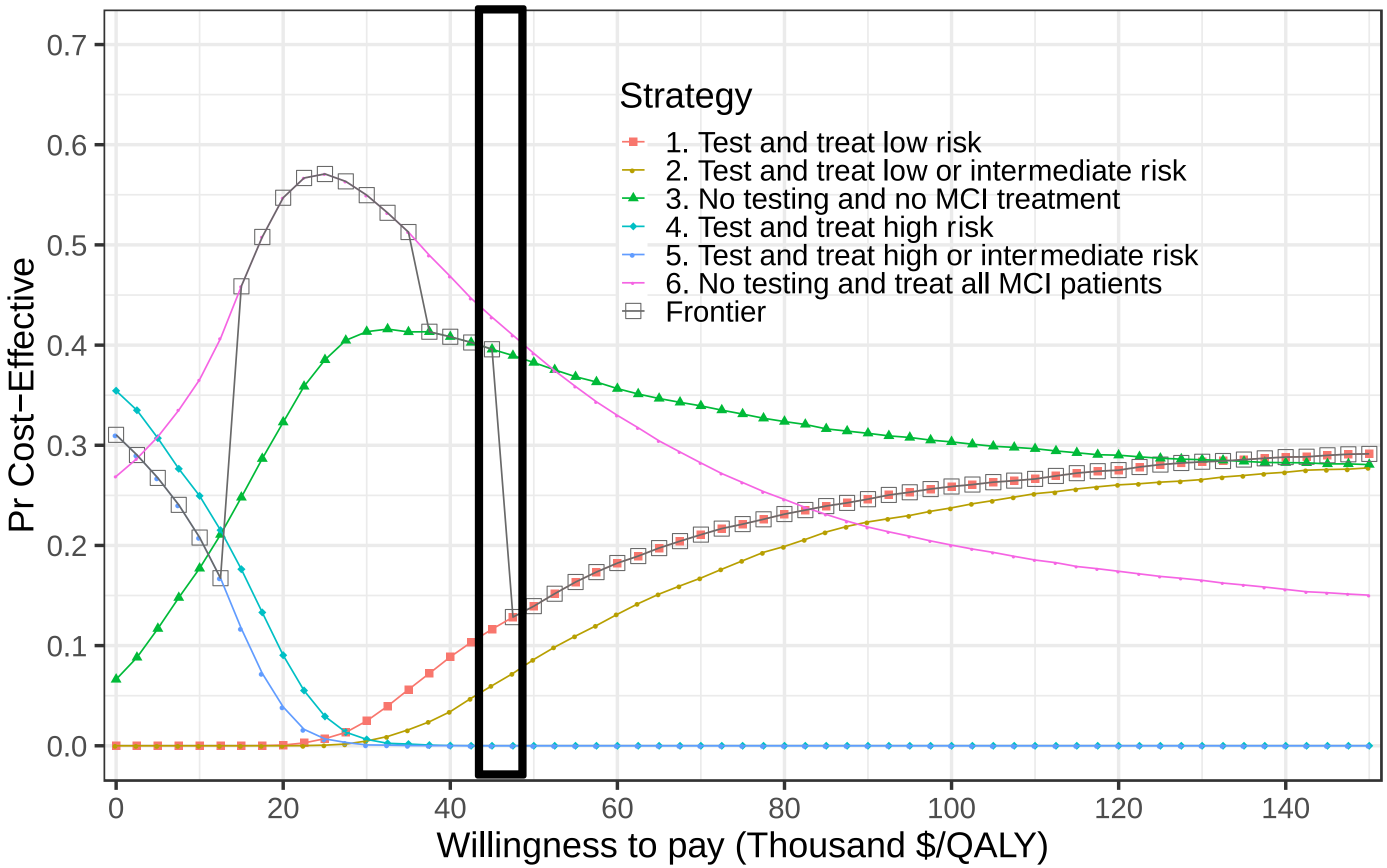
# Sim	NMB A	NMB B	NMB C	Best Strategy	Highest NMB	Loss A	Loss B	Loss C
1	442531	**446259**	445305	B	446259	3728	0	953
2	443420	445029	**445305**	C	445305	1885	277	0
3	**470225**	448650	445305	A	470225	0	21575	24920
4	**475179**	442967	445305	A	475179	0	32212	29874
5	**454703**	436838	445305	A	454703	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
					Expectd Loss ->	**4256**	**7658**	**10827**

Lowest expected loss = Optimal strategy

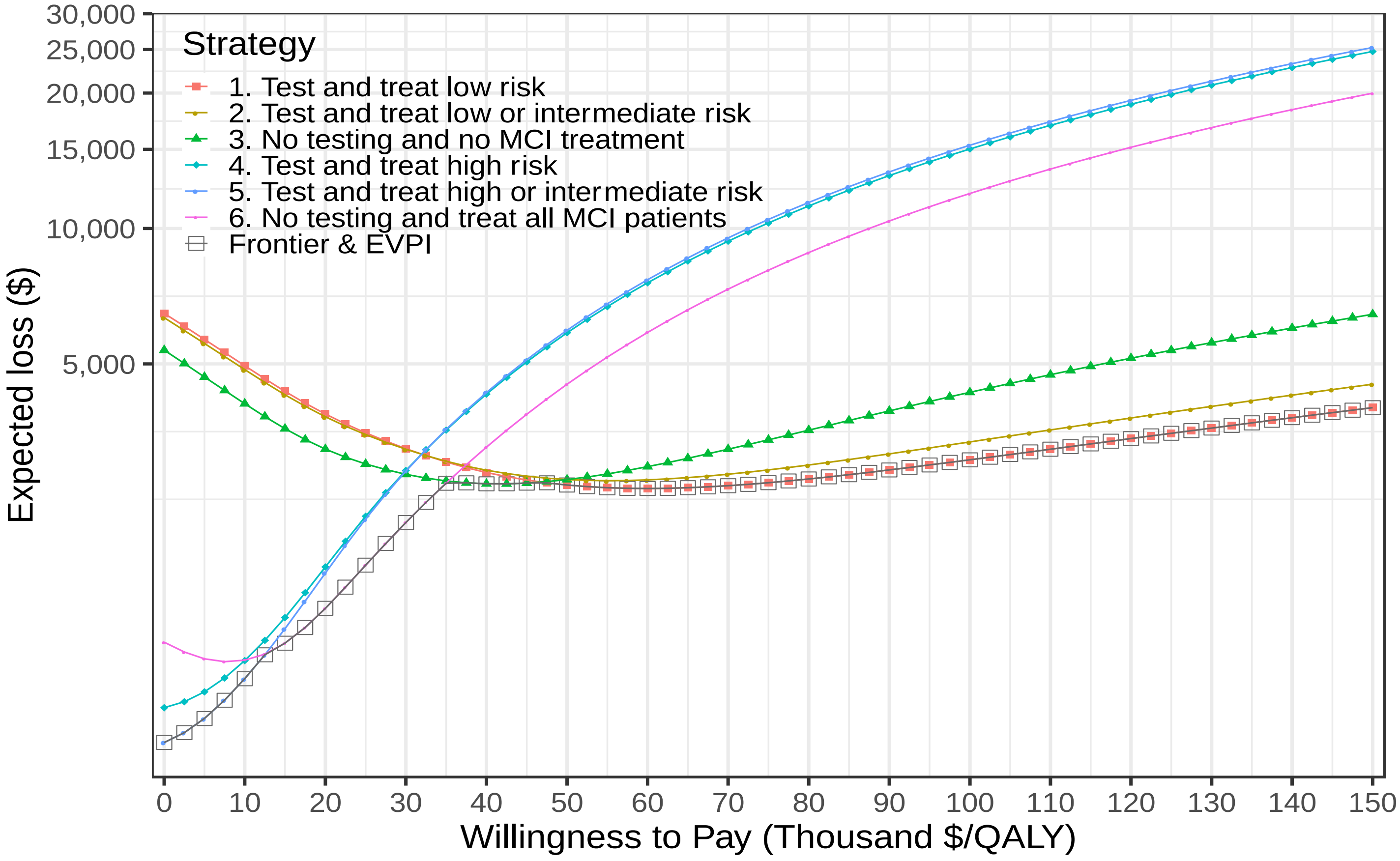
CEACs and CEAF



CEACs and CEAF

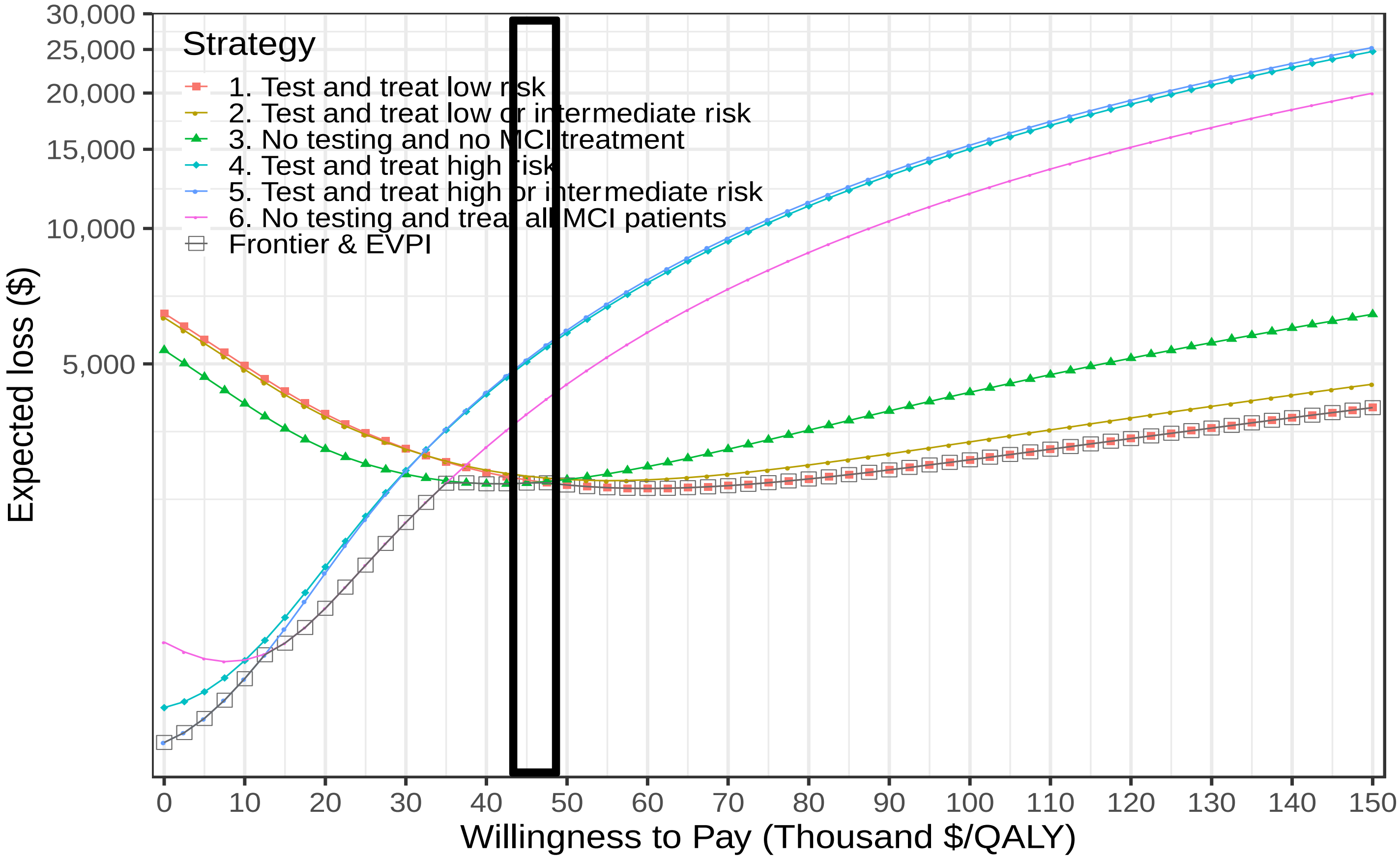


ELCs



Strategy
1. Test and treat low risk
2. Test and treat low or intermediate risk
3. No testing and no MCI treatment
4. Test and treat high risk
5. Test and treat high or intermediate risk
6. No testing and treat all MCI patients
Frontier & EVPI
Expected loss ($)
30,000
25,000
20,000
15,000
10,000
5,000
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
Willingness to Pay (Thousand $/QALY)

ELCs



Strategy
1. Test and treat low risk
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3. No testing and no MCI treatment
4. Test and treat high risk
5. Test and treat high or intermediate risk
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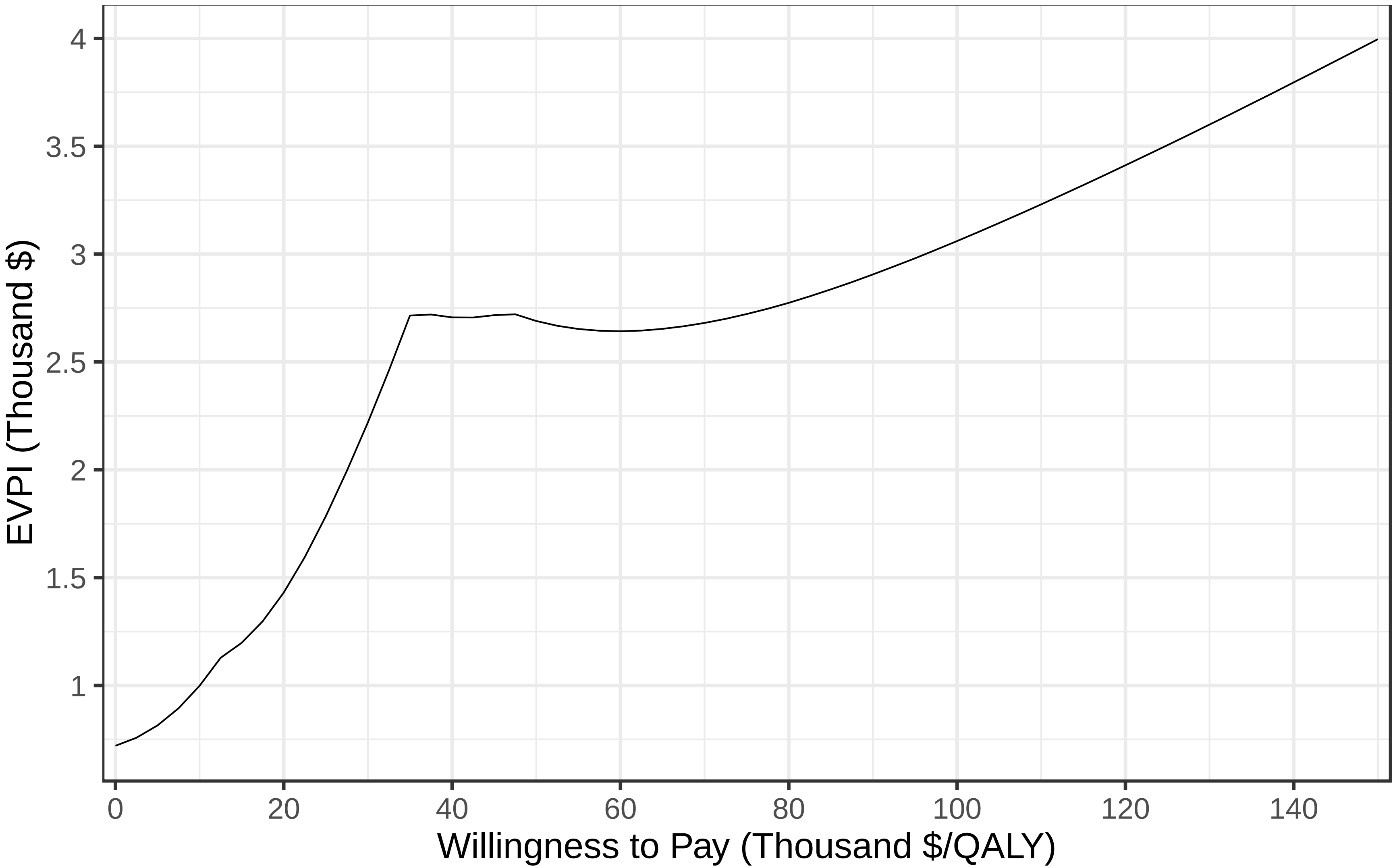
Frontier & EVPI
Expected loss ($)
30,000
25,000
20,000
15,000
10,000
5,000
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
Willingness to Pay (Thousand $/QALY)

EVPI



EVPI (Thousand $)
4
3.5
3
2.5
2
1.5
1
0
20
40
60
80
100
120
140
Willingness to Pay (Thousand $/QALY)

$\mathbb{R}$ Session

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