

Expected value of sample information accounting for heterogeneous treatment effects

Chengyang Gao, Gianluca Baio, Nathan Green

University College London

EVSI-CATE: Value of Information Analysis for Jointly Learning Heterogeneous Treatment Effects

A Decision-Theoretic Framework for Optimise Trial Subgroup Compositions

Why consider Heterogeneous treatment effects?

- Especially when its still uncertain

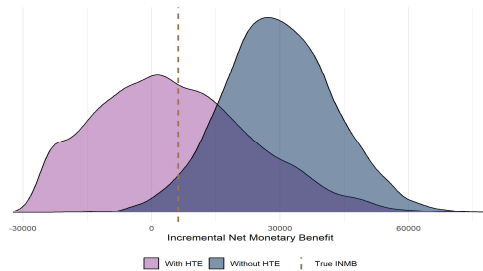


Figure 1. Posterior distributions of target population incremental net monetary benefits (INMB) under decreasing treatment effects. Brown dashed line represents the true target population INMB

- When the underlying treatment effects are decreasing, ignoring the uncertainty heterogeneous treatment effects (HTE) can overestimate of the target population net benefits.
- Ignoring uncertain HTE also leads to overconfidence:
 - The model-based predictions assigns high probability of cost-effectiveness based on limited data
 - Value of information analysis would indicate no further research is required

Why we need EVSI-CATE for uncertainty quantification?

- We already have EVSI, right?

- **Key distinction:**
 - Standard EVSI is mostly being designed for learning treatment effect parameters independently, whereas a trial exploring HTE requires jointly learning all treatment effects parameters;
 - The subgroup composition in this context becomes a random variable, an additional optimization objective needs to be defined.
- **EVSI vs. EVSI-CATE**

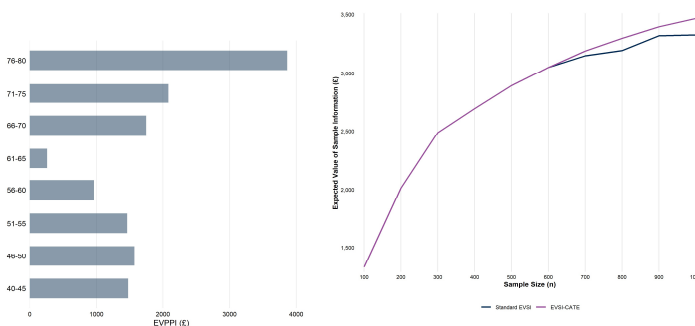


Figure 2: Expected value of partial perfect information of subgroup-specific treatment effects. The treatment effects in the top age group dominates the decision uncertainty.

- In the situation where the uncertainty of one subgroup-specific treatment effect dominates the decision uncertainty, the maximum of EVSI-CATE is similar to EVSI – the optimal subgroup allocation is to prioritise the subgroup with highest EVPPI;
- The flip side is that EVSI-CATE could help find alternative subgroup compositions that offer a similar level of information gain when focusing on one single subgroup is deemed undesirable;
- It is also foreseeable that learning treatment parameters jointly can be more efficient when the distribution of single parameter EVPPI is less skewed, and the subgroup-level correlation is high.

Value of information analysis for HTE: EVSI-CATE

- Extending standard EVSI for subgroup effects

- **Rational:** for population-level decision making, subgroups matter differently based on the target population composition
- Parameter setup: θ_s - subgroup-specific effects; $\tilde{S}_i$ - subgroup proportion in the target population; NB^P - target population net benefits
- Value of current decision accounting for HTE:

$$\max_d E_{\theta} [NB^P(d, \theta)] = \max_d E_{\theta} \left[\sum_{i=1}^S NB(d, \theta_s) \tilde{S}_i \right]$$

- **EVSI-CATE:**
 - The goal should be to choose the subgroup composition maximizes the information gains;
 - Suppose the probability simplex $\alpha = \{\alpha_1, \alpha_2, \dots, \alpha_S\}$ represents the subgroup composition in a future trial;
 - EVSI-CATE requires solving the following optimization:

$$\alpha^* = \underset{\alpha}{\operatorname{argmax}} \left(E_{X|\alpha} \left\{ \max_d E_{\theta|X} [NB^P(d, \theta)] \right\} - \max_d E_X \left\{ E_{\theta|X} [NB^P(d, \theta)] \right\} \right)$$

- The outermost loop involves optimizations in the probability simplex space
- The computation of NB^P requires efficient approximation methods [1-3], with regression-based methods [1] being most direct. However:
 - Each subgroup-specific parameter requires a set of summary statistics;
 - The model could involve complex interactions among summary statistics;
 - Model fitting needs to be fast (Exact GP can be too computational intensive).

The road ahead for EVSI-CATE

- Practical considerations of EVSI-CATE in trial design

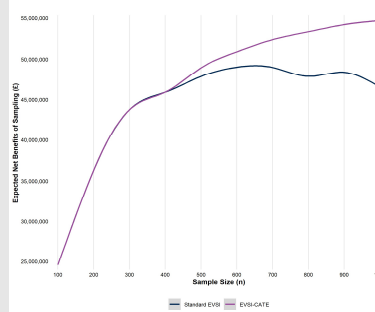


Figure 4: Expected net benefits of sampling (ENBS) of a potential trial at various sample sizes designed according to EVSI or EVSI-CATE.

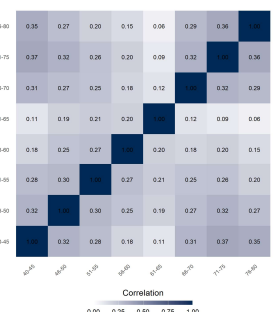
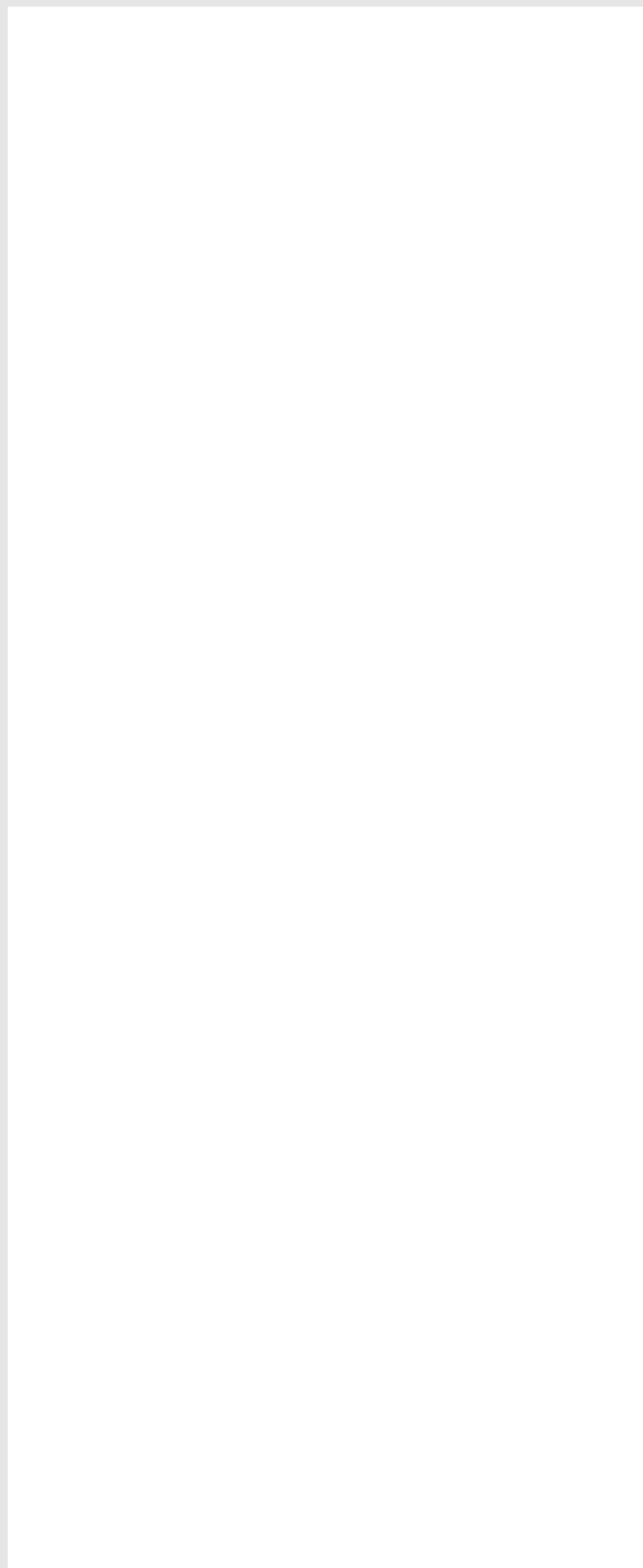


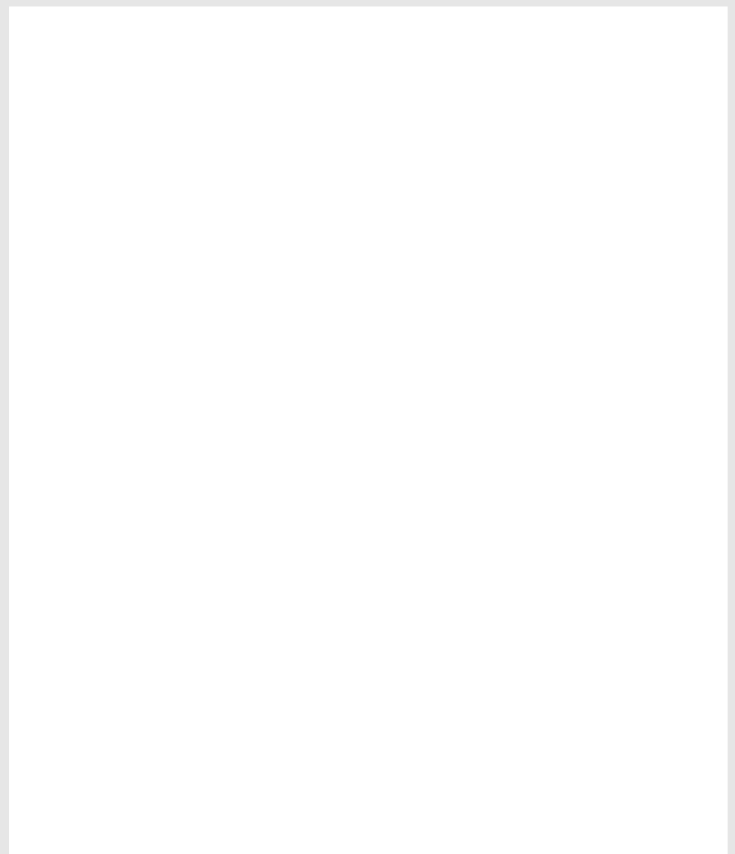
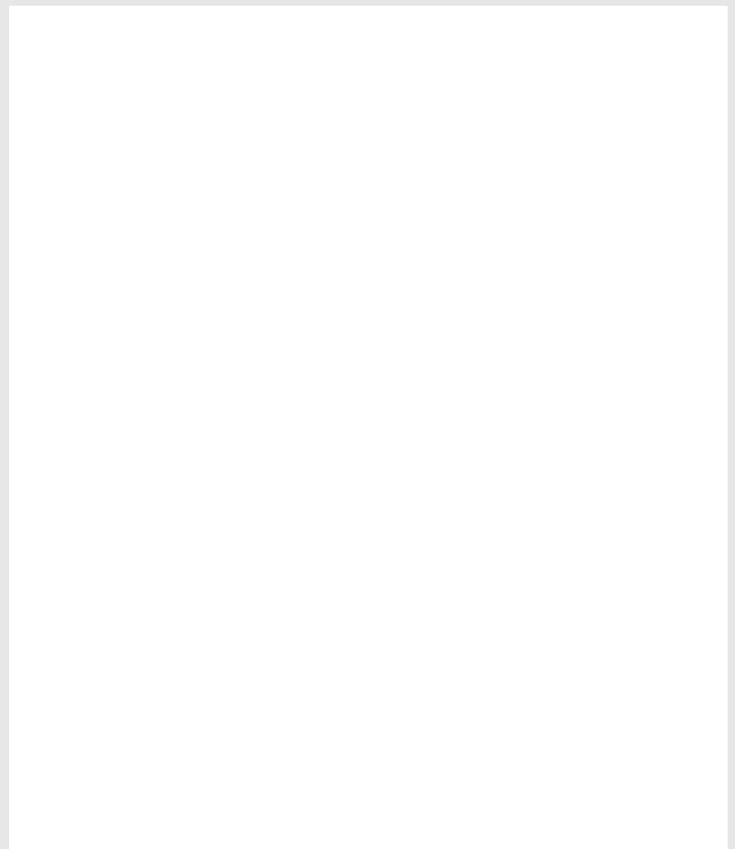
Figure 5: Posterior correlation structure of the subgroup-specific treatment effects

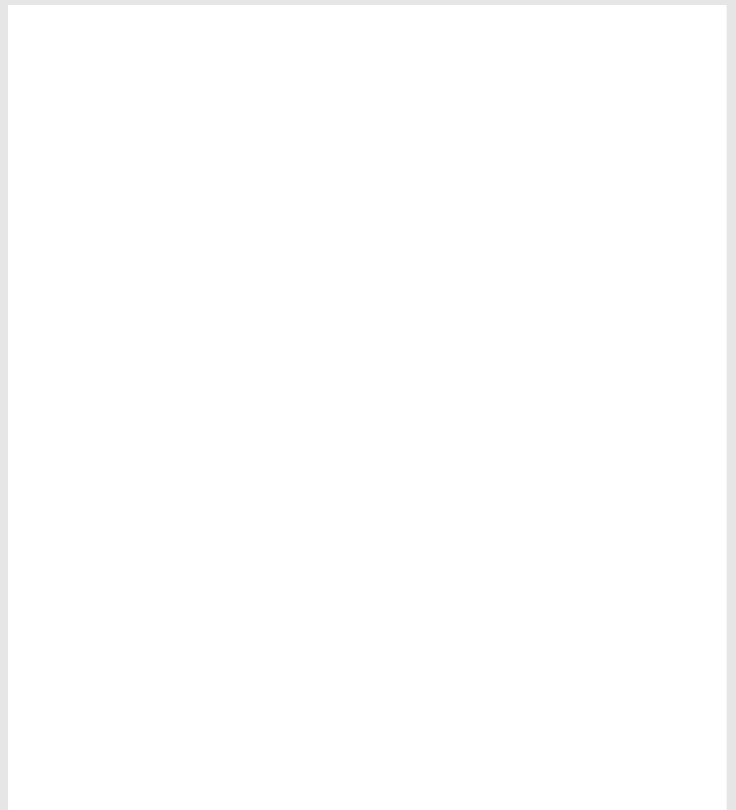
- Adding costs considerations would change the optimisation question – the sampling costs for the most important subgroup could be high and prioritizing this group alone might lead to designs with sub-optimal economic values;
- Intuitions on why alternative subgroup compositions might be optimal:
 - When learning all treatment effect parameters jointly, different subgroups could cross-inform each other under a hierarchical model – allows 'direct' and 'indirect' learning of subgroup-specific effects
- **Limitations and future direction:**
 - The computation of NB^P is based on non-parametric regression, which requires re-implement the optimisation for different sample size and willingness-to-pay threshold, making it impractical for realistic trial planning;
 - Extending other efficient computation methods for multi-parameter settings would be a promising direction

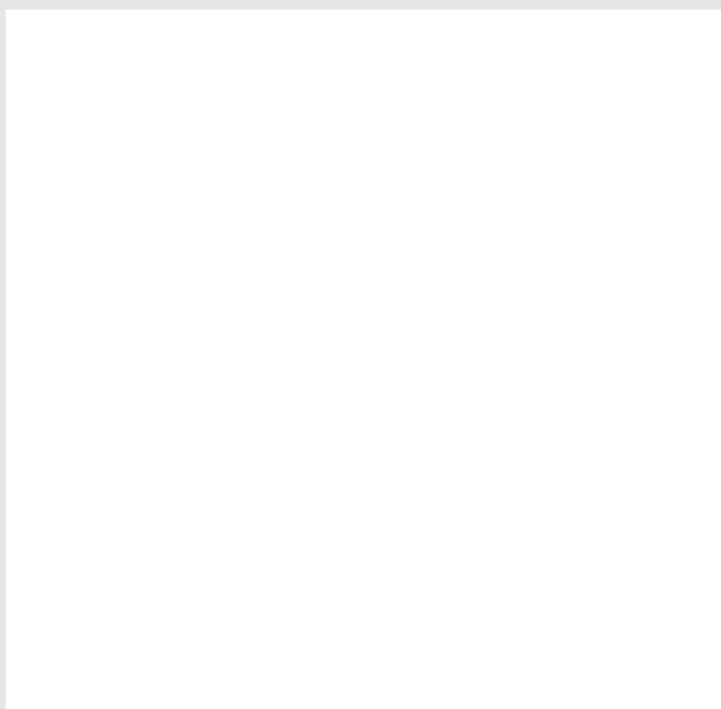
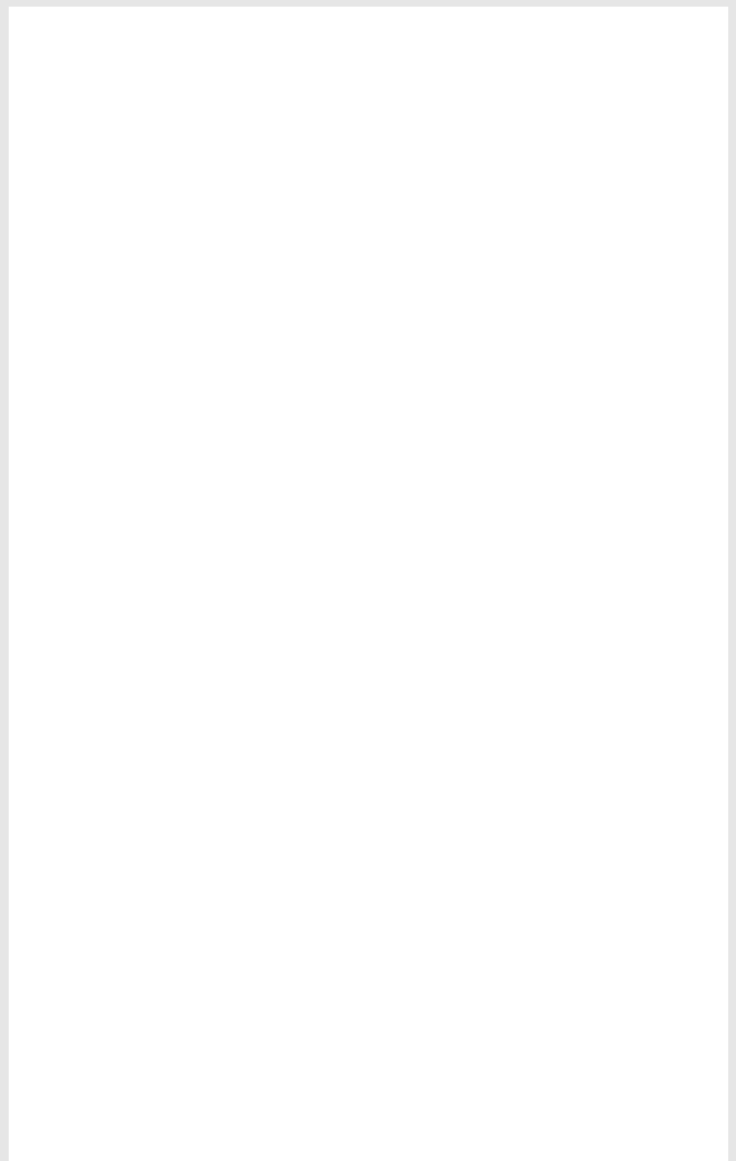
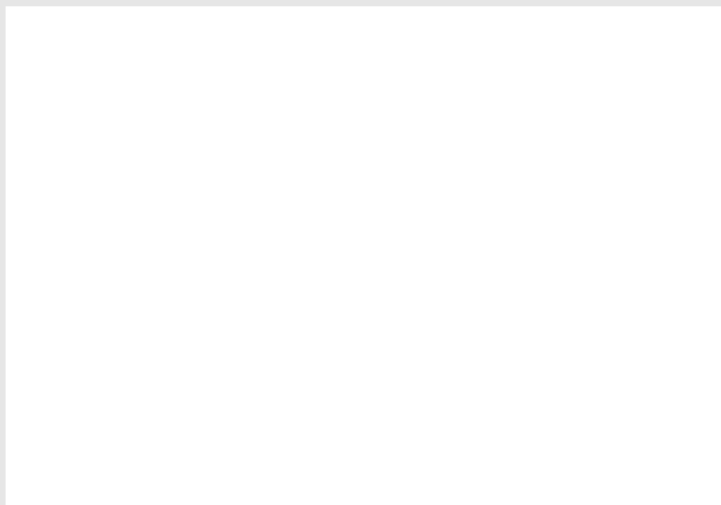
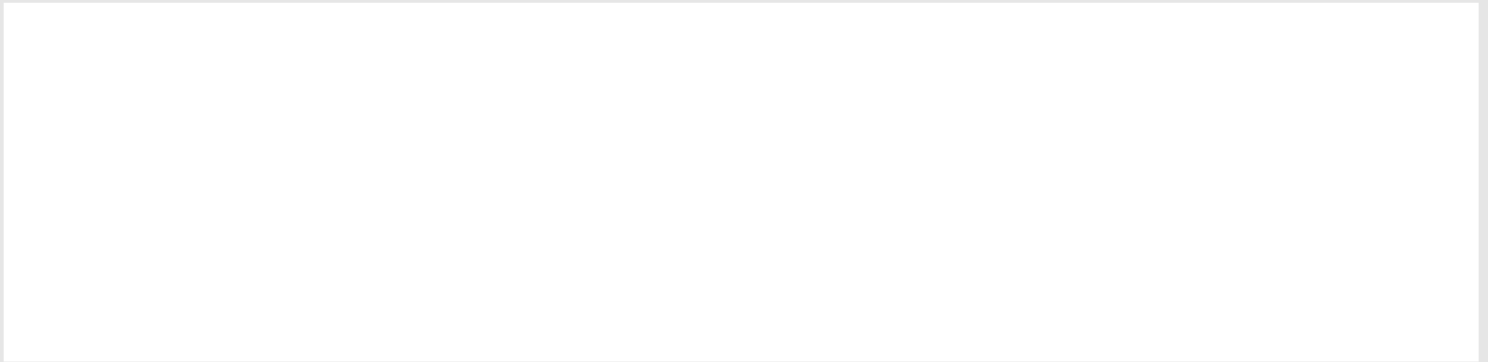
References:

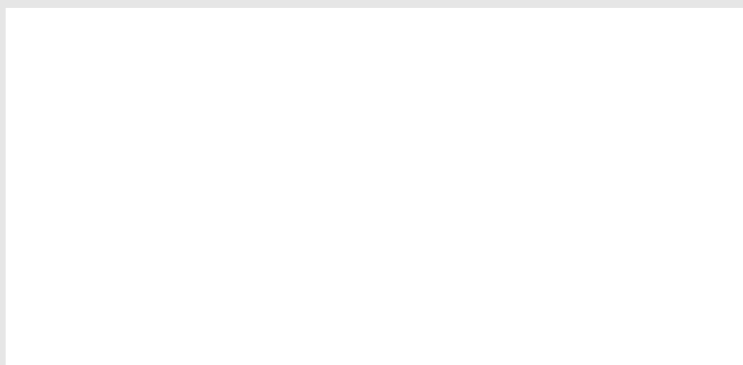
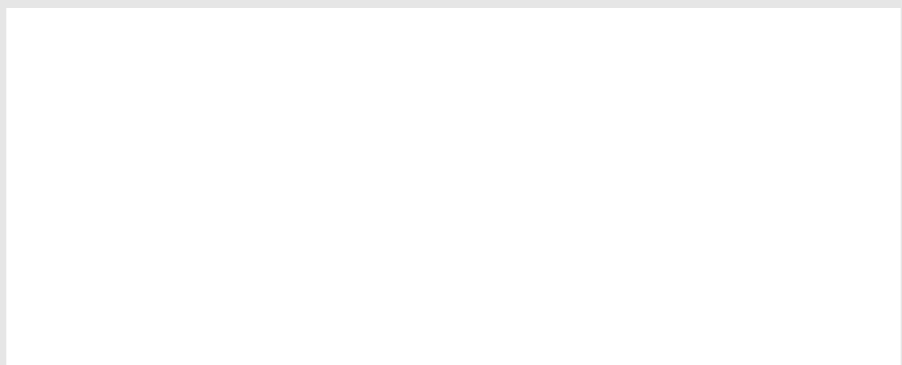
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2. Heath A, Manolopoulou I, Baio G. Estimating the expected value of sample information across different sample sizes using moment matching and nonlinear regression. Medical Decision Making. 2019 May;39(4):347-59.
3. Jalal H, Alarid-Escudero F. A Gaussian approximation approach for value of information analysis. Medical Decision Making. 2018 Feb;38(2):174-88.











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