

Confirmation of diagnostic biomarker accuracy

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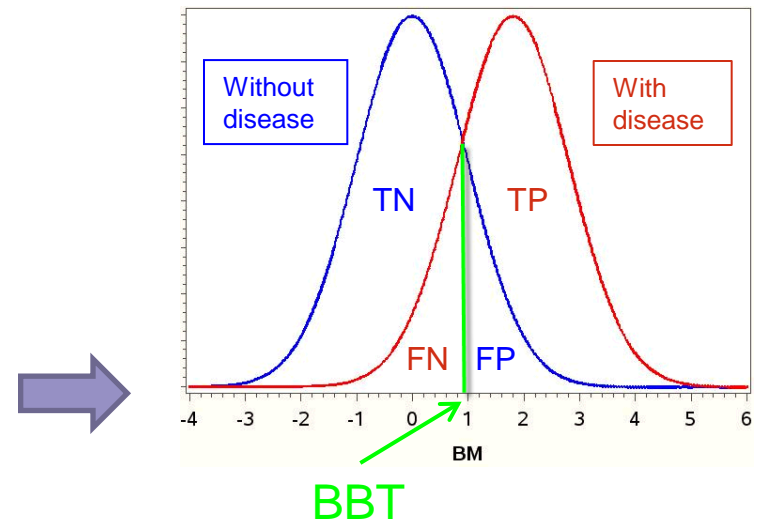
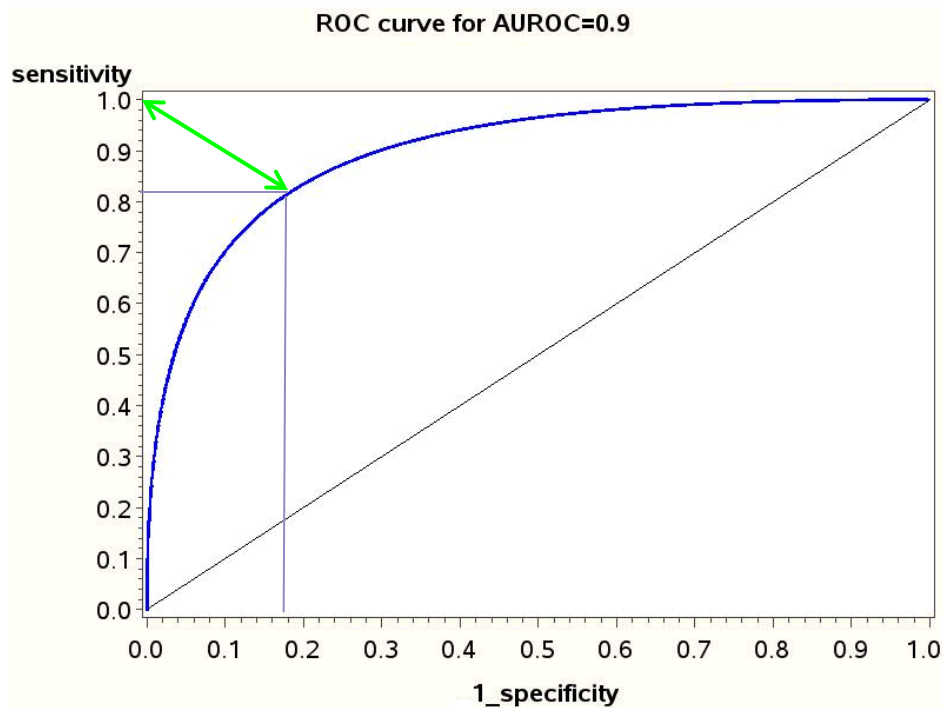
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Introduction

- Replicability is a fundamental principle of good scientific practice
 - A claimed research finding is more convincing if it is replicated
 - Lack of replicability observed in genomic research, drug development or medical research in general
- But replicability would not be needed for findings found on the whole population or on very large sample size highly representative of the population
 - Link between replicability and sampling (overfitting)
 - Link between replicability and sample size
 - Link between replicability and confidence intervals
 - Link between replicability and multiplicity (Bretz and Westfall – Pharmaceutical Statistics 2014)
- A study showing performance of a single BM with 10 000 subjects might not need replicability
 - But maybe different for a combination of 1000 BMs in this study
 - Link between replicability and ratio of number of subjects versus number of parameters of a model to estimate

How to confirm diagnostic biomarker best threshold

- Replicability in the scope of confirmation of best biomarker threshold?
- Biomarker best threshold (BBT) determined on ROC curves



$$\min[(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2]$$

How to confirm diagnostic biomarker best threshold

- Replicability in the scope of confirmation of biomarker best threshold?
 - Bias of the threshold
 - Bias of sensitivity and of specificity
 - Coverage probability of 95% confidence intervals of sensitivity and of specificity

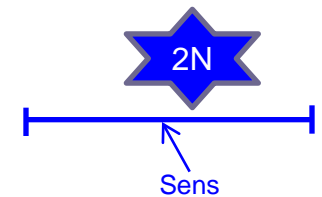
How to confirm diagnostic biomarker best threshold

- Simulations to assess these biases in various study designs/statistical approaches

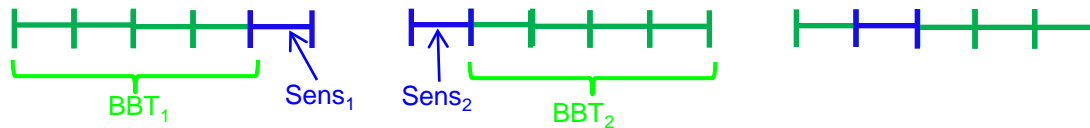
1. Simple case of one stand alone study



2. Confirmation in one independent study



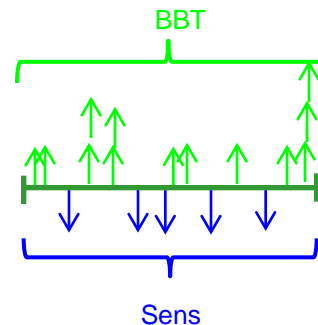
3. 5-fold cross validation



... All 5 combinations

4. 200-fold Repeated 5-fold cross validation (5-fold cross validation repeated 200 times with random seeds)

5. Bootstrap (1000 sampling replicates with replacement)



How to confirm diagnostic biomarker best threshold

- **Simulation details**

- **2 sets of simulations**

- With only 1 binormal biomarker in each study
- Winner's curse case with 5, 10 and 20 **uncorrelated** binormal biomarkers in each study, i.e. keeping the best one of each study separately (overfitting)

- **For each set of simulation**

- AUROC = 0.8 and 0.9
- Ncontrol = Ndisease = 50 and 100
- Number of studies for each setting = 1000
- ROC estimates via empirical ROC curves

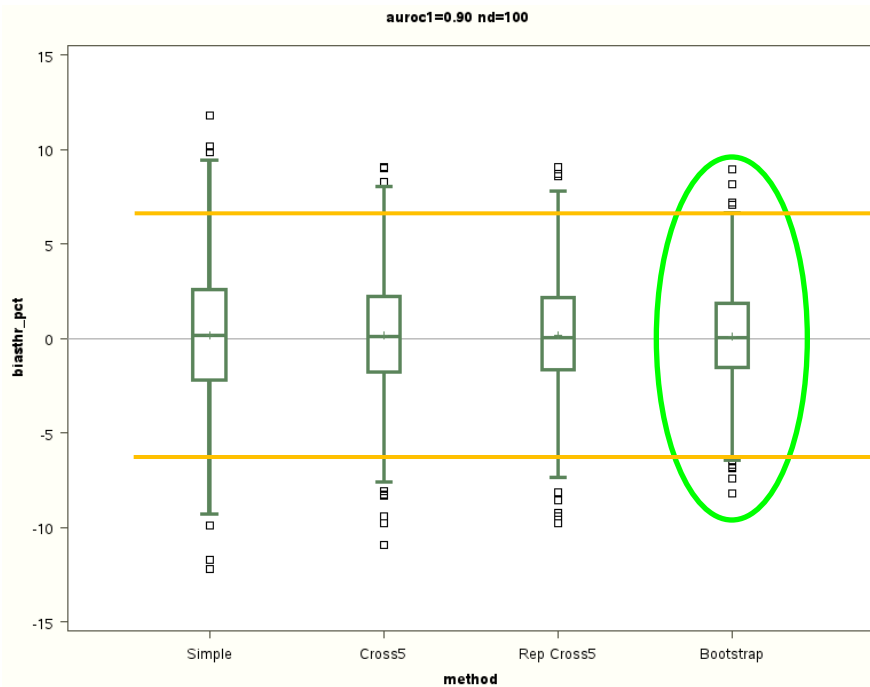
- **Results of 1000 studies summarized in boxplots**

- Boxplots of bias of best biomarker threshold (%)
- Boxplots of bias of best biomarker threshold's sensitivity (%)
- Coverage probability of 95% binomial (Wilson) confidence intervals of sensitivity

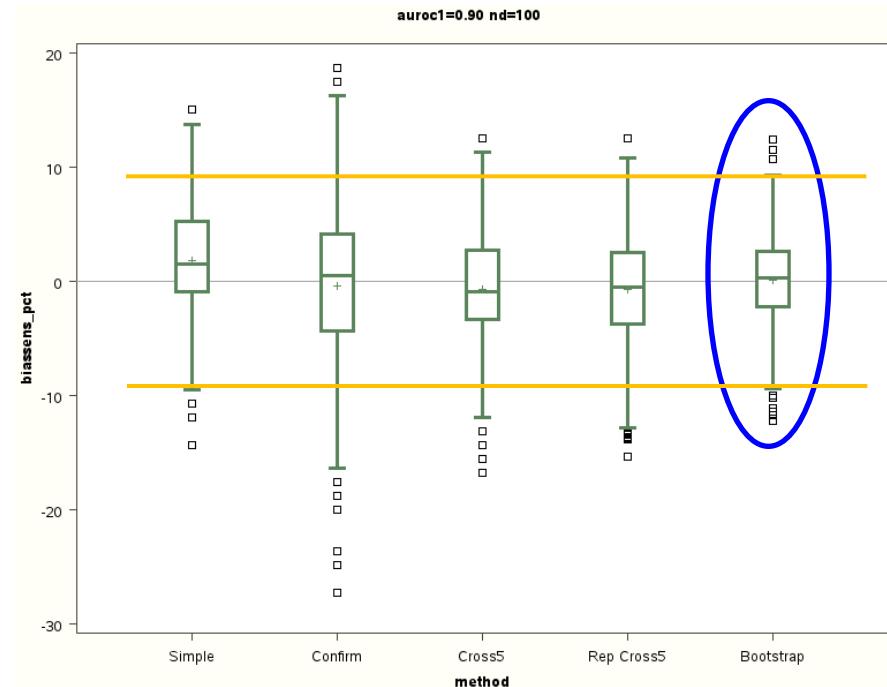
How to confirm diagnostic biomarker best threshold

- Simulation results with only 1 biomarker in each study

- Threshold



- Sensitivity



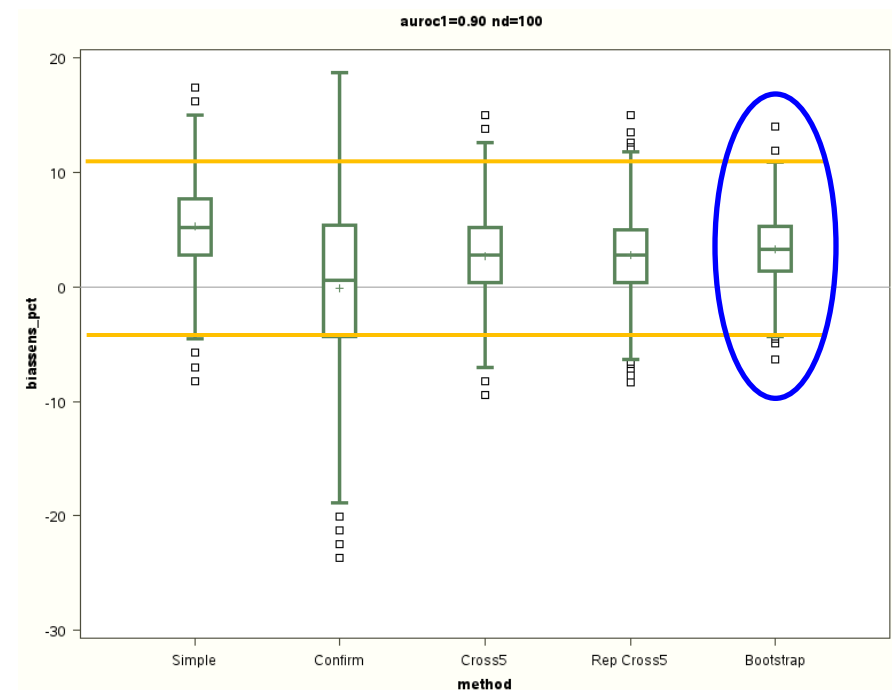
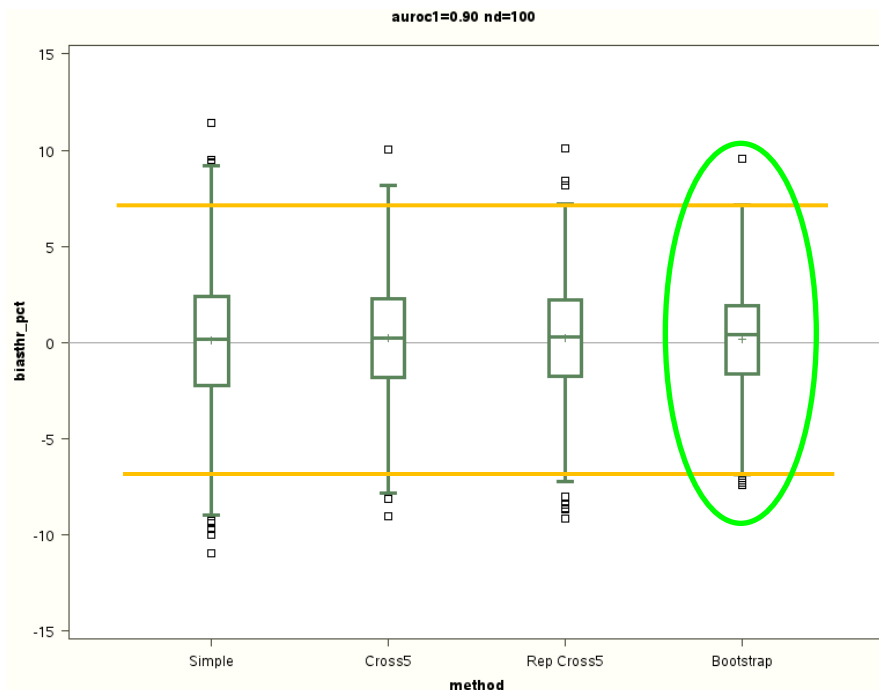
How to confirm diagnostic biomarker best threshold

- Simulation results with only 1 biomarker in each study
 - Coverage probability of 95% confidence intervals of sensitivity

method	coverage_probability
Bootstrap	98.8
Rep Cross5	95.4
Cross5	94.6
Simple	92.3
Confirm	85.5

How to confirm diagnostic biomarker best threshold

- Simulation results with 5 biomarkers in each study, keeping the best one of each study separately
 - Threshold
 - Sensitivity



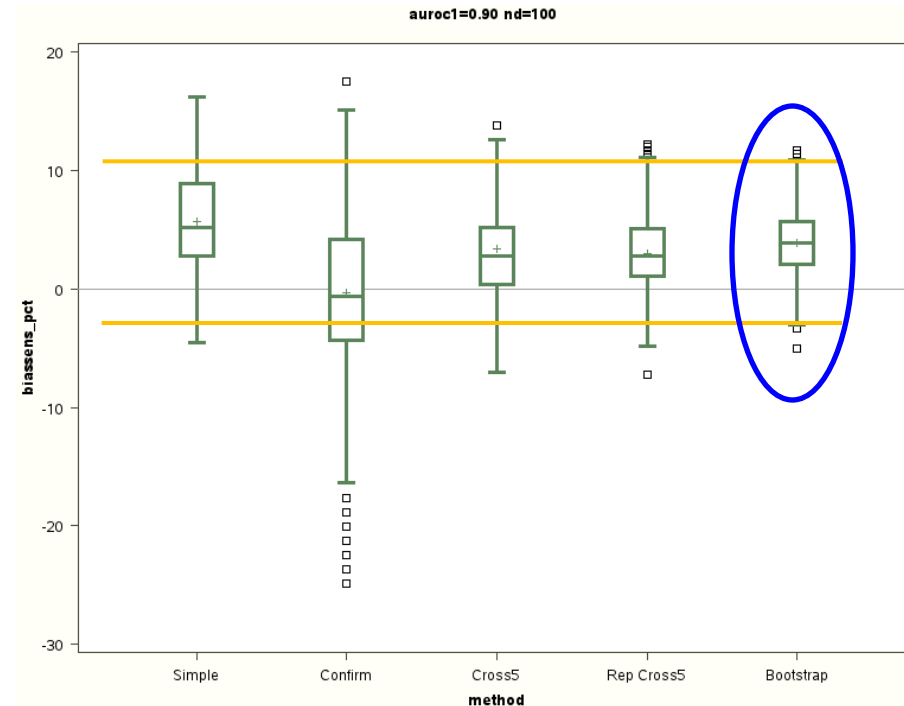
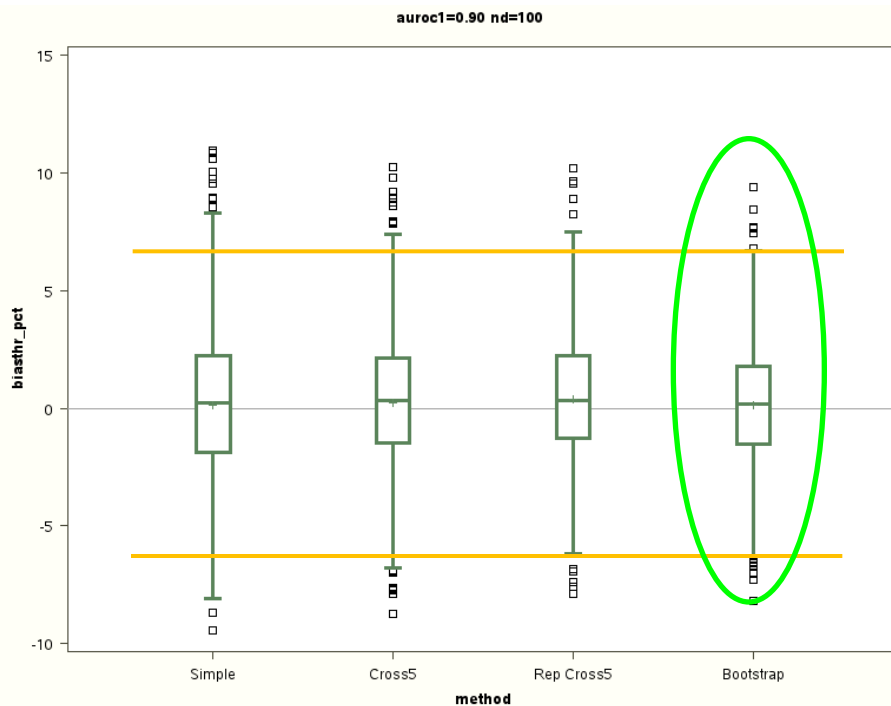
How to confirm diagnostic biomarker best threshold

- Simulation results with **5** biomarkers in each study, keeping the best one of each study separately
 - Coverage probability of 95% confidence intervals of sensitivity

method	coverage_probability
Bootstrap	98.7
Rep Cross5	96.9
Cross5	96.8
Confirm	86.5
Simple	85.5

How to confirm diagnostic biomarker best threshold

- Simulation results with **10** biomarkers in each study, keeping the best one of each study separately
 - **Threshold**
 - **Sensitivity**



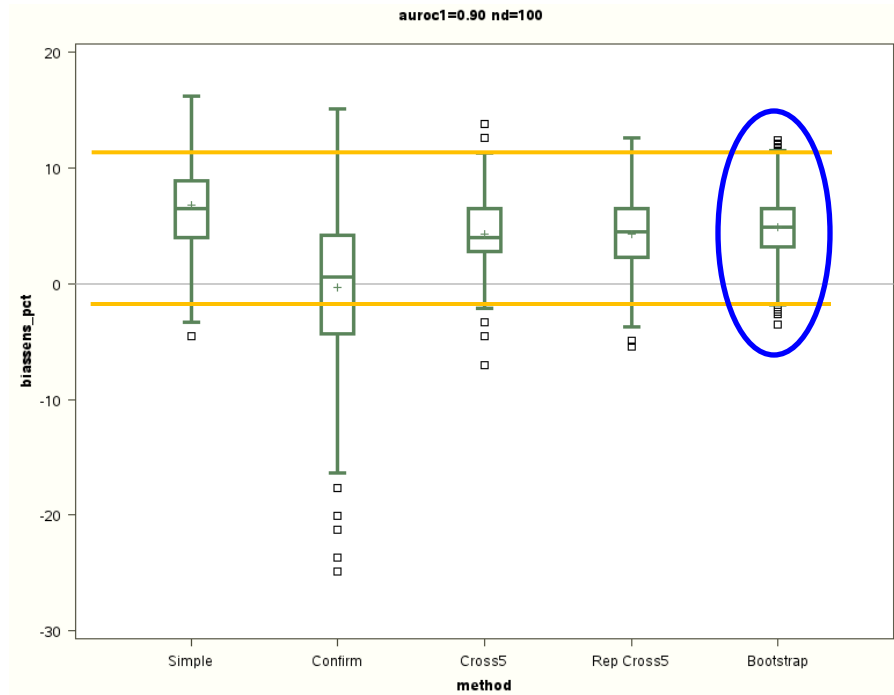
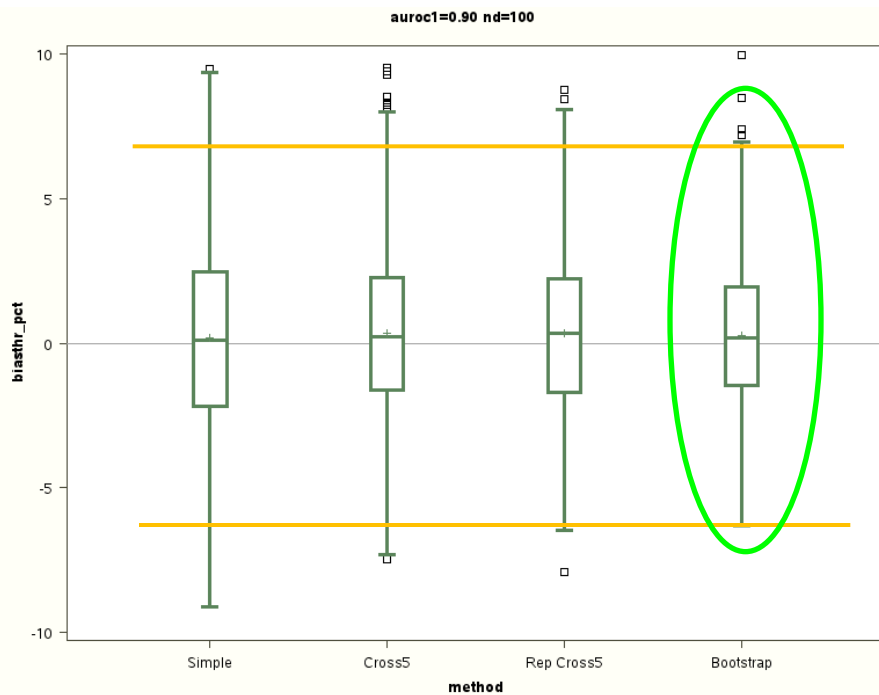
How to confirm diagnostic biomarker best threshold

- Simulation results with **10** biomarkers in each study, keeping the best one of each study separately
 - Coverage probability of 95% confidence intervals of sensitivity

method	coverage_probability
Bootstrap	97.5
Rep Cross5	96.4
Cross5	95.0
Confirm	86.4
Simple	83.7

How to confirm diagnostic biomarker best threshold

- Simulation results with **20** biomarkers in each study, keeping the best one of each study separately
 - **Threshold**
 - **Sensitivity**



How to confirm diagnostic biomarker best threshold

- Simulation results with **20** biomarkers in each study, keeping the best one of each study separately
 - Coverage probability of 95% confidence intervals of sensitivity

method	coverage_probability
Bootstrap	96.0
Rep Cross5	95.4
Cross5	95.0
Confirm	87.1
Simple	77.2

How to confirm diagnostic biomarker best threshold

- Simulation conclusion

- For the winner's curse case (usual studies cases), using standard ROC curves and BBT's sensitivity estimation leads to biased estimation and to low coverage probability of confidence intervals
- Using an independent study (doubling the sample size) for the confirmation of BBT's sensitivity leads to no bias in average but to higher false positive and false negative biomarkers due to high variability of the estimation in the confirmation study (low coverage probability of confidence intervals)
- For the winner's curse case (usual studies cases), resampling techniques (especially bootstrap) leads to little biased estimation but to correct coverage probability of BBT's sensitivity

How to confirm diagnostic biomarker best threshold

- In the case of these simulation setting, resampling statistical techniques allow a good estimation of diagnostic biomarker best threshold and its sensitivity, without increasing the sample size
 - If two independent studies exist, best estimates will come from using resampling statistical techniques on the pooled dataset
- Simulation to be pursued
 - To look at the multivariate case (combination of BMs)

Thank you