



GMDS 2021

Blinded sample size re-estimation in a paired diagnostic study

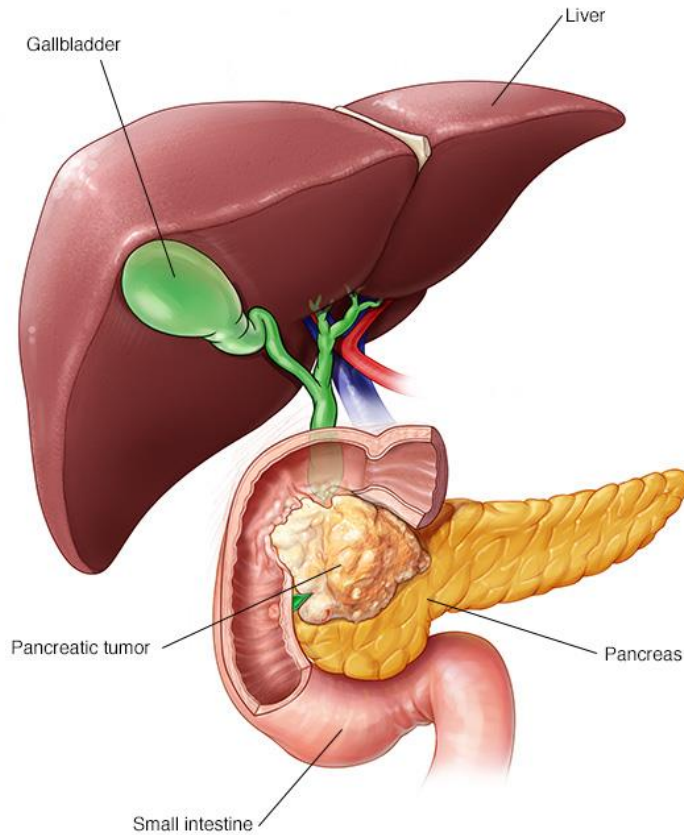
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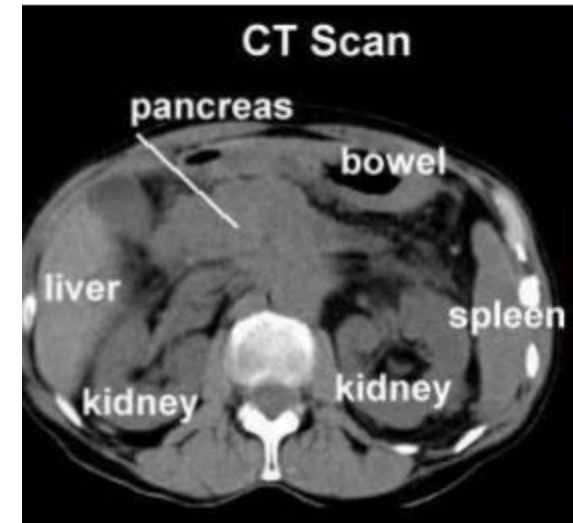


University Medical Center Hamburg-Eppendorf

CT and PET/CT to diagnose pancreatic cancer

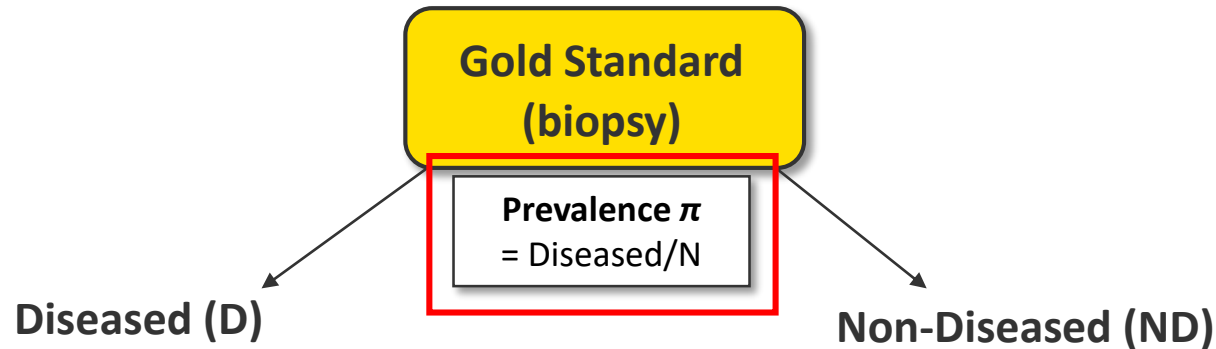


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[McCray et al., 2017]

Procedure of a paired diagnostic study



		Comparator Test (CT)				Comparator Test (CT)	
Exp. Test (PET/CT)	True Positive TP_E	True Positive TP_C ++	False Negative FN_C +-	Exp. Test (PET/CT)	False Positive FP_E	False Positive FP_C ++	True Negative TN_C +-
	False Negative FN_E	-+	ψ_D --		True Negative TN_E	-+	ψ_{ND} --

Sensitivity Se_E
= TP_E /Diseased

Sensitivity Se_C
= TP_C /Diseased

Specificity Sp_E
= TN_E /Non-diseased

Specificity Sp_C
= TN_C /Non-diseased

Notation N = total number of individuals
D = number of diseased individuals
ND = number of non-diseased individuals

π = prevalence
 ψ_D = number of discordant test results in diseased population
 ψ_{ND} = number of discordant test results in non-diseased popul.

Sample size calculation

Sensitivity and specificity are **independent co-primary endpoints**



Intersection-Union-Test:

$$H_{0_{se}}: Se_C = Se_E \text{ and } H_{0_{sp}}: Sp_C = Sp_E$$

$$H_{0_{global}}: H_{0_{se}} \cup H_{0_{sp}}$$

$$\text{Overall Power} = \text{Power}_{Se} \cdot \text{Power}_{Sp}$$

Optimal sample size calculation (Stark & Zapf, 2020)

$$N_{Se} \stackrel{!}{=} N_{Sp}$$



Split overall power to both endpoints

Fixed vs. Adaptive Design

Fixed design

1. Calculate initial sample size based on assumptions about nuisance parameters π , ψ_D and ψ_{ND}
2. Recruit the calculated sample size
3. Analyze the study

Blinded adaptive design

1. Calculate minimal possible initial sample size with minimal ψ_D and ψ_{ND} and assumption about π
2. Recruit the calculated initial minimal sample size
3. Re-estimate nuisance parameters $\hat{\pi}$, $\hat{\psi}_D$ and $\hat{\psi}_{ND}$
4. Re-estimate sample size
5. Recruit further patients until final sample size
6. Analyze the study

Notation N = total number of individuals
 D = number of diseased individuals
 ND = number of non-diseased individuals

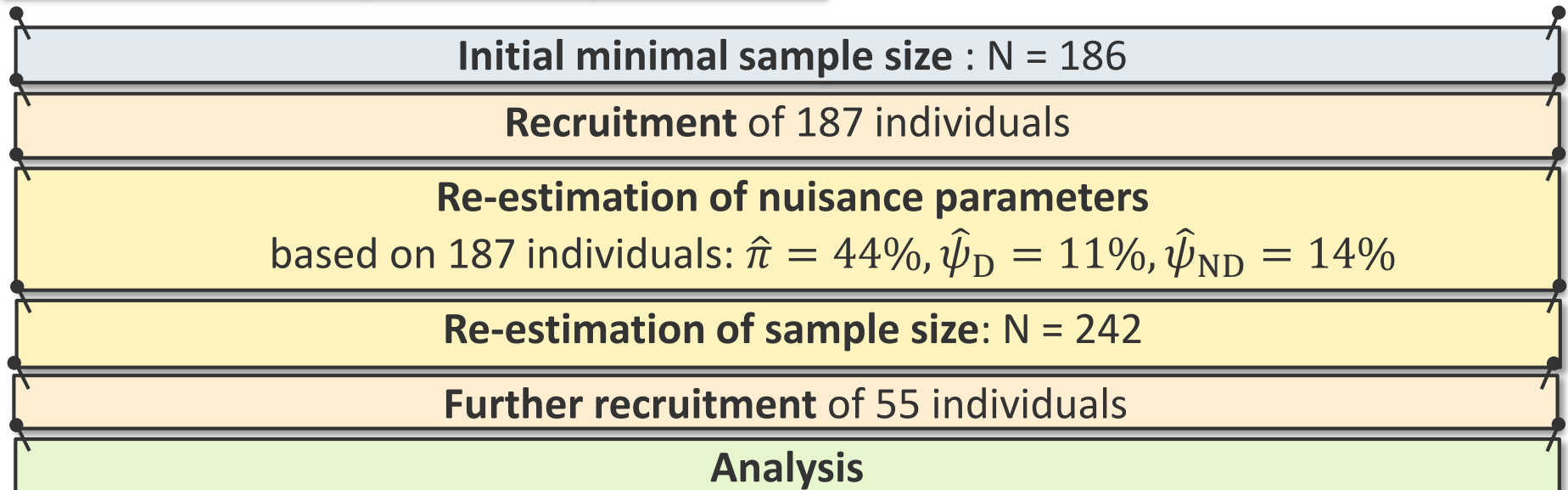
π = prevalence
 ψ_D = number of discordant test results in diseased population
 ψ_{ND} = number of discordant test results in non-diseased popul.

Example

Assumptions: $\alpha = 5\%$ (two-sided), $\beta = 20\%$

[McCray et al., 2017]

Diagnostic test	Sensitivity	Specificity	$\pi = 47\%$	Diseased	Non-Diseased
CT	81%	66%	Minimal disc. results	$\psi_D = 9\%$	$\psi_{ND} = 14\%$
PET/CT	90%	80%			



Notation		
N	= total number of individuals	π = prevalence
D	= number of diseased individuals	ψ_D = number of discordant test results in diseased population
ND	= number of non-diseased individuals	ψ_{ND} = number of discordant test results in non-diseased popul.

Simulation study

True parameters : $\alpha = 5\%$ (two-sided), $\beta = 20\%$ (overall)

[McCray et al., 2017]

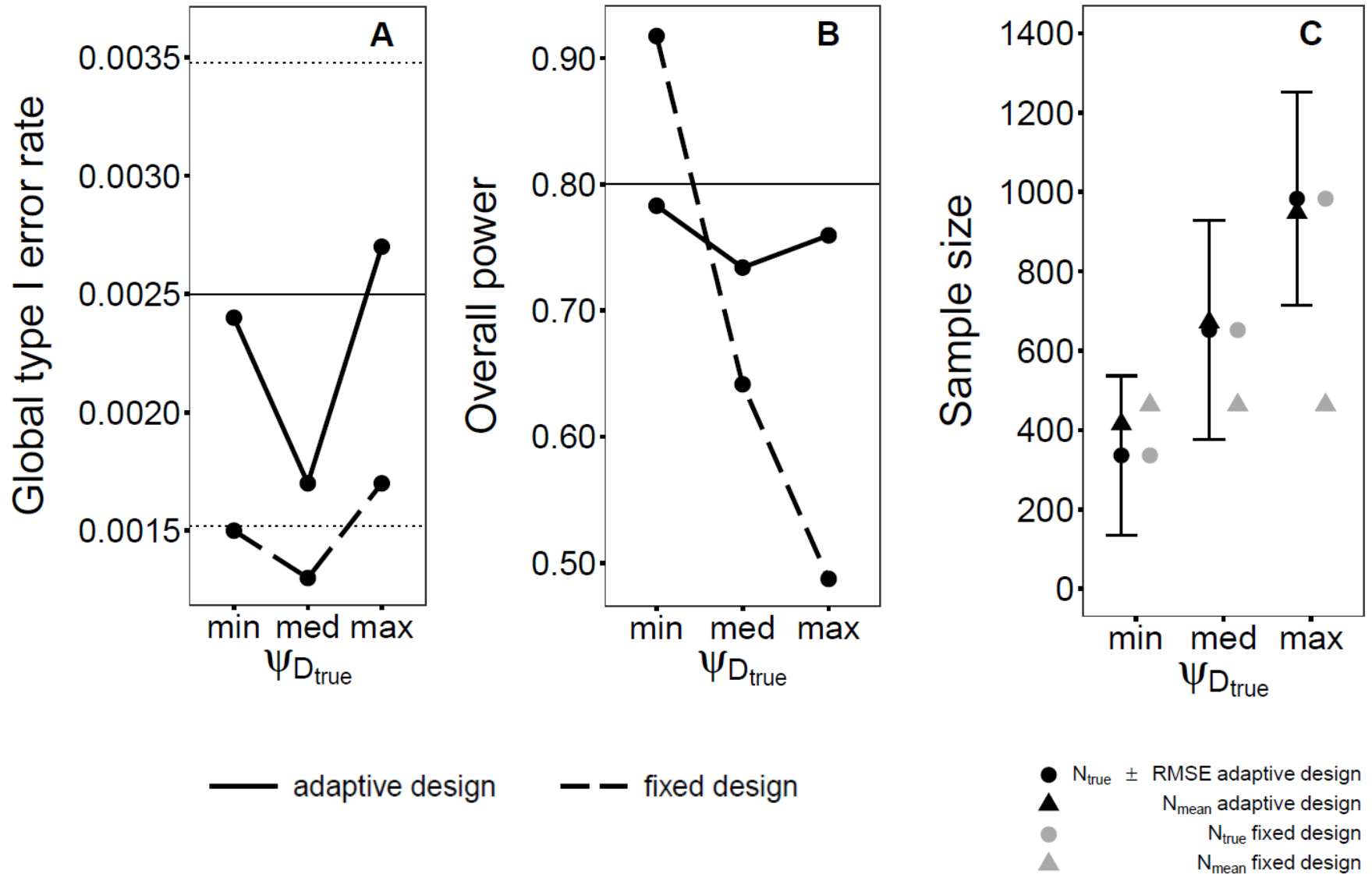
Diagnostic test	Sensitivity	Specificity	$\pi = 20\%$	Diseased	Non-Diseased
CT	80%	70%	True disc. results	$\psi_D = 11\%$	$\psi_{ND} = 14\%$
PET/CT	90%	80%			

Variation of true ψ_D
 min = 11%
 med = 18%
 max = 26%

Assumed prevalence
 $\pi = 30\%$
 Re-estimation of the prevalence
 in the single-test design:
 Stark & Zapf, 2020

Assumed discordant results
 $\psi_D = 18\%$
 $\psi_{ND} = 24\%$

Notation	N = total number of individuals	π = prevalence
	D = number of diseased individuals	ψ_D = number of discordant test results in diseased population
	ND = number of non-diseased individuals	ψ_{ND} = number of discordant test results in non-diseased popul.



Conclusion and next steps

Conclusion:

- Blinded adaptive design developed for paired diagnostic study
- Fixed and adaptive design hold type I error rate
- Power in the fixed design strongly depends on the assumptions. It can be over- or underpowered.
- Power in the adaptive design comes close to the target power, independent of the initial assumptions.

Next steps:

- R-package for adaptive designs in diagnostic studies

References

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