Reducing Decision Errors in the Paired Comparison of the Diagnostic Accuracy of Continuous Screening Tests

Brandy M. Ringham,[1] Todd A. Alonzo,[2] John T. Brinton,[1]
Aarti Munjal,[1] Keith E. Muller,[3] Deborah H. Glueck[1]

[1]Department of Biostatistics and Informatics, University of Colorado Denver
[2]Department of Preventive Medicine, University of Southern California
[3]Department of Health Outcomes and Policy, University of Florida

Acknowledgements

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Outline

Science	• Case Study • Cancer Screening Trial Design • Cancer Screening Analysis
Statistics	• Bias Correction Algorithm • Evaluation Studies • Oral Cancer Screening Demonstration

Oral Cancer Screening Case Study

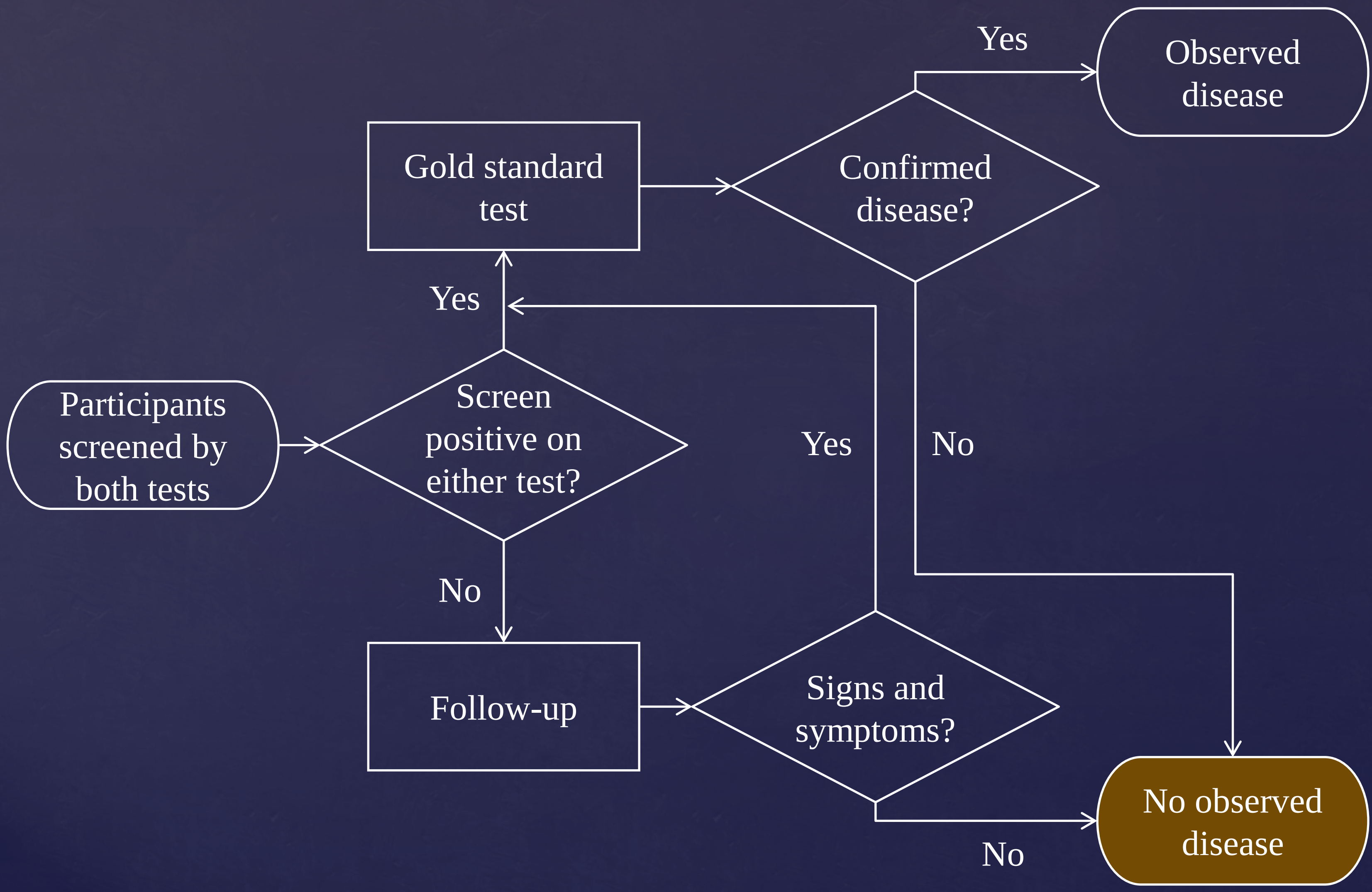
VISIBLE LIGHT

No visible lesion

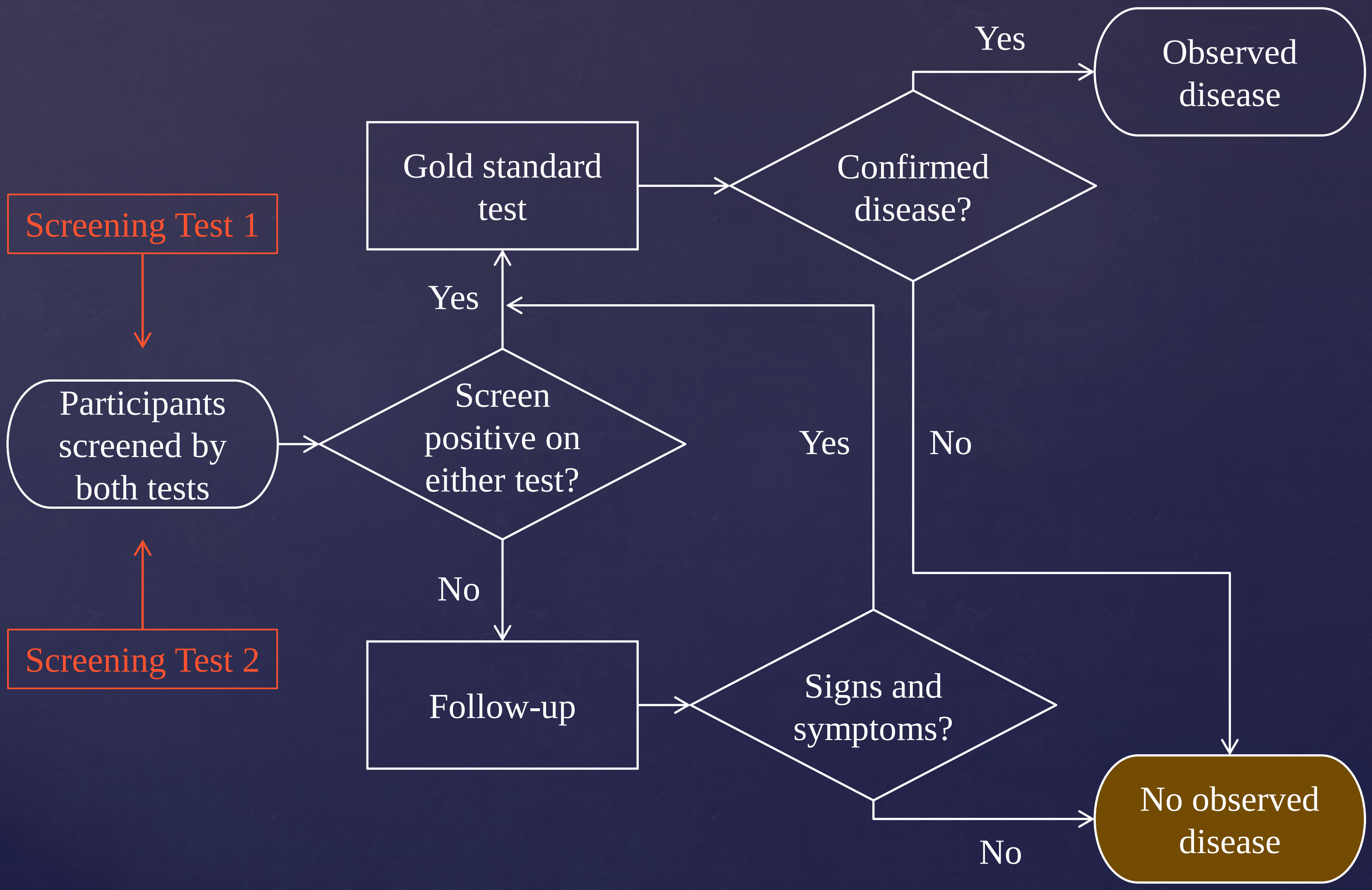
AUTOFLUORESCENCE

Dark region confirmed to be carcinoma in situ

Paired Cancer Screening Trial



Paired Cancer Screening Trial



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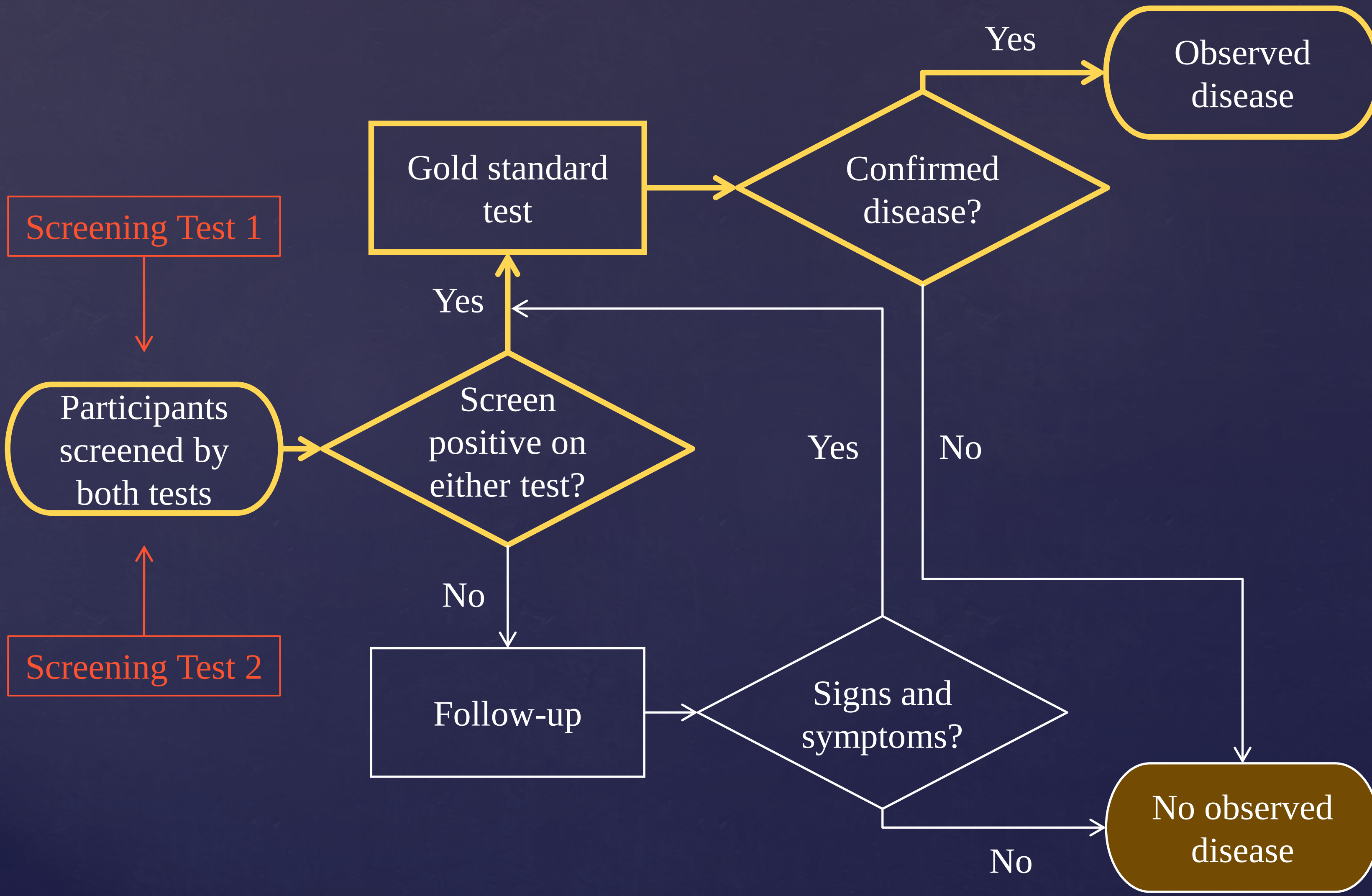

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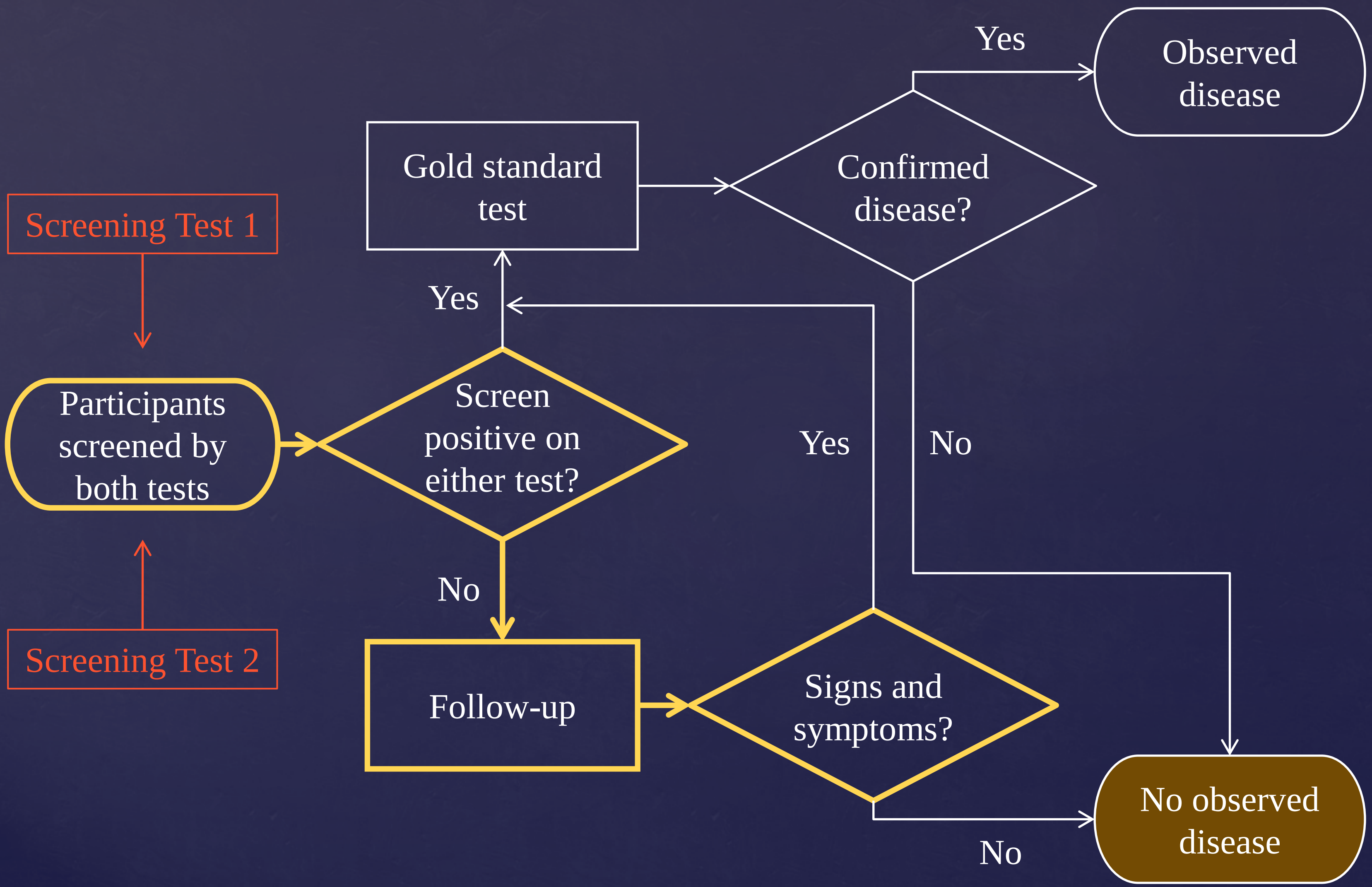

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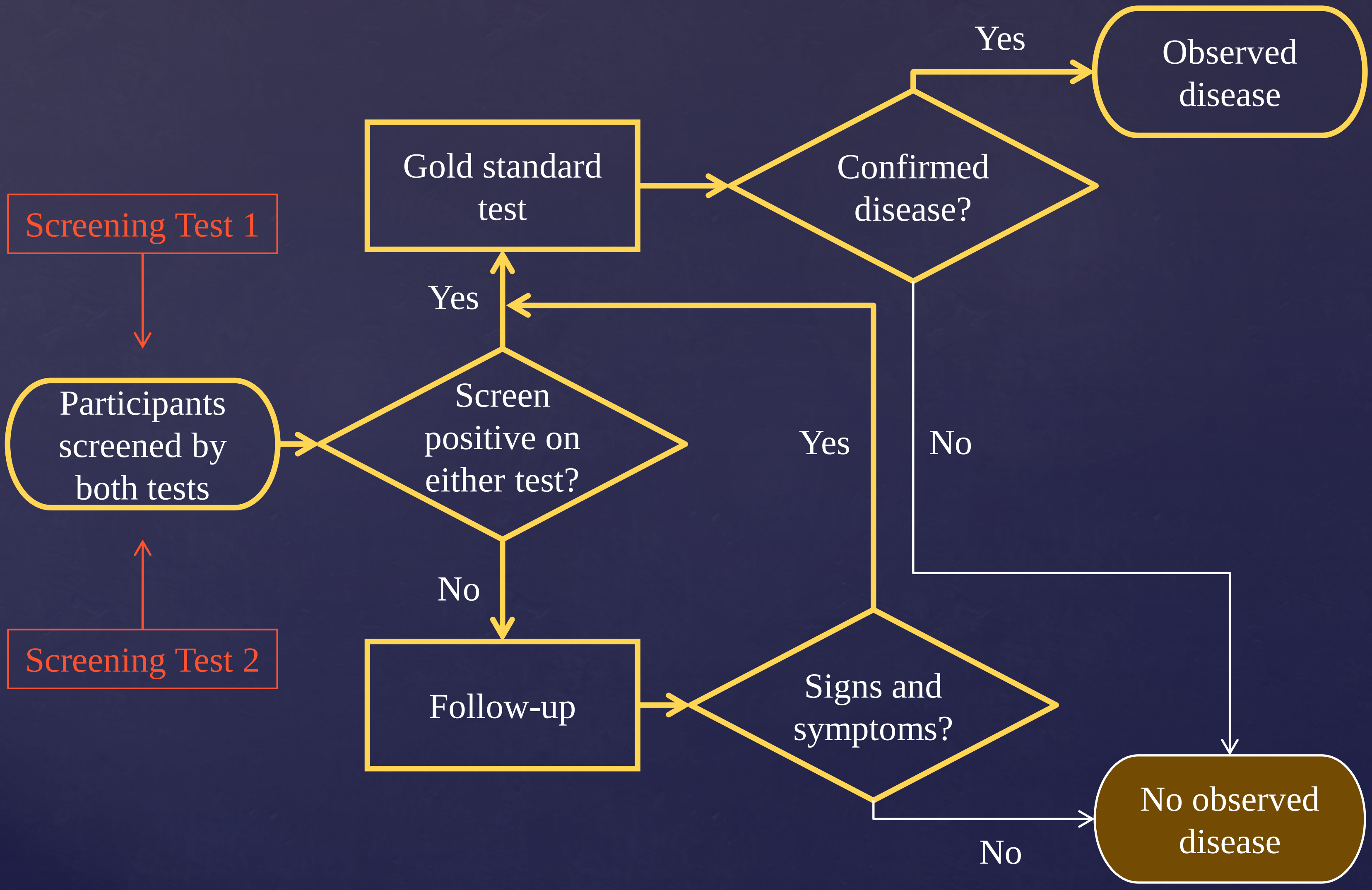

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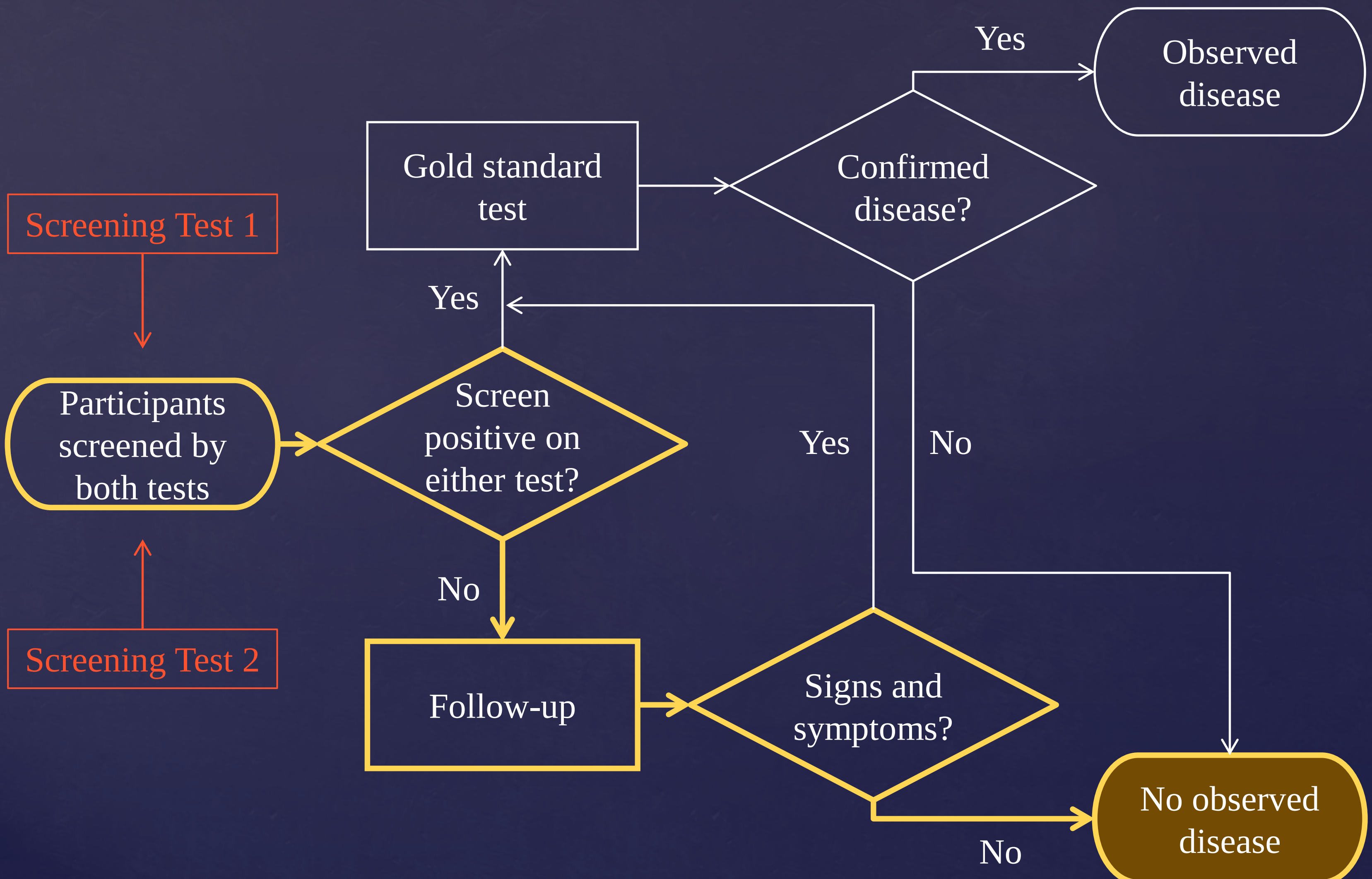
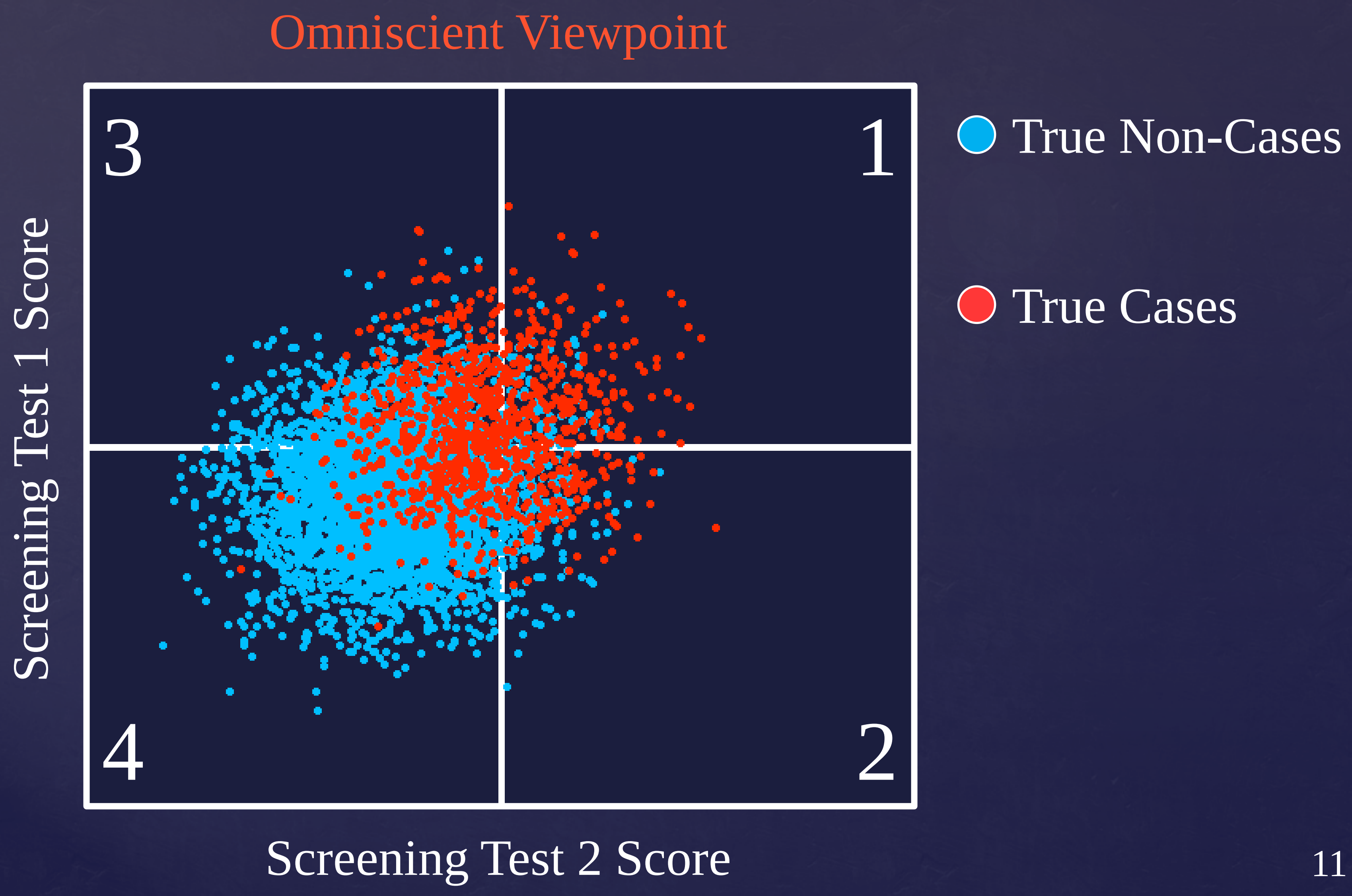


Hypothetical Cancer Screening Data



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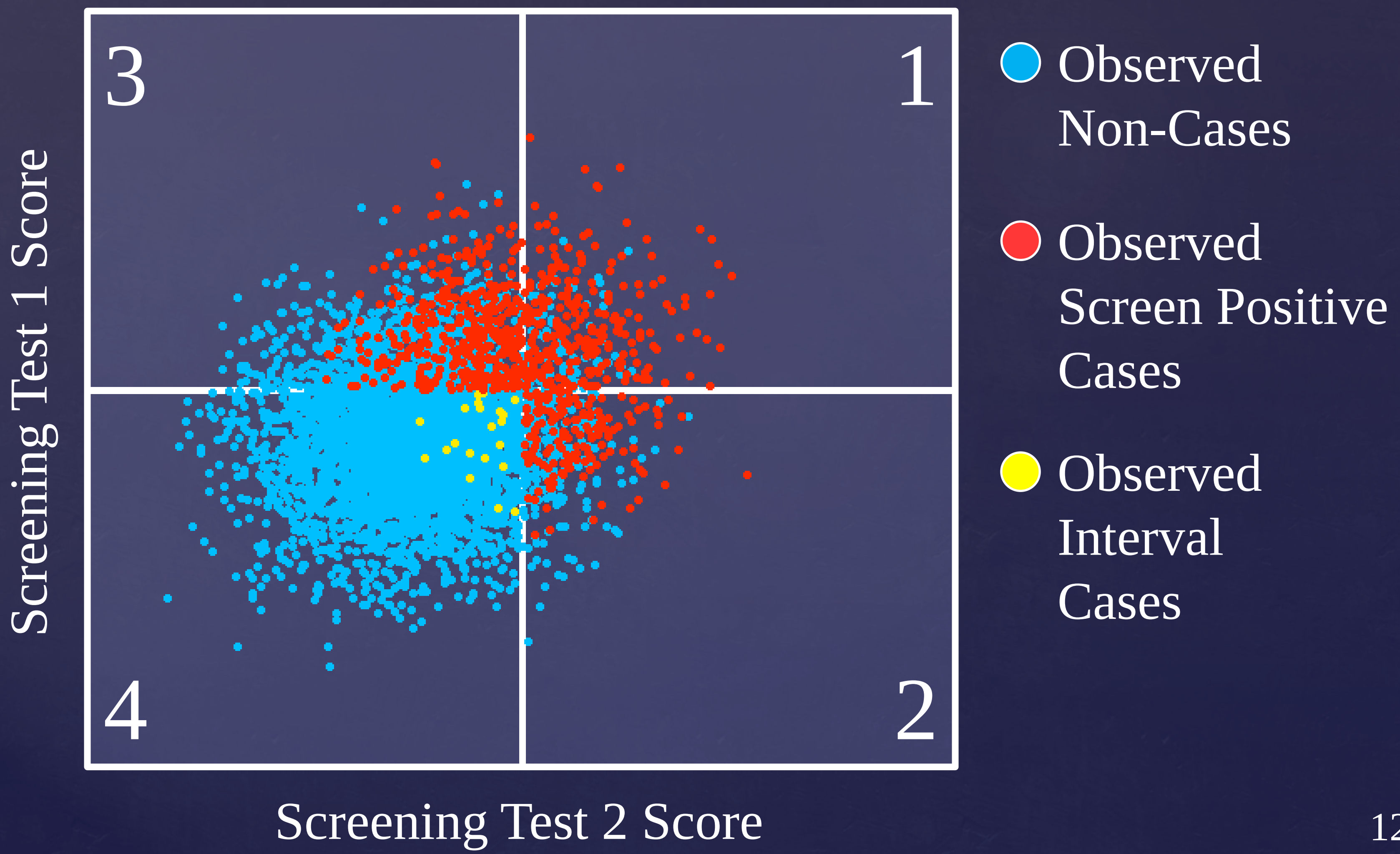
Study Investigator's Viewpoint



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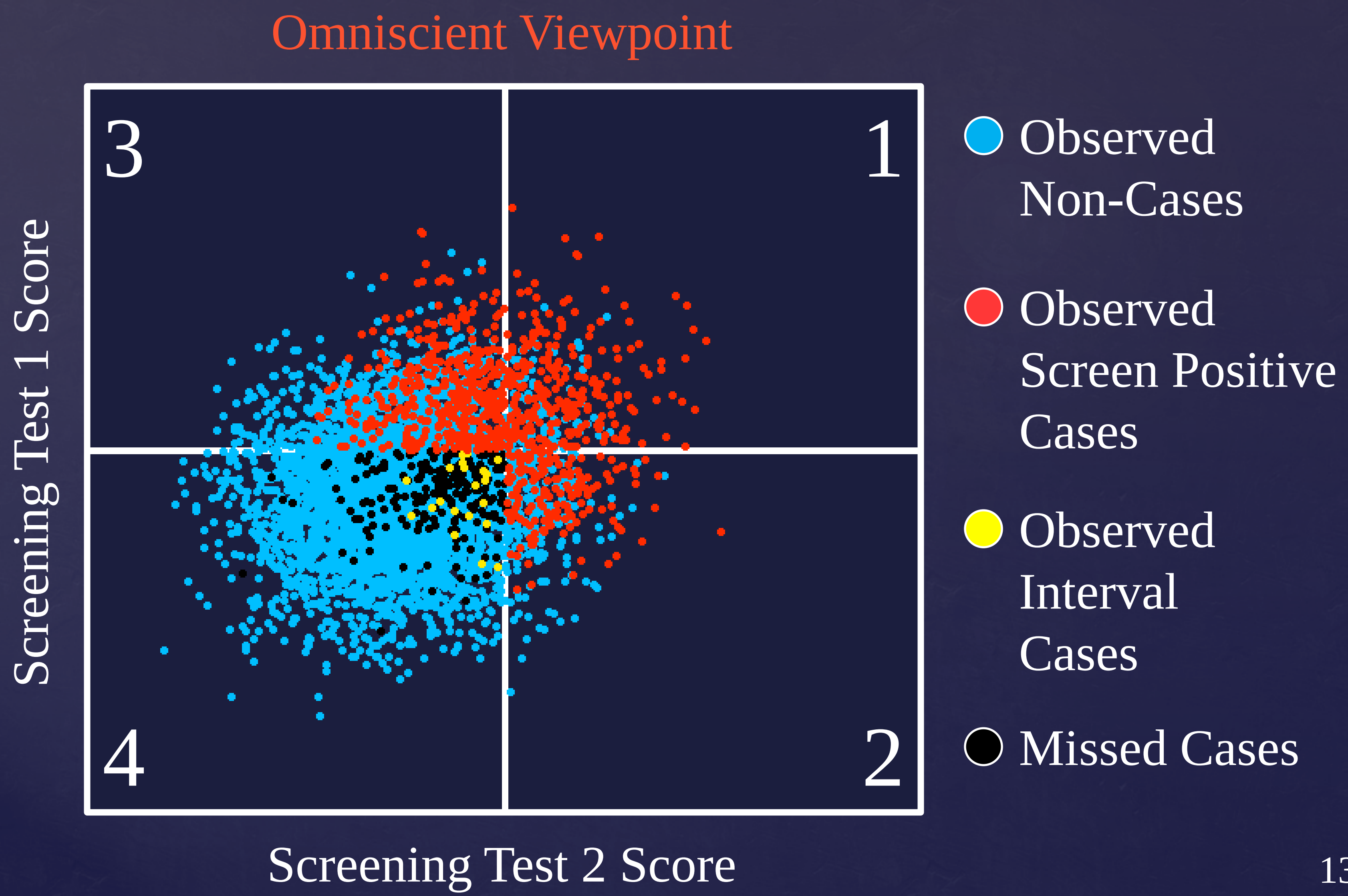
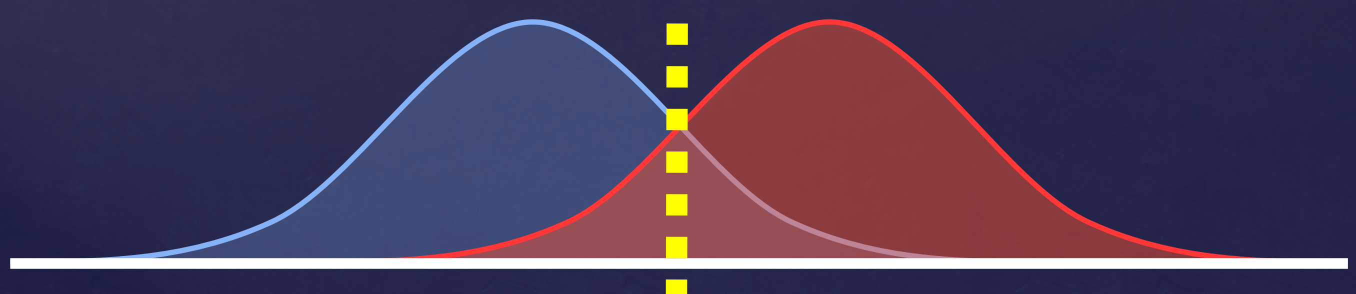


Analysis of Cancer Screening Studies

Screening Test	Disease Status +	Disease Status -
+	a	b
-	c	d



Analysis of Cancer Screening Studies

Screening Test	Disease Status +	Disease Status -
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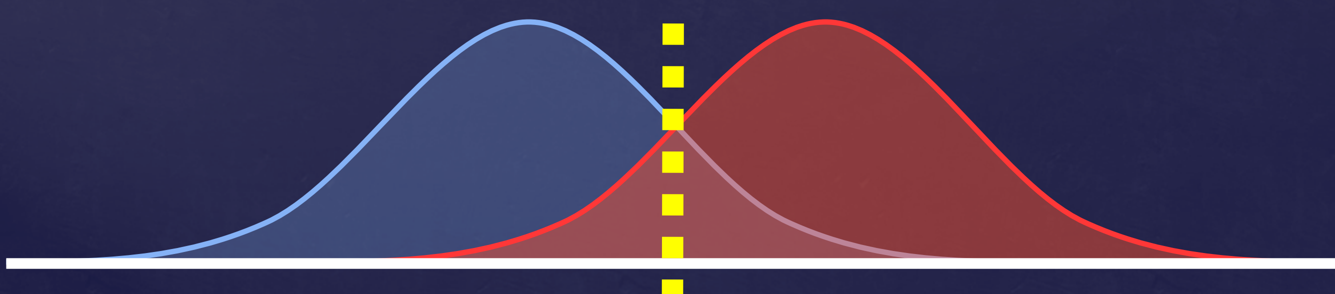
$$\text{Sensitivity} = \frac{a}{a+c}$$



Analysis of Cancer Screening Studies

Screening Test	Disease Status +	Disease Status -
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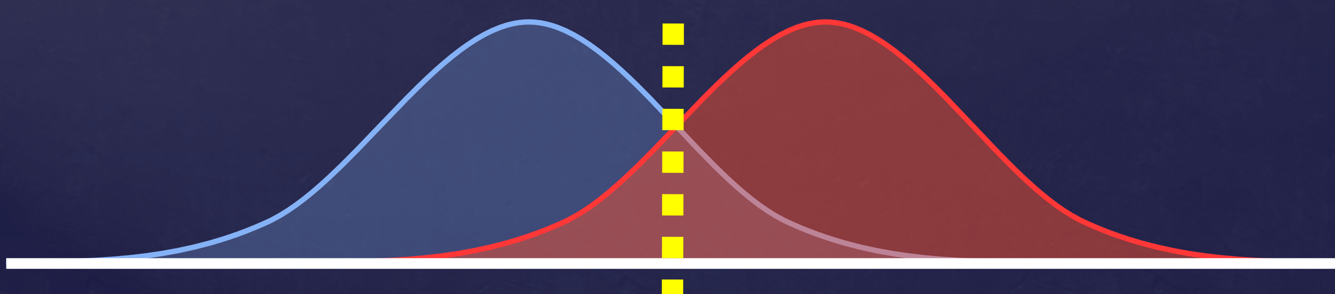
$$\text{Sensitivity} = \frac{a}{a+c}$$

$$\text{Specificity} = \frac{d}{b+d}$$



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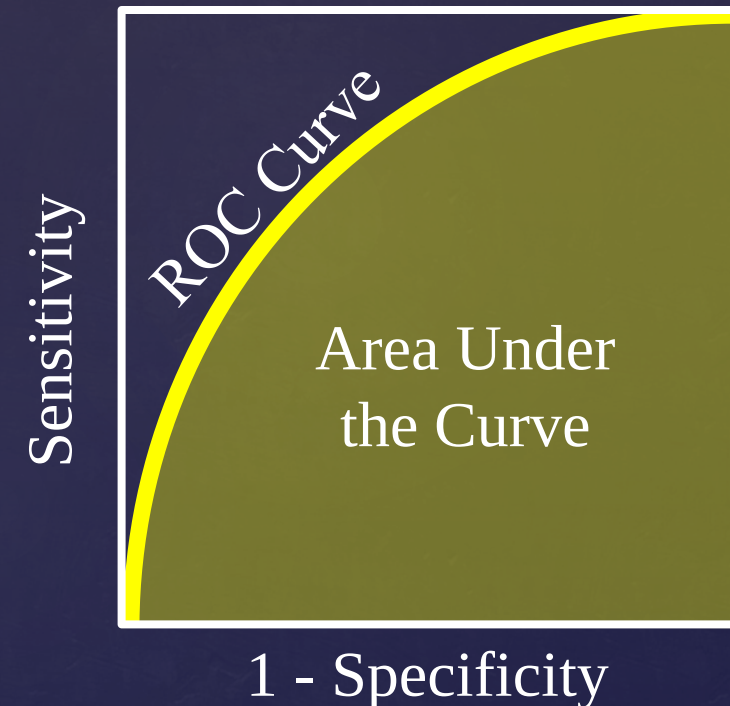
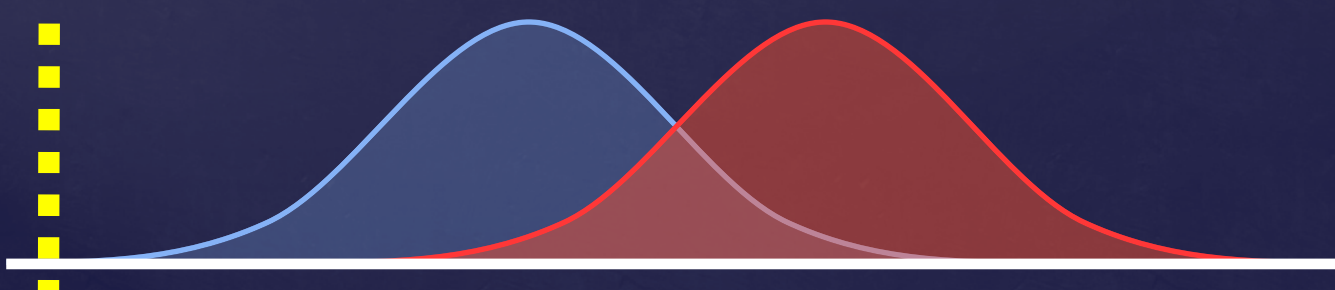
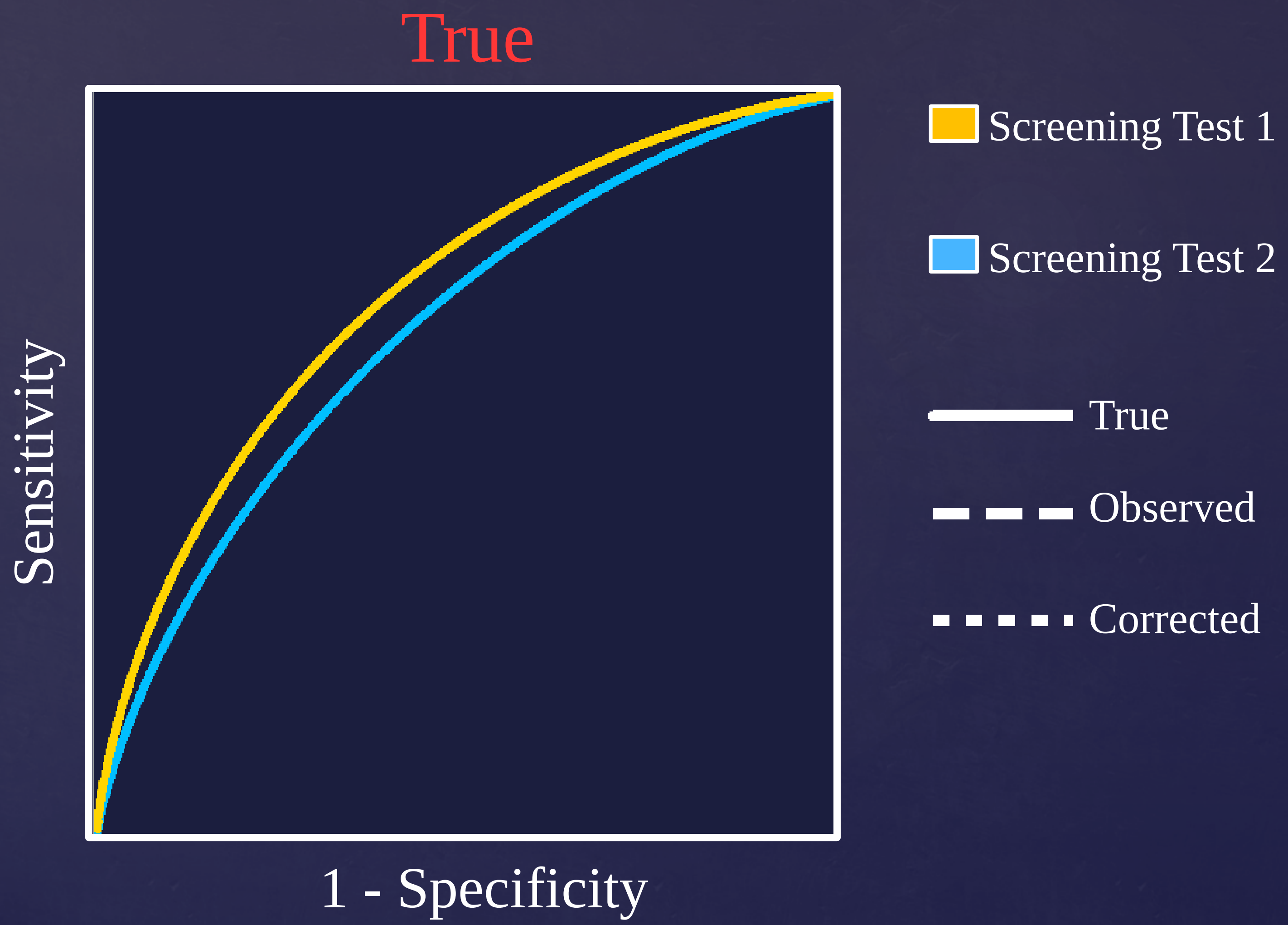




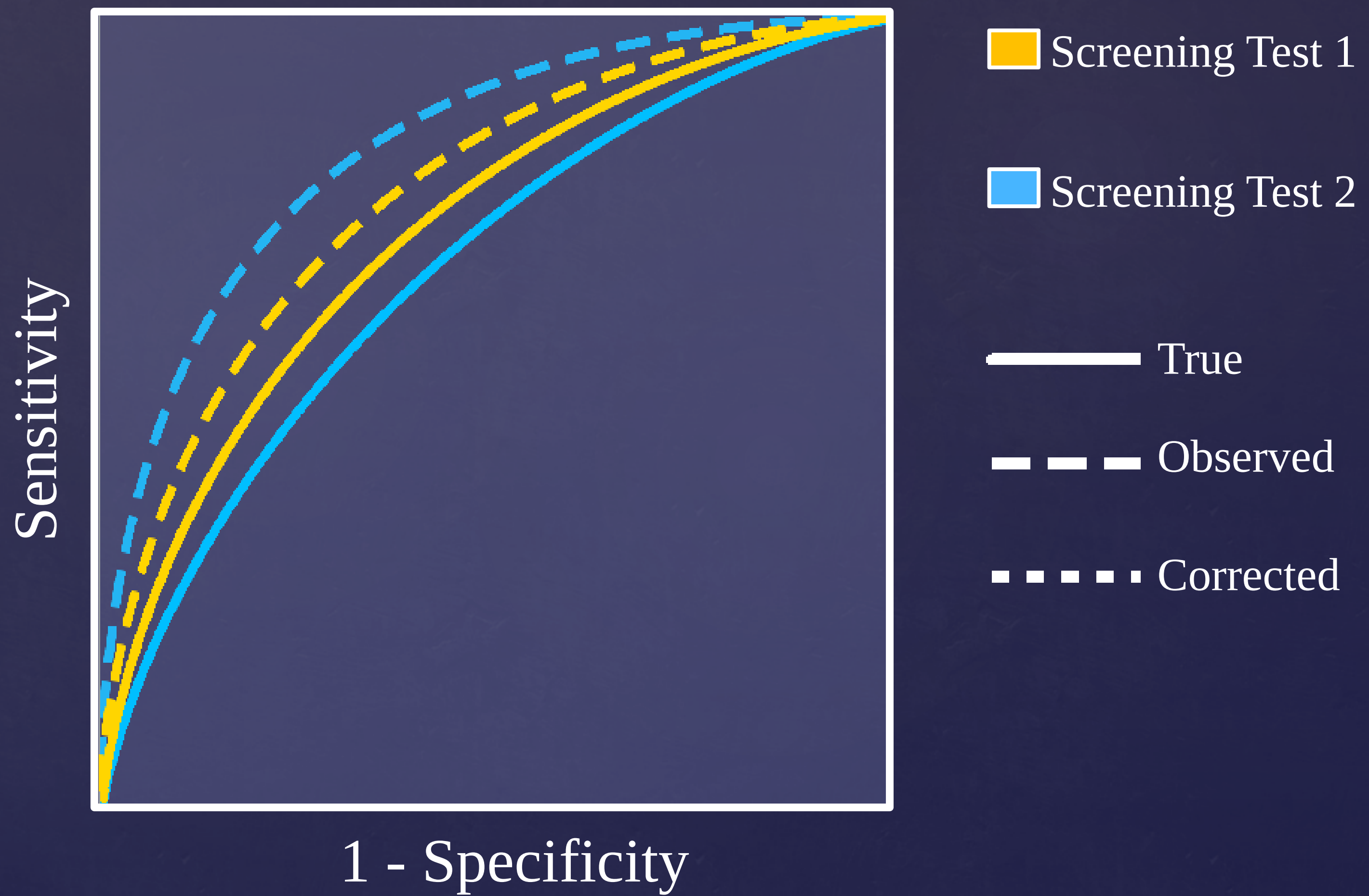
Comparing Two Continuous Screening Tests



(Glueck *et al.*, 2009)

Comparing Two Continuous Screening Tests

Observed



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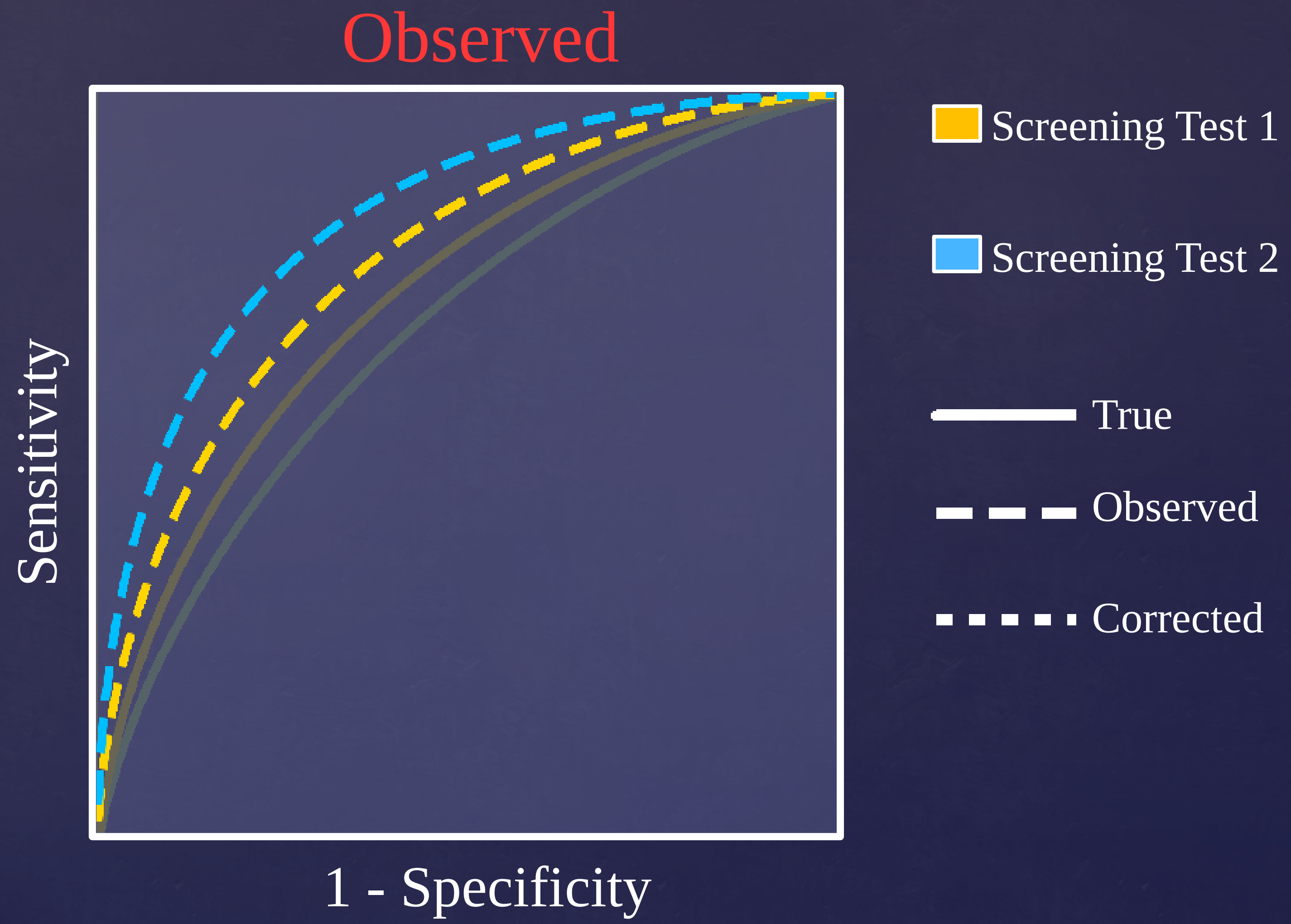

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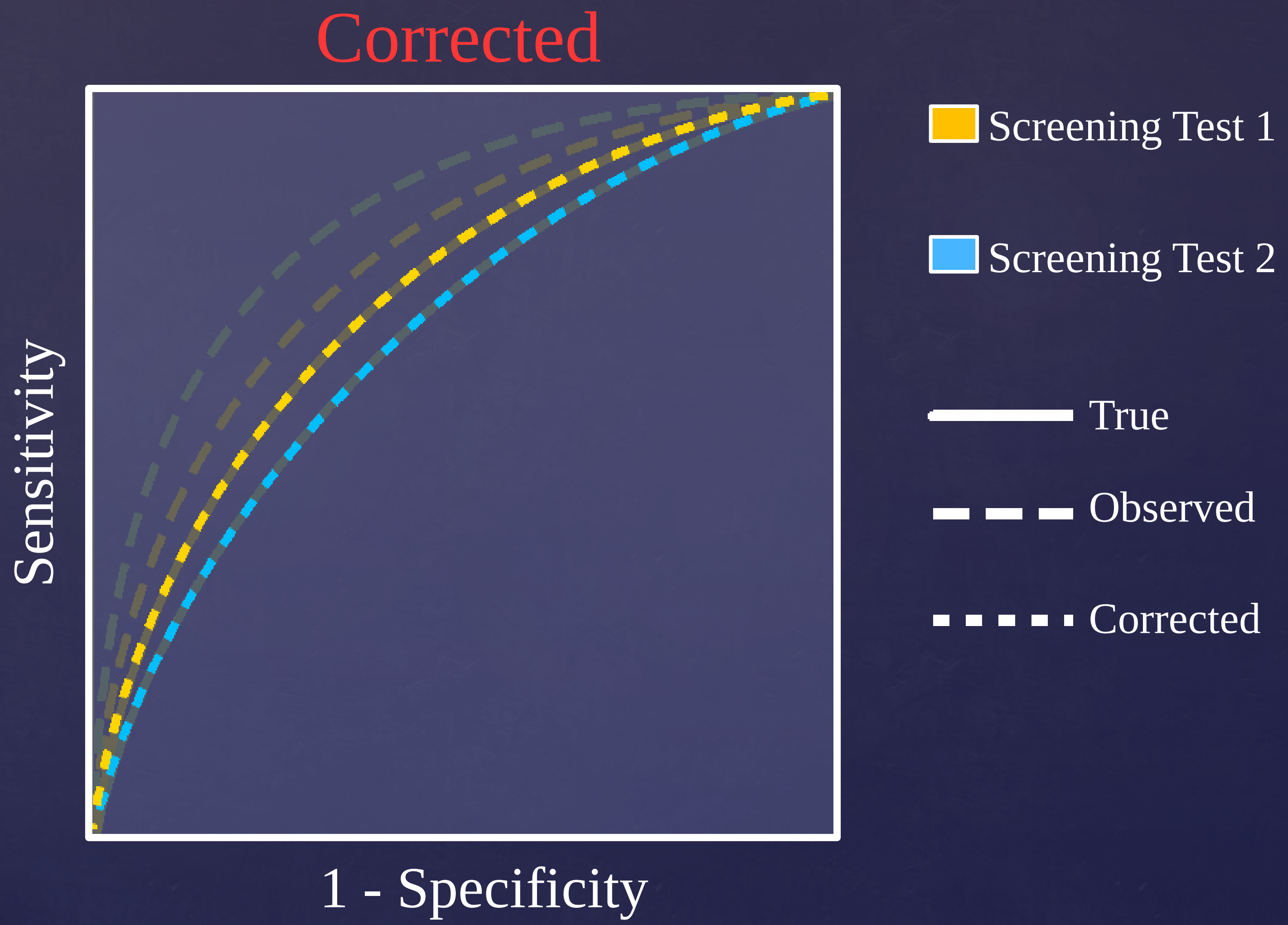

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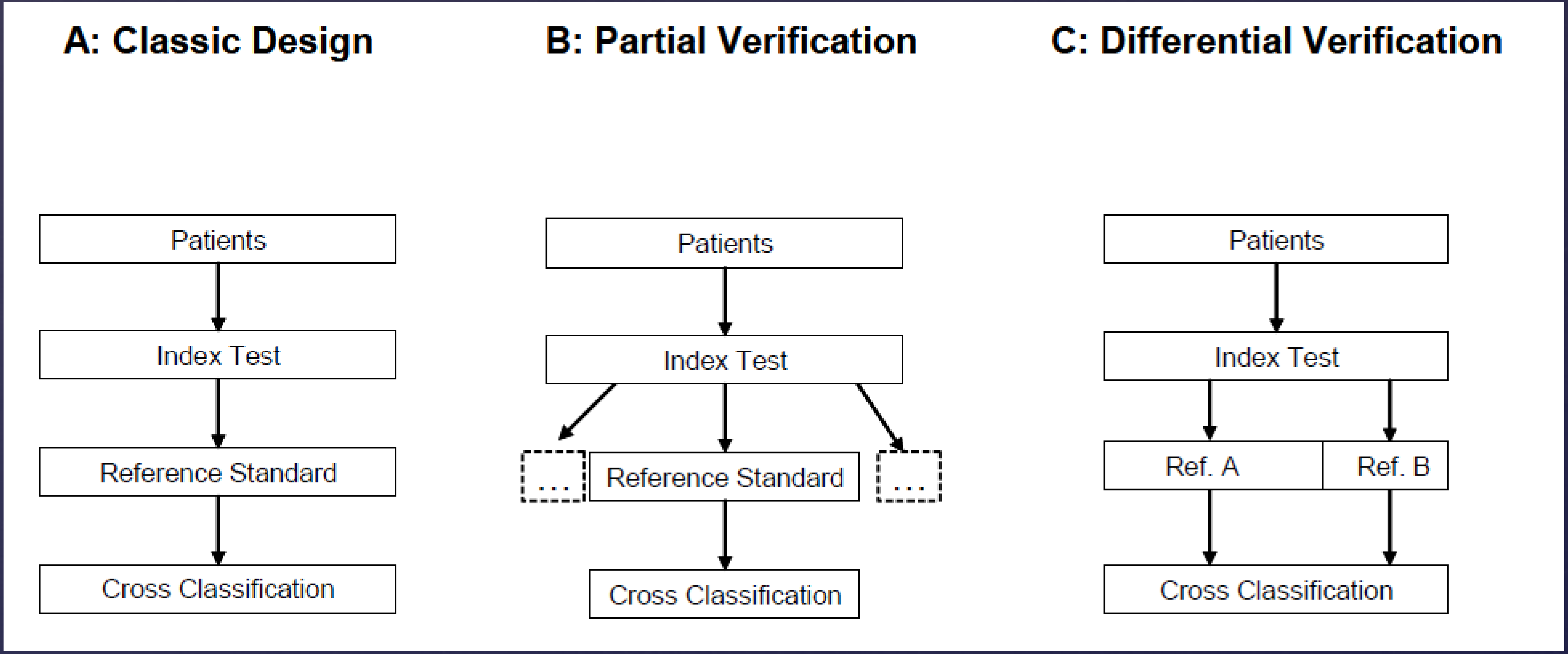
Types of Bias



(Rutjes *et al.*, 2007)

Bias Correction Algorithm

1. Find the maximum likelihood estimates of the parameters of the bivariate Gaussian distribution of test scores for the cases.

2. Use the maximum likelihood estimates and the sampling fractions in each partition to calculate weighted estimates.

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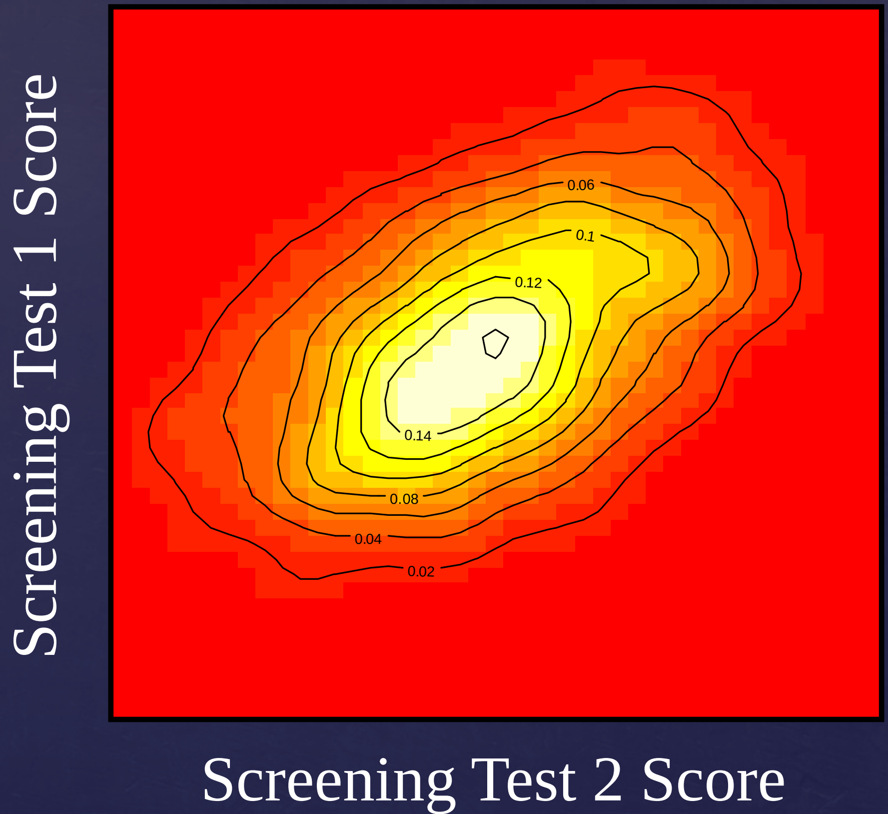

(Nath, 1971)

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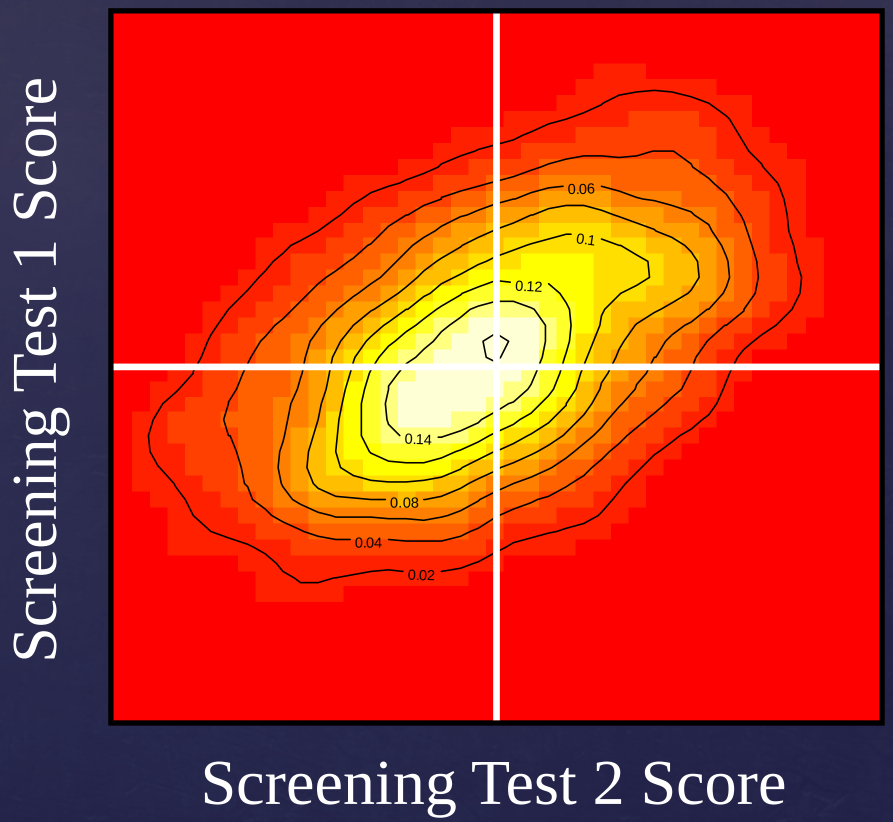

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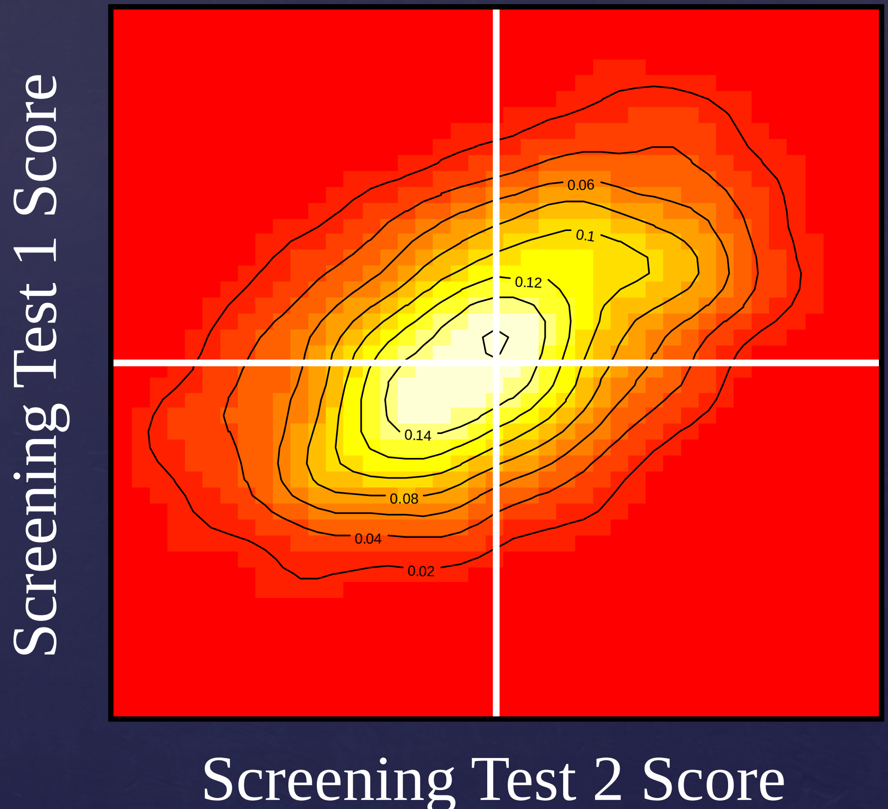

μ_1

μ_2

$\sigma^2{}_1$

$\sigma^2{}_2$

ρ

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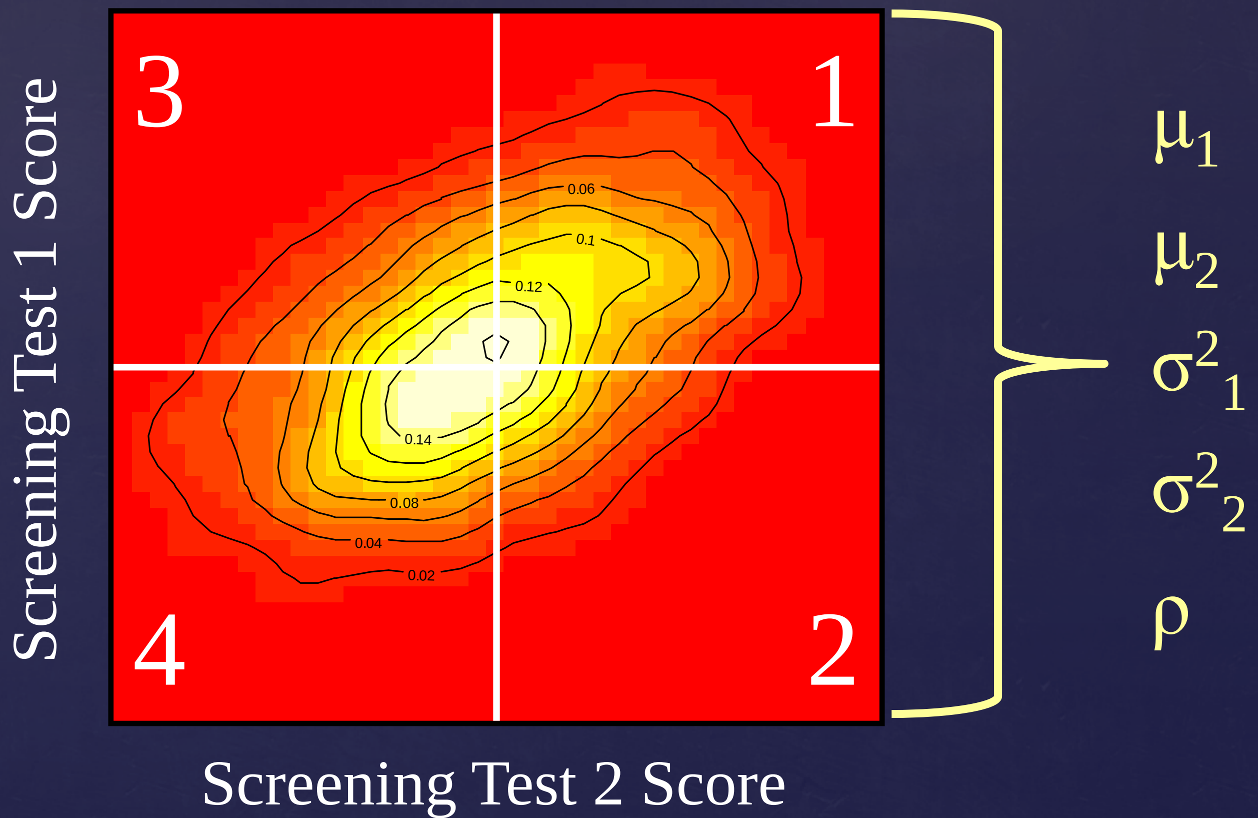

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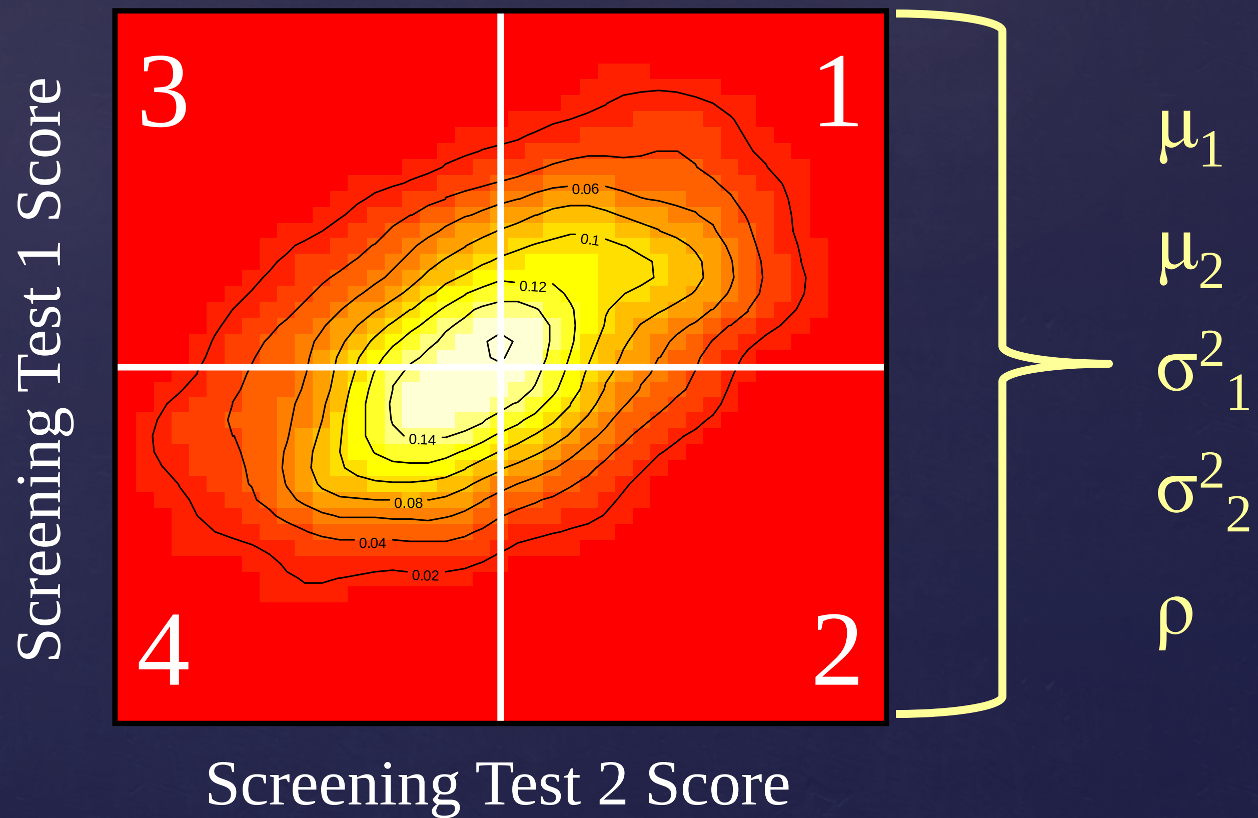

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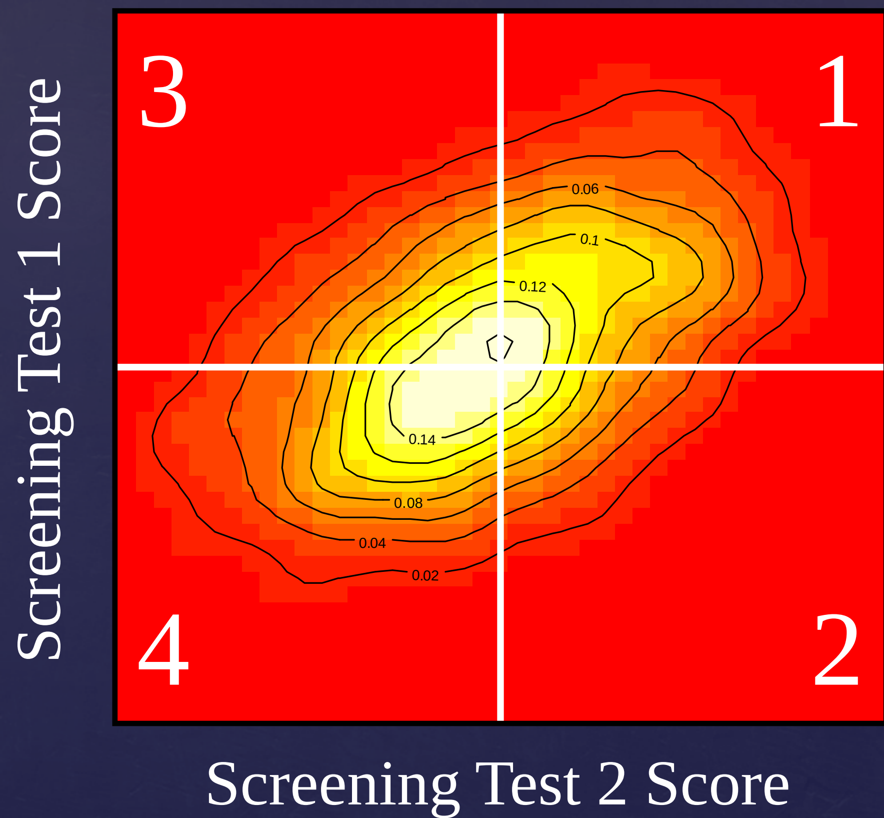

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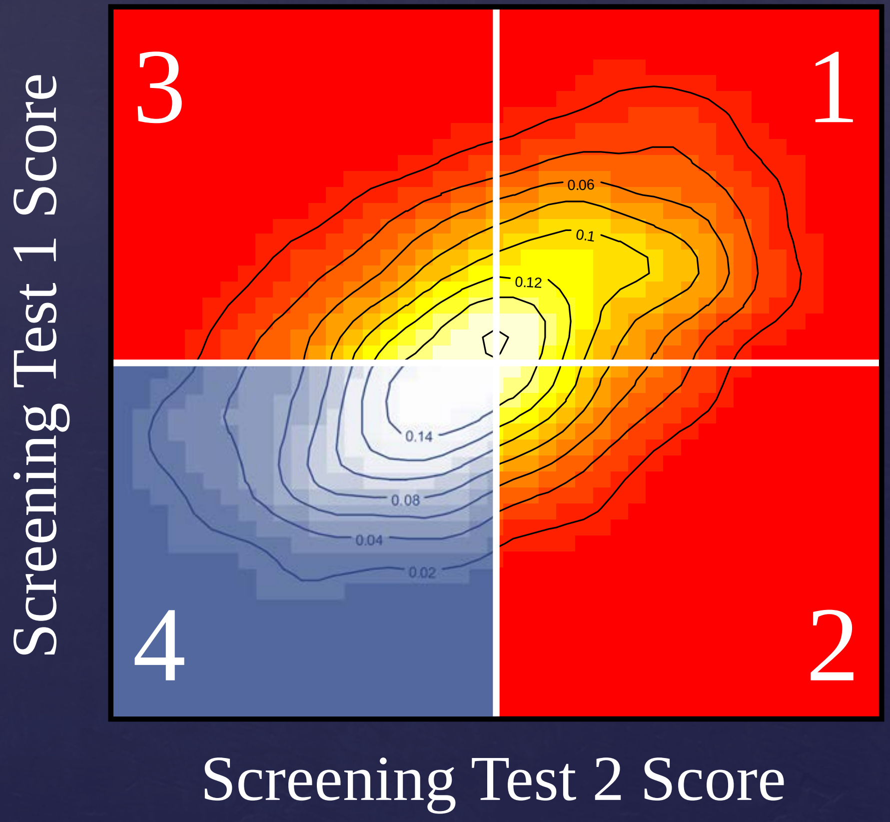

Weighted Estimates

$$\widehat{\lambda} = 1 - \Phi\left(\frac{a_1 - \widehat{\mu}_{11,N}}{\widehat{\sigma}_{11,N}}, \frac{a_2 - \widehat{\mu}_{21,N}}{\widehat{\sigma}_{21,N}}, \widehat{\rho}_{1,N}\right)$$

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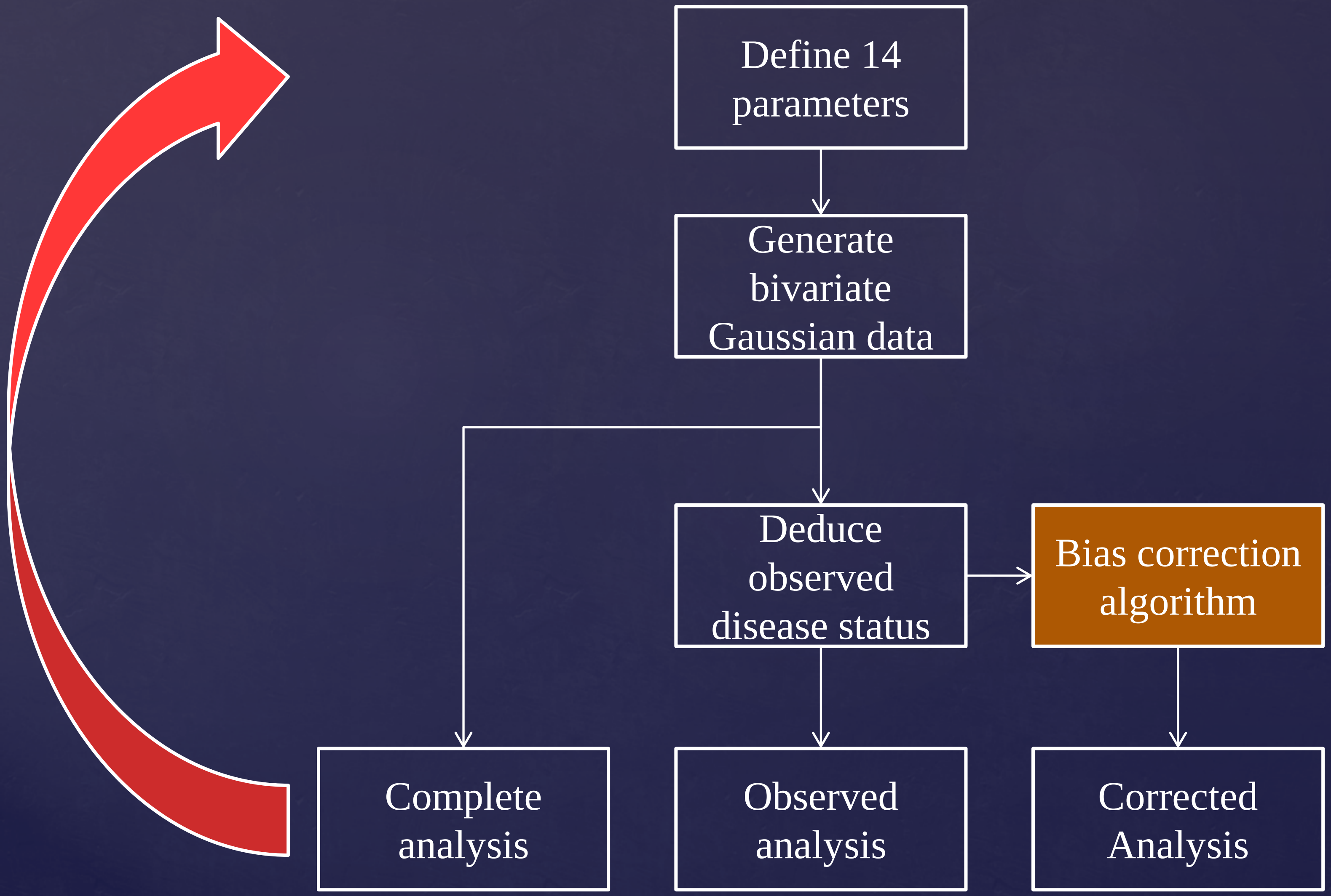
Design for Simulation Studies



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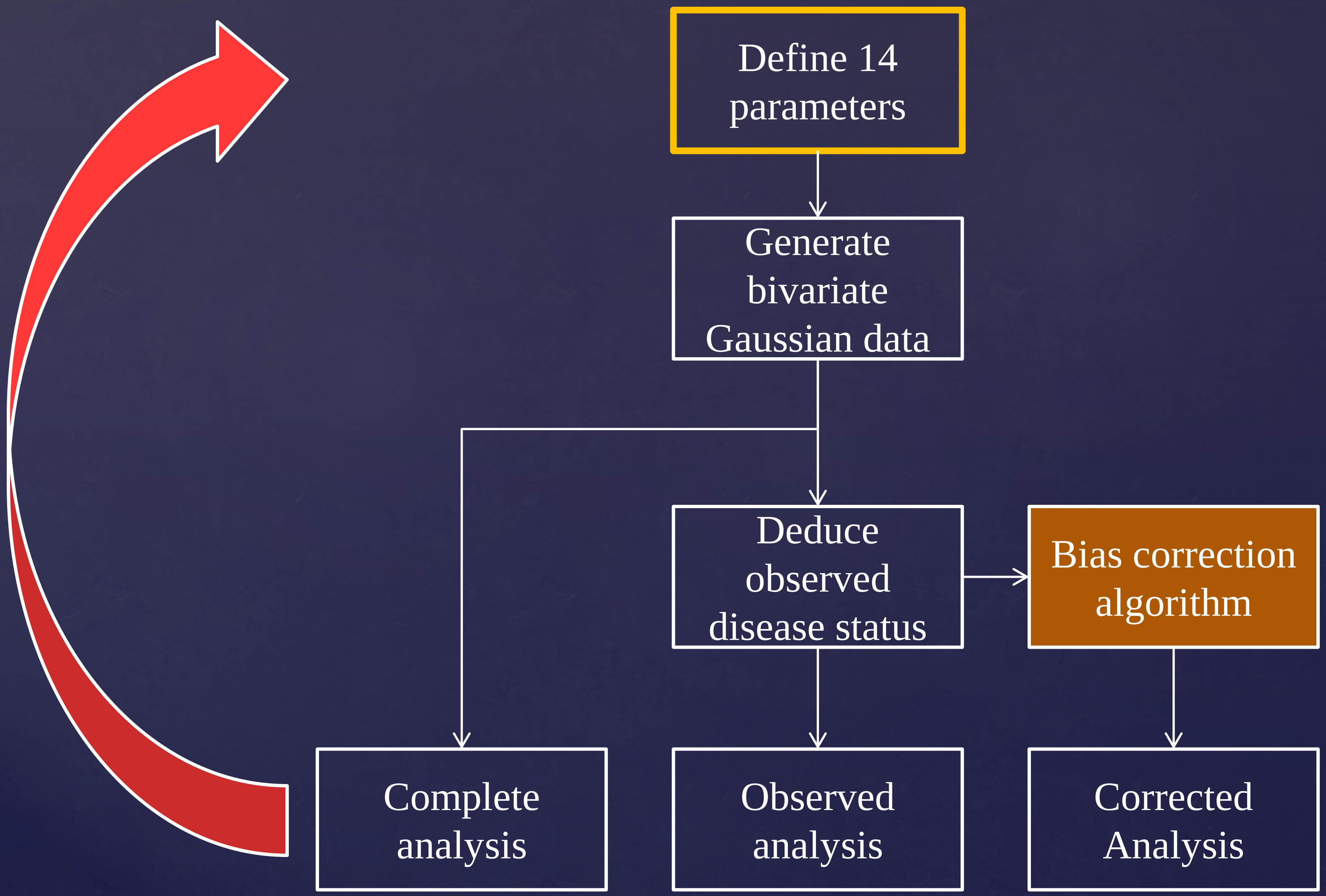

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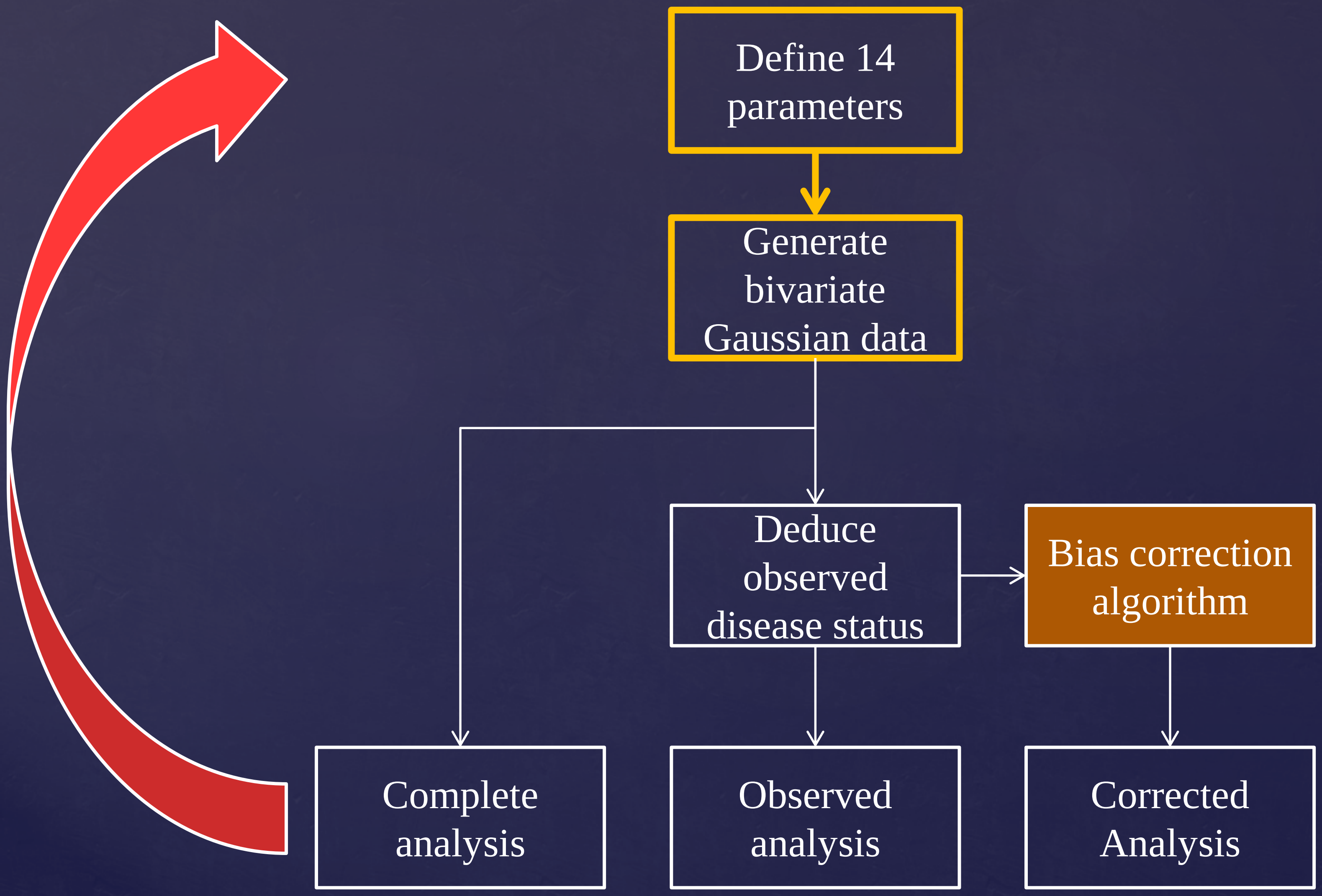

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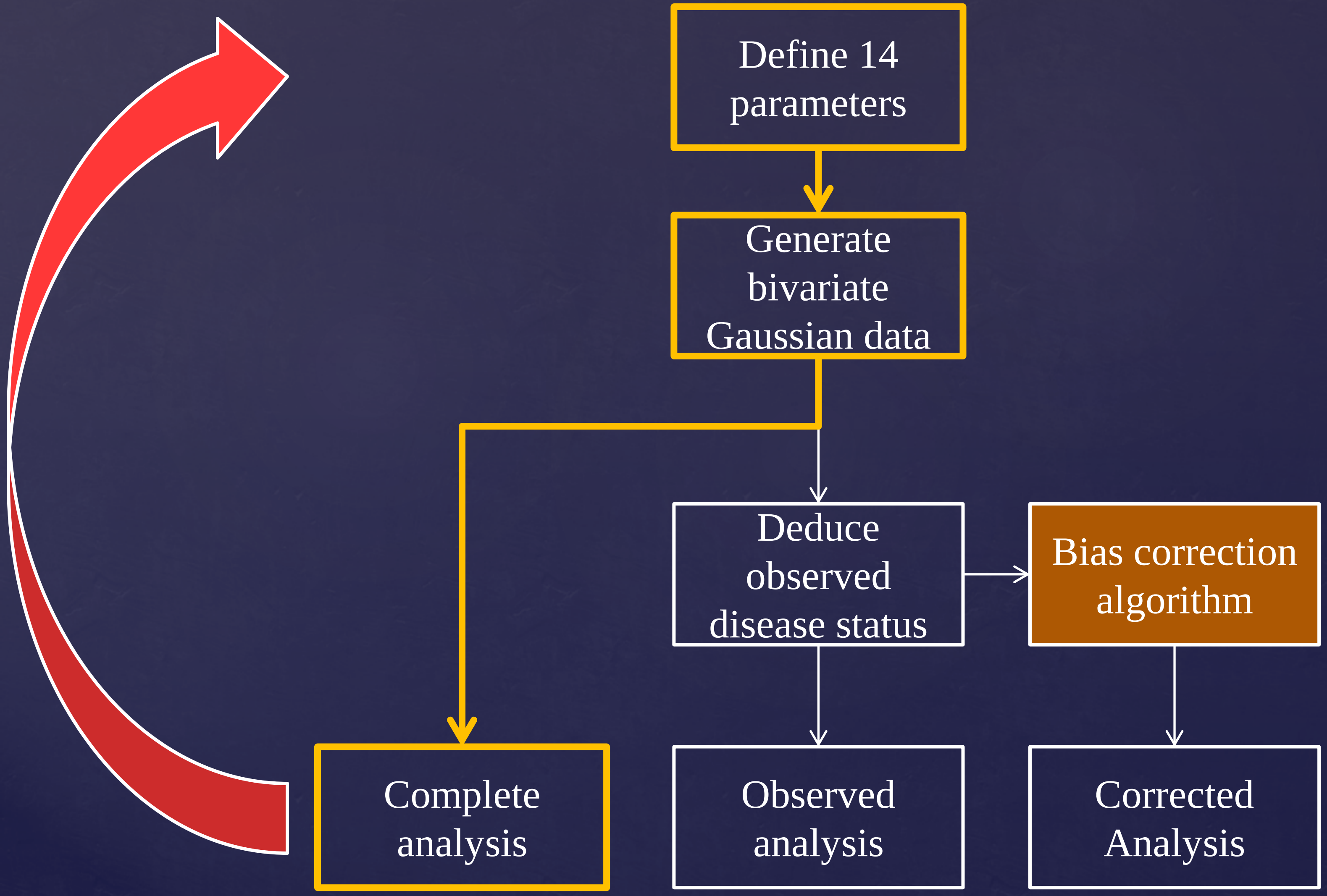

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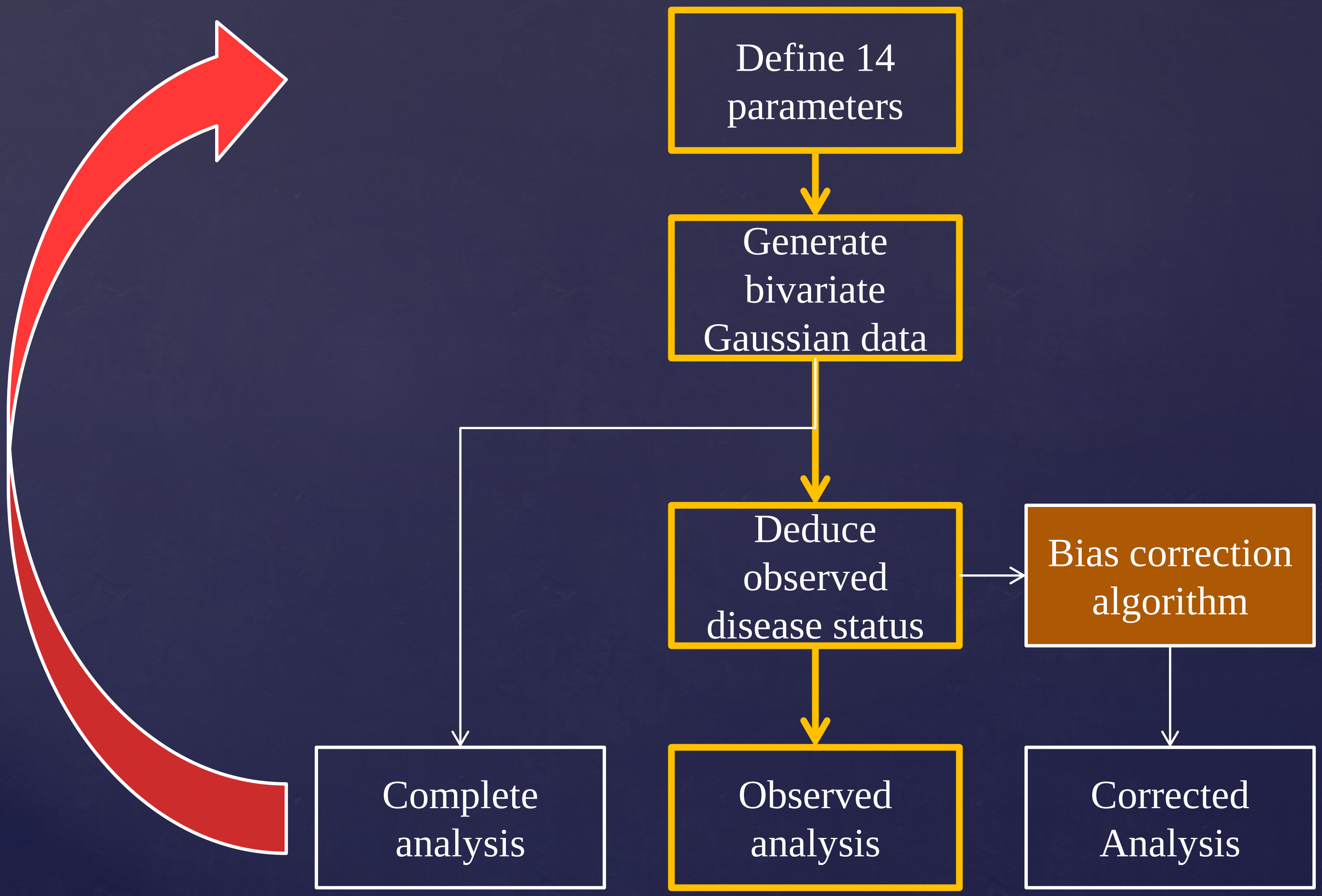

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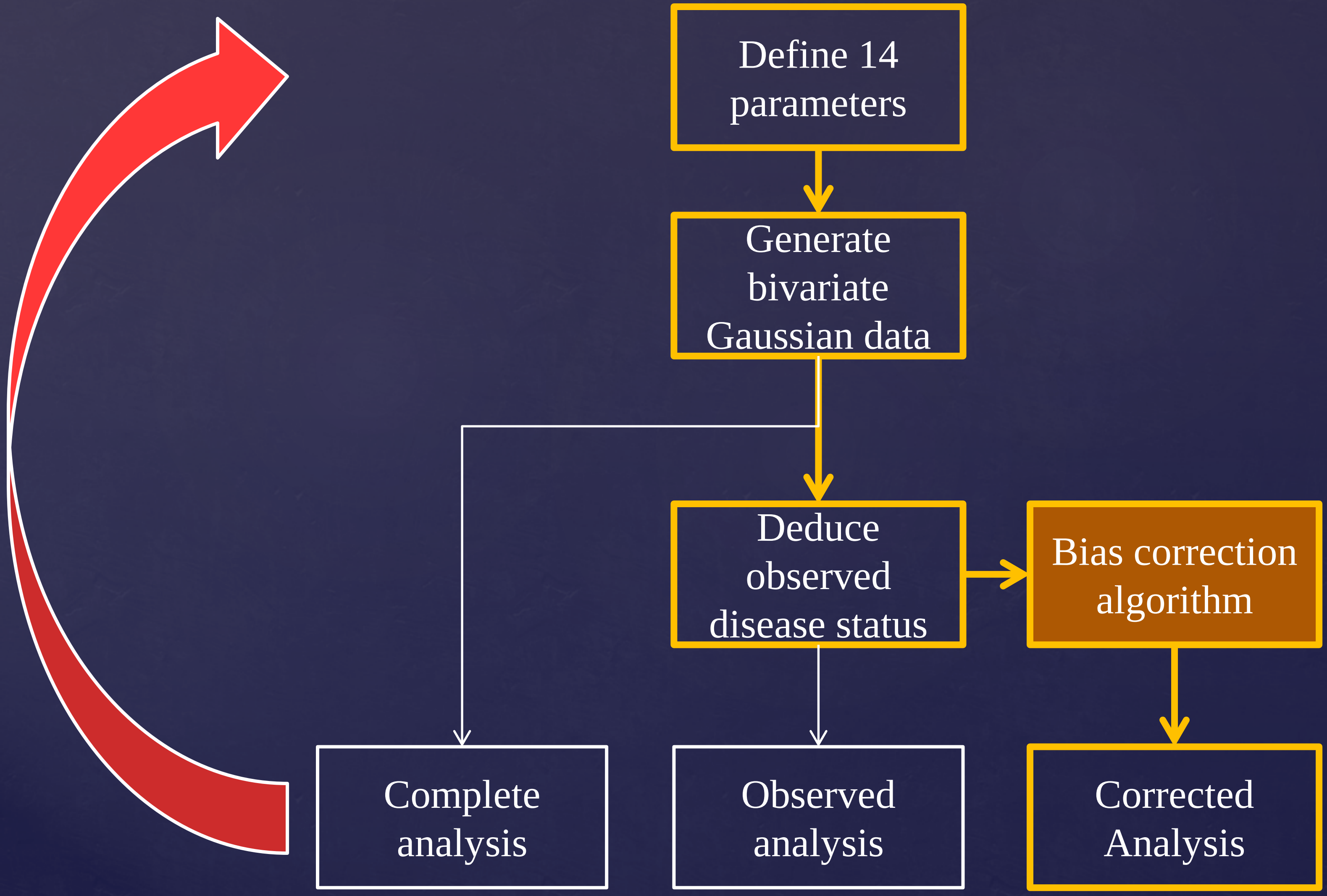
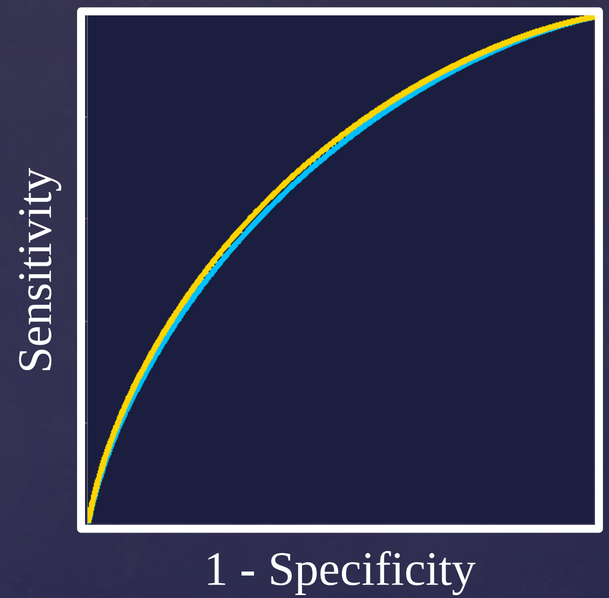
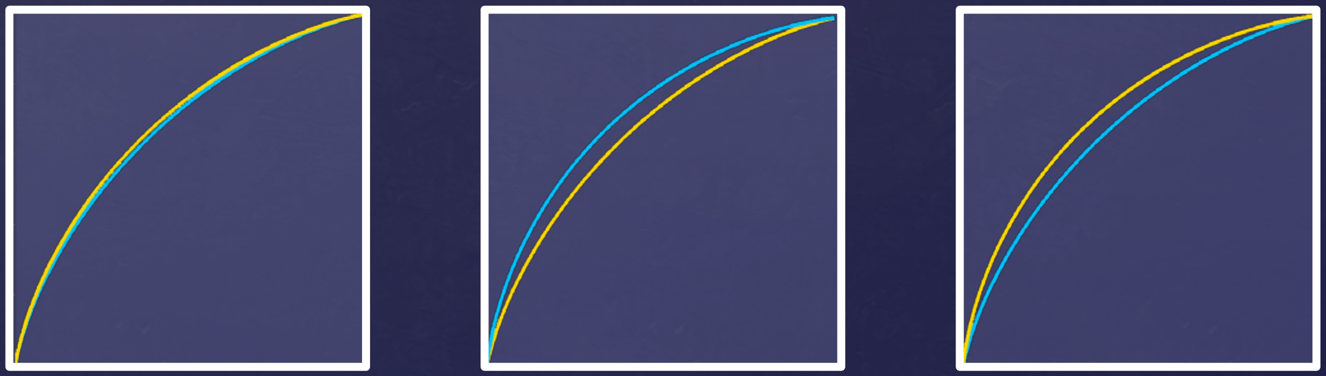


Evaluation of the Method





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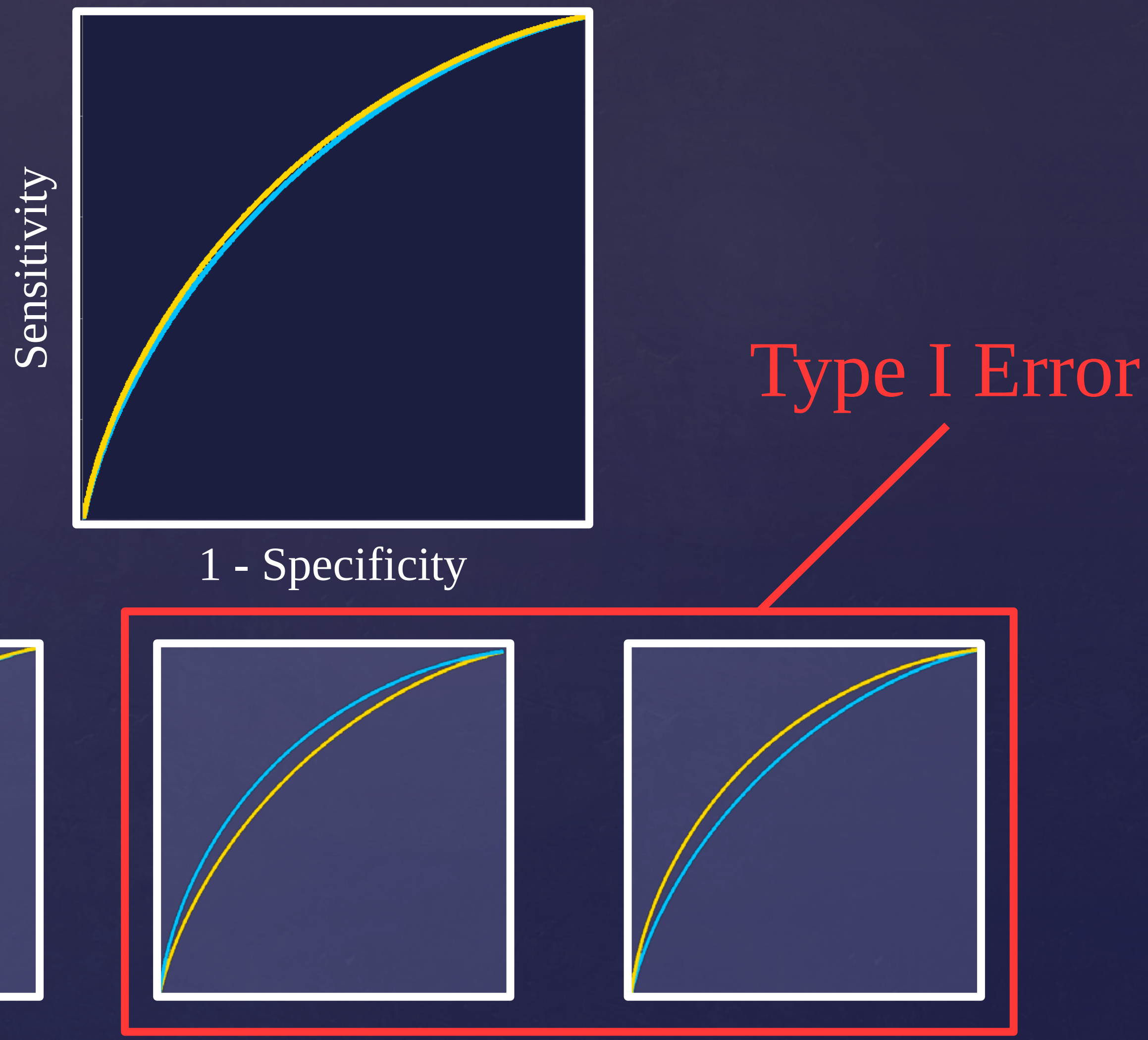

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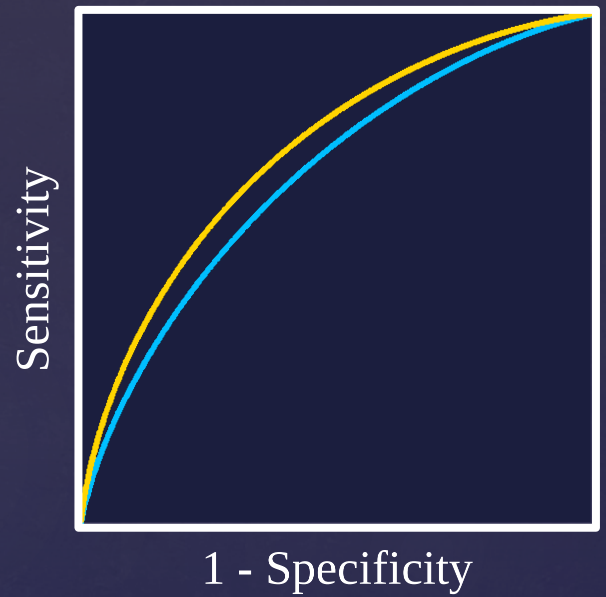

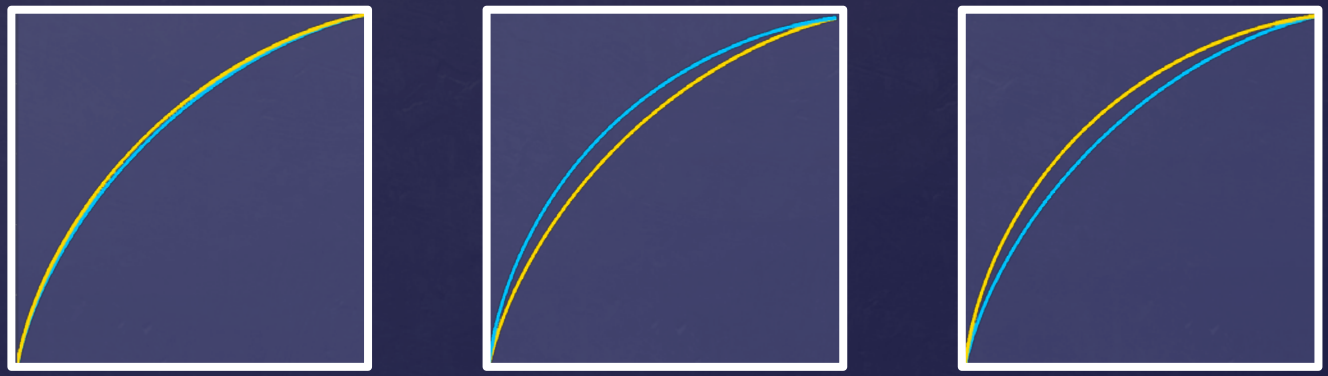

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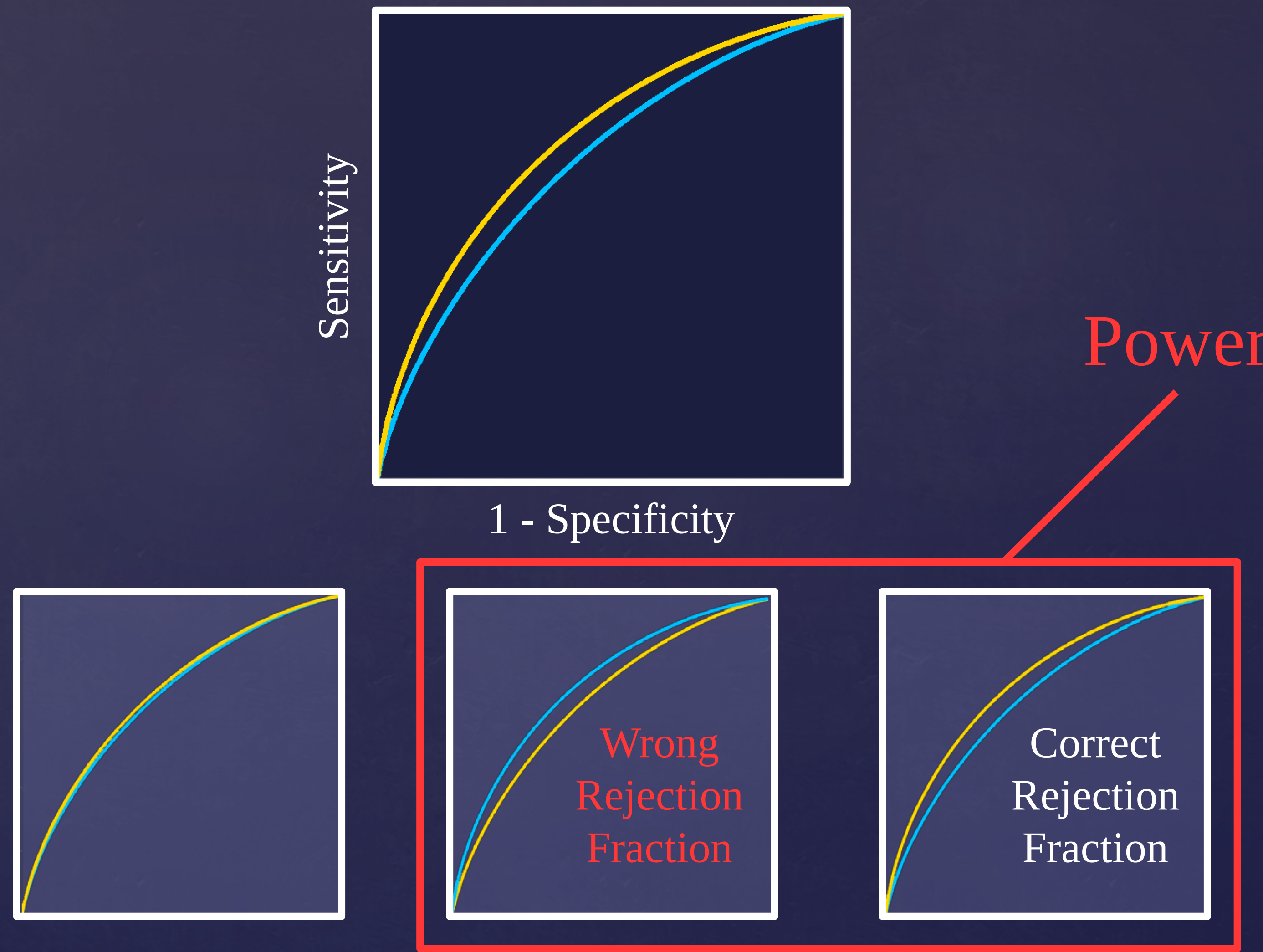
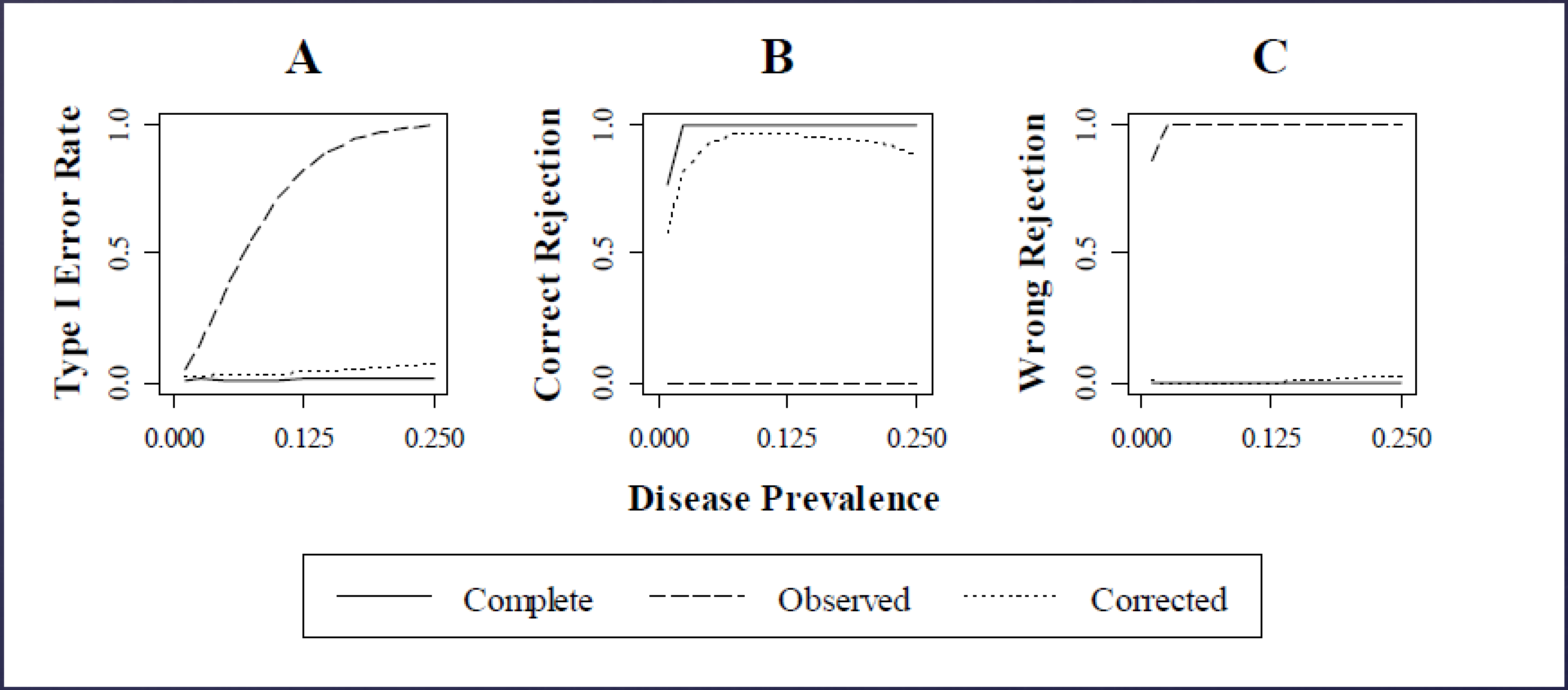


Disease Prevalence Simulation Study



Percent Identified Simulation Study

Bias?	Percent Identified (Test 1 / Test 2)	Complete Type I Error	Observed Type I Error	Corrected Type I Error
Yes	15/50	0.01	0.89	0.36
	15/80	0.02	0.95	0.25
	50/80	0.01	0.23	0.12
No	15/15	0.01	0.02	0.23
	50/50	0.01	0.02	0.12
	80/80	0.02	0.02	0.18

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Recommendation

- Study investigators should conduct a simulation of their study using both the standard analysis and the bias correction method.
- Study investigators should choose the analysis plan that has a nominal Type I error rate and the highest power for the correct decision.

Oral Cancer Screening Demonstration

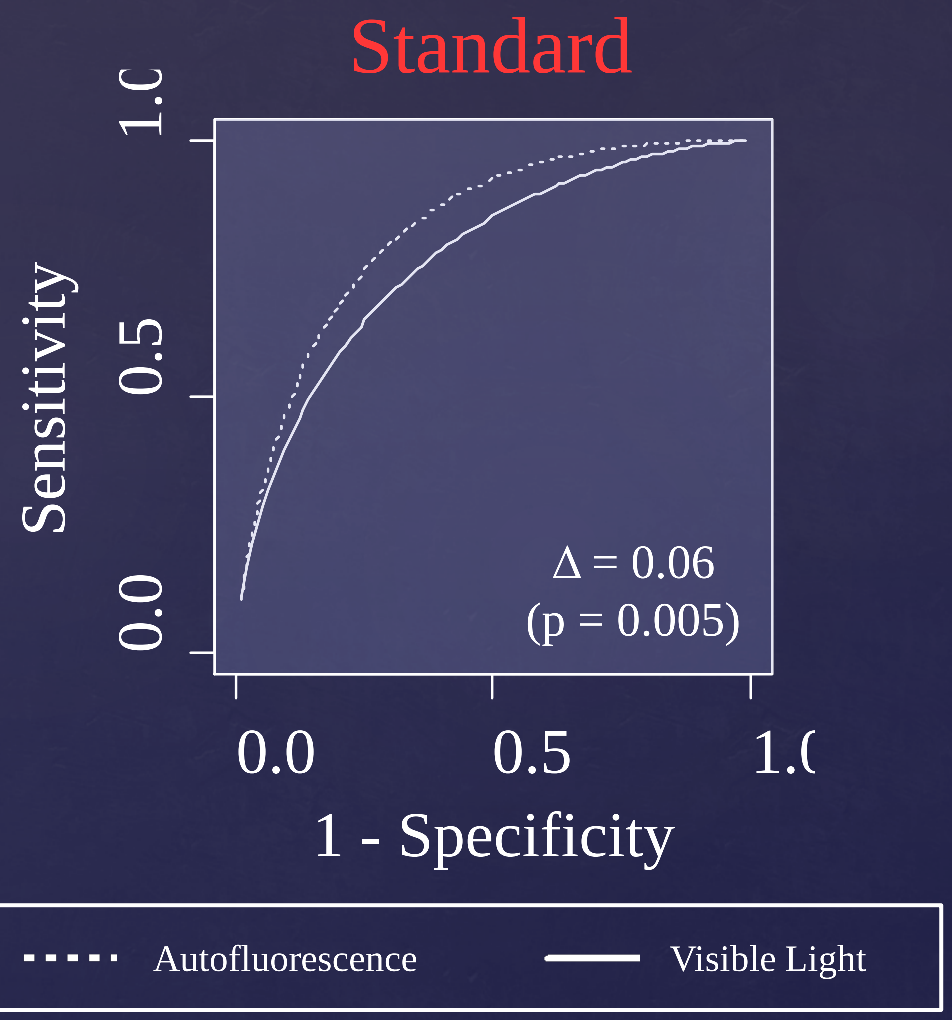
VISIBLE LIGHT

No visible lesion

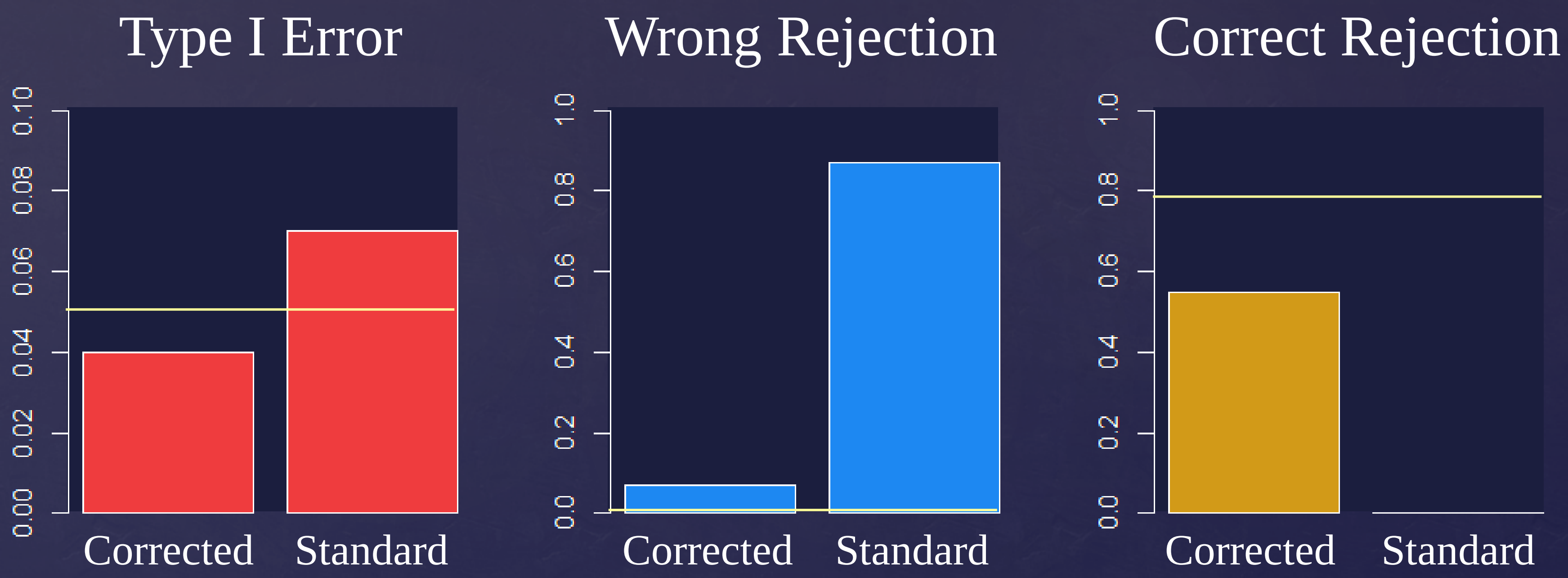
AUTOFLUORESCENCE

Dark region confirmed to be carcinoma in situ

Oral Cancer Screening Analysis



Decision Errors Simulation



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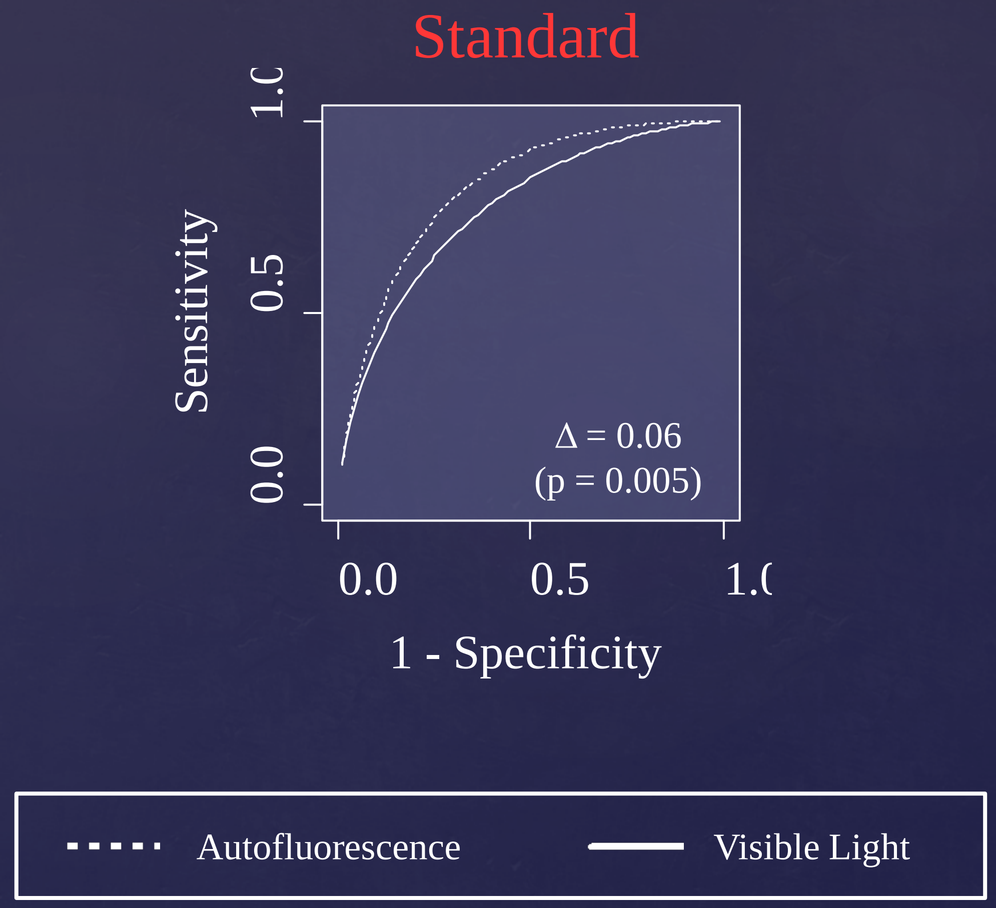

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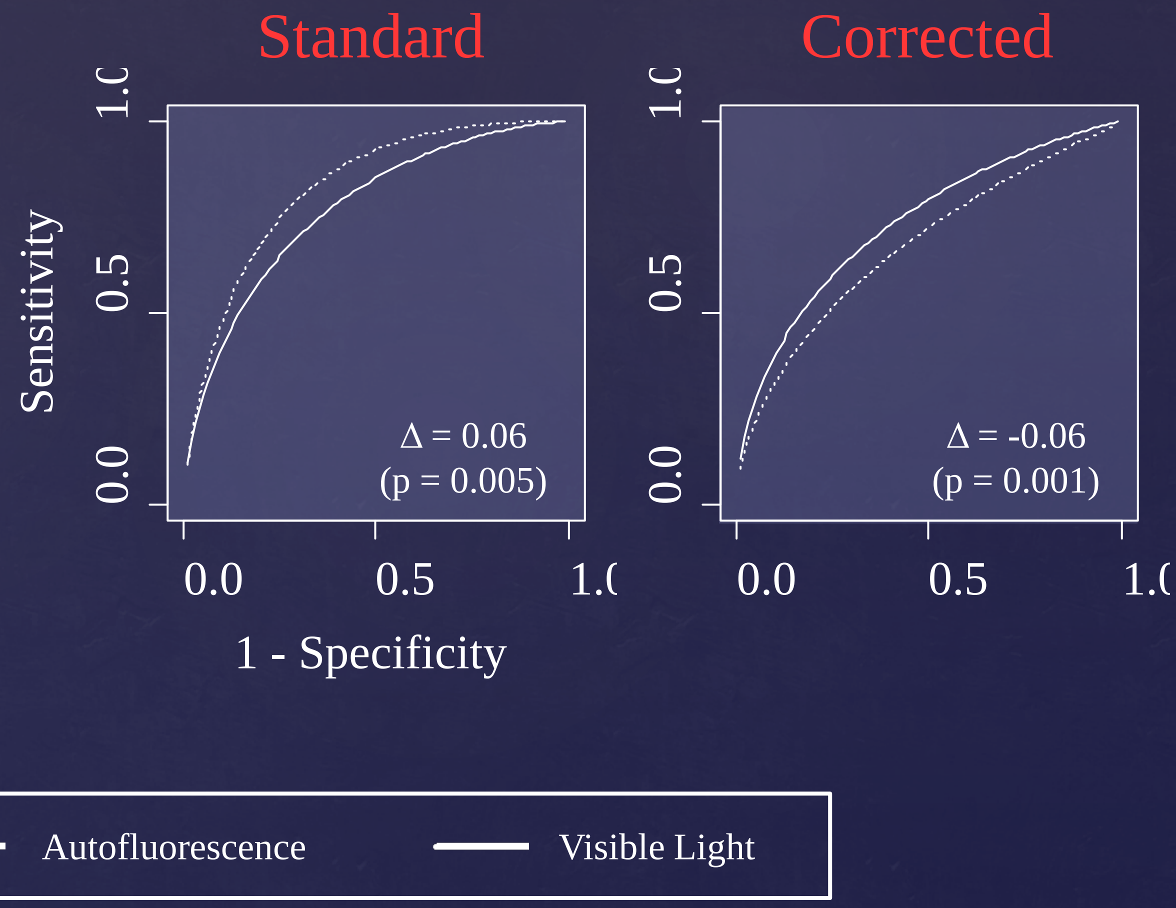

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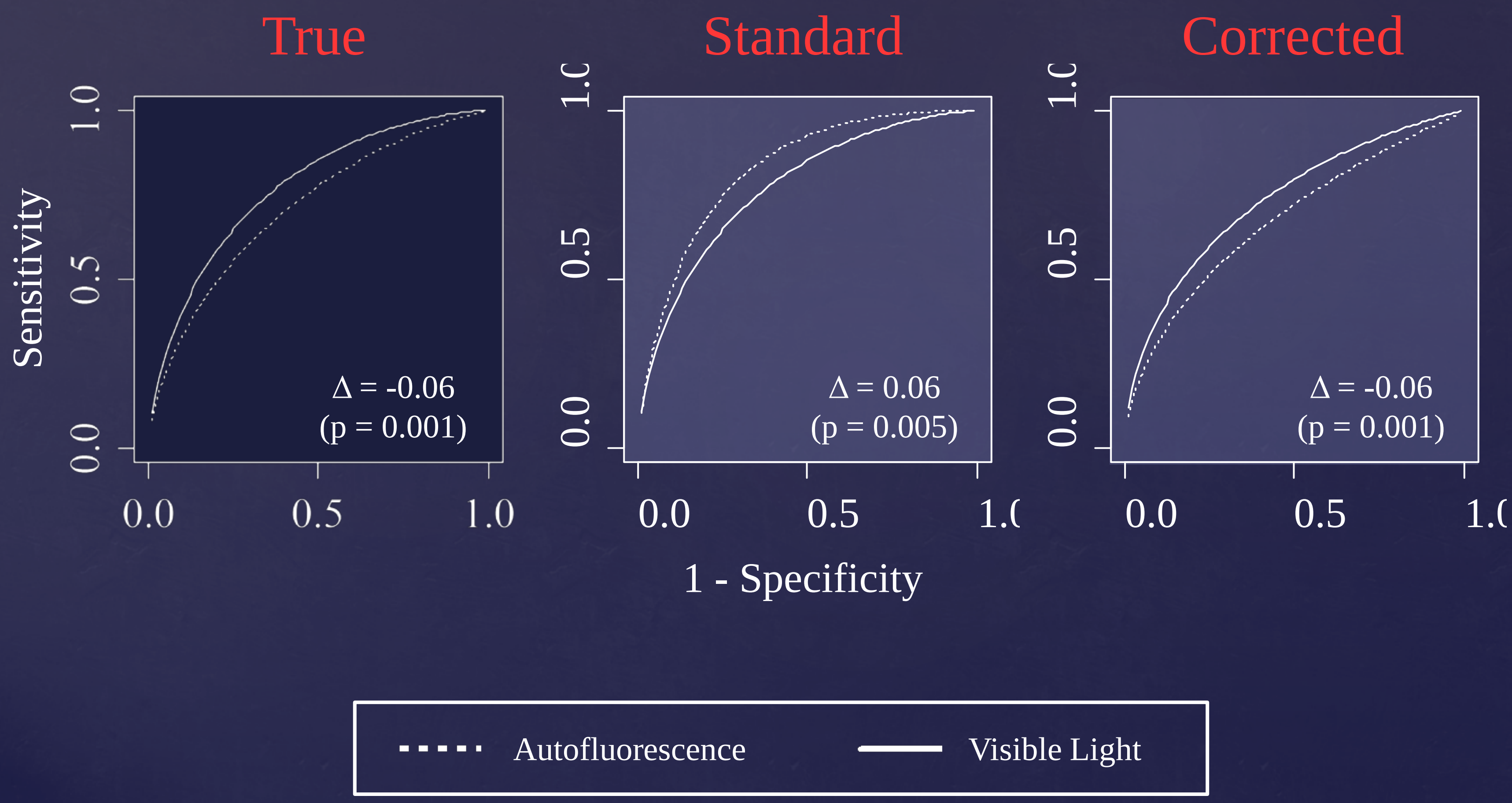

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Zhou, X.-H., McClish, D. K., & Obuchowski, N. A. (2002). Statistical Methods in Diagnostic Medicine (1st ed.). Wiley-Interscience.

Literature Review

- Re-weighting, imputation, and Bayesian approaches have been proposed to reduce the effect of partial verification bias
- Maximum likelihood methods and latent class models have been proposed to estimate diagnostic accuracy in the presence of imperfect reference standard bias
- A method using general estimating equations can correct for missing disease status, but does not account for misclassification of disease status.
- We have not found any methods that reduce the effect of paired screening trial bias.

Nath Algorithm

$$\widehat{\mu}_1 = \overline{x} - \left(\widehat{P} + \widehat{\rho}\widehat{Q}\right)\widehat{\sigma}_1$$

$$\widehat{\mu}_2 = \overline{y} - \left(\widehat{Q} + \widehat{\rho}\widehat{P}\right)\widehat{\sigma}_2$$

$$\widehat{\sigma}_1 = s_1\left[\left(1 + \widehat{\xi}\widehat{P}\right) + \widehat{\rho}^2\left(\widehat{A} + \widehat{\eta}\widehat{Q}\right) - \left(\widehat{P} + \widehat{\rho}\widehat{Q}\right)^2\right]^{-\frac{1}{2}}$$

$$\widehat{\sigma}_1 = s_2\left[\left(1 + \widehat{\eta}\widehat{Q}\right) + \widehat{\rho}^2\left(\widehat{A} + \widehat{\xi}\widehat{P}\right) - \left(\widehat{Q} + \widehat{\rho}\widehat{P}\right)^2\right]^{-\frac{1}{2}}$$

$$\widehat{\rho} = rs_1s_2(\widehat{\sigma}_1\widehat{\sigma}_2)^{-1}\Big[\left(1 + \widehat{\xi}\widehat{P} + \widehat{\eta}\widehat{Q} + \widehat{A}\right) - \left(\widehat{P} + \widehat{\rho}\widehat{Q}\right)\left(\widehat{Q} + \widehat{\rho}\widehat{P}\right)/\widehat{\rho}\Big]^{-1}$$

(Nath, 1971)

Nath Algorithm

$$\widehat{\mu}_1 = \overline{x} - \left(\widehat{P} + \widehat{\rho}\widehat{Q}\right)\widehat{\sigma}_1$$

$$\widehat{\mu}_2 = \overline{y} - \left(\widehat{Q} + \widehat{\rho}\widehat{P}\right)\widehat{\sigma}_2$$

1 $$\widehat{\sigma}_1 = s_1\left[\left(1 + \widehat{\xi}\widehat{P}\right) + \widehat{\rho}^2\left(\widehat{A} + \widehat{\eta}\widehat{Q}\right) - \left(\widehat{P} + \widehat{\rho}\widehat{Q}\right)^2\right]^{-\frac{1}{2}}$$

1 $$\widehat{\sigma}_1 = s_2\left[\left(1 + \widehat{\eta}\widehat{Q}\right) + \widehat{\rho}^2\left(\widehat{A} + \widehat{\xi}\widehat{P}\right) - \left(\widehat{Q} + \widehat{\rho}\widehat{P}\right)^2\right]^{-\frac{1}{2}}$$

$$\widehat{\rho} = rs_1s_2(\widehat{\sigma}_1\widehat{\sigma}_2)^{-1}\left[\left(1 + \widehat{\xi}\widehat{P} + \widehat{\eta}\widehat{Q} + \widehat{A}\right) - \left(\widehat{P} + \widehat{\rho}\widehat{Q}\right)\left(\widehat{Q} + \widehat{\rho}\widehat{P}\right)/\widehat{\rho}\right]^{-1}$$

(Nath, 1971)

Nath Algorithm

2 $$\widehat{\mu}_1 = \overline{x} - \left(\widehat{P} + \widehat{\rho}\widehat{Q}\right)\widehat{\sigma}_1$$

2 $$\widehat{\mu}_2 = \overline{y} - \left(\widehat{Q} + \widehat{\rho}\widehat{P}\right)\widehat{\sigma}_2$$

$$\widehat{\sigma}_1 = s_1\left[\left(1 + \widehat{\xi}\widehat{P}\right) + \widehat{\rho}^2\left(\widehat{A} + \widehat{\eta}\widehat{Q}\right) - \left(\widehat{P} + \widehat{\rho}\widehat{Q}\right)^2\right]^{-\frac{1}{2}}$$

$$\widehat{\sigma}_1 = s_2\left[\left(1 + \widehat{\eta}\widehat{Q}\right) + \widehat{\rho}^2\left(\widehat{A} + \widehat{\xi}\widehat{P}\right) - \left(\widehat{Q} + \widehat{\rho}\widehat{P}\right)^2\right]^{-\frac{1}{2}}$$

$$\widehat{\rho} = rs_1s_2(\widehat{\sigma}_1\widehat{\sigma}_2)^{-1}\left[\left(1 + \widehat{\xi}\widehat{P} + \widehat{\eta}\widehat{Q} + \widehat{A}\right) - \left(\widehat{P} + \widehat{\rho}\widehat{Q}\right)\left(\widehat{Q} + \widehat{\rho}\widehat{P}\right)/\widehat{\rho}\right]^{-1}$$

(Nath, 1971)

Nath Algorithm

$$\widehat{\mu}_1 = \overline{x} - \left(\widehat{P} + \widehat{\rho}\widehat{Q}\right)\widehat{\sigma}_1$$

$$\widehat{\mu}_2 = \overline{y} - \left(\widehat{Q} + \widehat{\rho}\widehat{P}\right)\widehat{\sigma}_2$$

$$\widehat{\sigma}_1 = s_1\left[\left(1 + \widehat{\xi}\widehat{P}\right) + \widehat{\rho}^2\left(\widehat{A} + \widehat{\eta}\widehat{Q}\right) - \left(\widehat{P} + \widehat{\rho}\widehat{Q}\right)^2\right]^{-\frac{1}{2}}$$

$$\widehat{\sigma}_1 = s_2\left[\left(1 + \widehat{\eta}\widehat{Q}\right) + \widehat{\rho}^2\left(\widehat{A} + \widehat{\xi}\widehat{P}\right) - \left(\widehat{Q} + \widehat{\rho}\widehat{P}\right)^2\right]^{-\frac{1}{2}}$$

3

$$\widehat{\rho} = rs_1s_2(\widehat{\sigma}_1\widehat{\sigma}_2)^{-1}\left[\left(1 + \widehat{\xi}\widehat{P} + \widehat{\eta}\widehat{Q} + \widehat{A}\right) - \left(\widehat{P} + \widehat{\rho}\widehat{Q}\right)\left(\widehat{Q} + \widehat{\rho}\widehat{P}\right)/\widehat{\rho}\right]^{-1}$$

(Nath, 1971)

We derived expressions for the weighted parameter estimates using the conditional covariance formula (Proposition 5.2, p. 348, Ross, 2009) and the definition of the weighted mean (Equation 3.2.1, p. 77, Kish, 1995). We define the estimates as follows:

$$\widehat{\mu}_{11,W} = \widehat{\lambda}\overline{X}_{11,A} + \left(1 - \widehat{\lambda}\right)\overline{X}_{11,B}, \quad (3)$$

$$\widehat{\mu}_{21,W} = \widehat{\lambda}\overline{X}_{21,A} + \left(1 - \widehat{\lambda}\right)\overline{X}_{21,B}, \quad (4)$$

$$\widehat{\sigma}^2_{11,W} = \mathcal{G}_1 + \mathcal{H}_1 - \widehat{\mu}^2_{11,W}, \quad (5)$$

$$\widehat{\sigma}^2_{21,W} = \mathcal{G}_2 + \mathcal{H}_2 - \widehat{\mu}^2_{21,W}, \quad (6)$$

and

$$\widehat{\rho}_{1,W} = \widehat{\sigma}^2_{11,W}\widehat{\sigma}^2_{21,W}\left(\mathcal{P} + \mathcal{Q} - \widehat{\mu}_{11,W}\widehat{\mu}_{21,W}\right) \quad (7)$$

where

$$\mathcal{G}_j = \widehat{\lambda}\left(\overline{X}^2_{j1,A} + S^2_{j1,A}\right),$$
$$\mathcal{H}_j = \left(1 - \widehat{\lambda}\right)\left(\overline{X}^2_{j1,B} + S^2_{j1,B}\right),$$
$$\mathcal{P} = \widehat{\lambda}\overline{X}_{11,A}\overline{X}_{21,A} + \widehat{\lambda}S_{11,A}S_{21,A}r_{1,A},$$

and

$$\mathcal{Q} = \left(1 - \widehat{\lambda}\right)\overline{X}_{11,B}\overline{X}_{21,B} + \left(1 - \widehat{\lambda}\right)S_{11,B}S_{21,B}r_{1,B}.$$