Statistical Considerations for BQ for Biomarker-Based Enrichment in Clinical Studies

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Outline

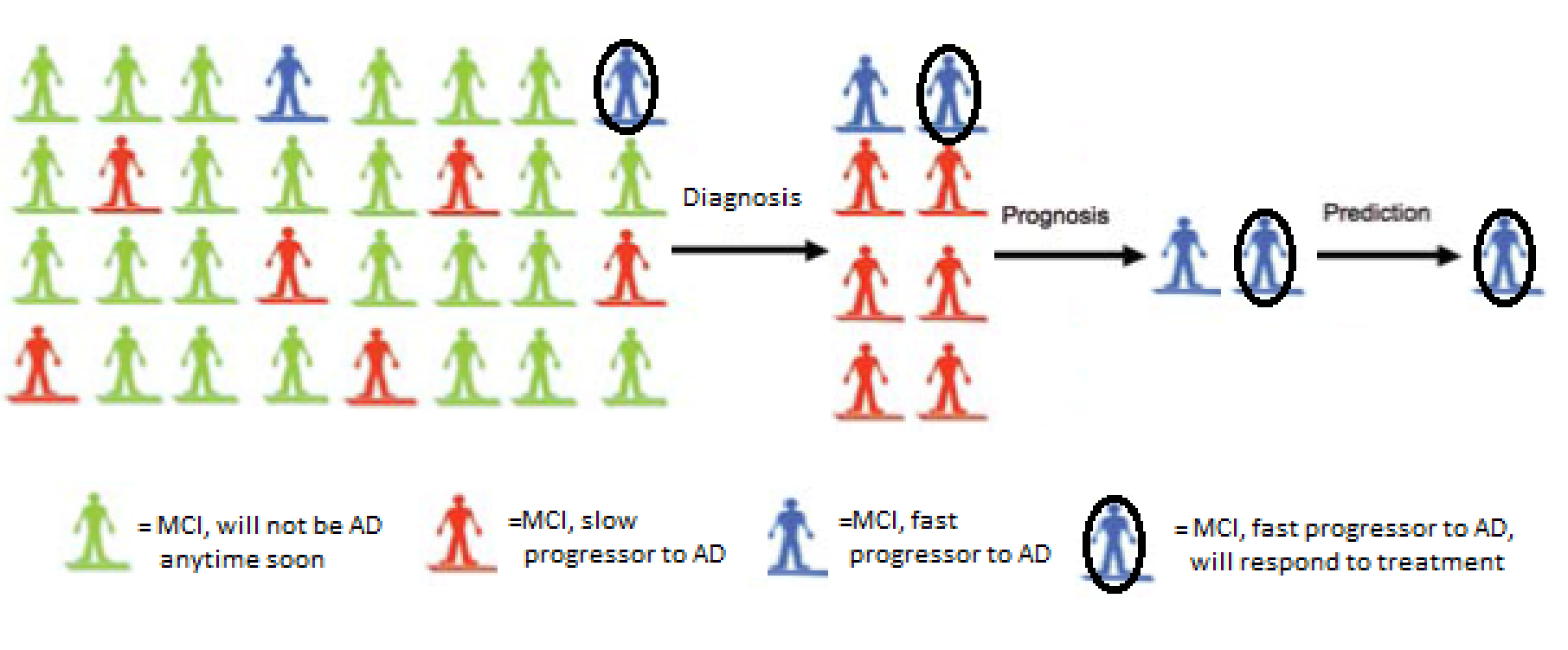
- Introduction to Enrichment in AD
- Examples in Alzheimer's Disease and MCI or prodromal AD
- Statistical Principles
- Conclusions

Introduction – Uses of "Enrichment" Biomarkers

- *Diagnosis* is included in inclusion/ exclusion criteria
- *Prognosis* may be used to separate groups or to enrich a diagnosed population
- *Prediction* of a treatment effect may depend on the putative mechanism of action

Introduction to Enrichment

Diagnosis -- Prognosis -- Prediction



Adapted from Nils Brunner, MD, University of Copenhagen, Denmark, Connection 2009
What Is the Difference Between "Predictive and Prognostic Biomarkers"?

Examples in Alzheimer's Disease & MCI/prodromal AD

- MRI Brain Volume
- CSF Abeta42
- CSF Abeta42 to CSF tau ratio

Statistical Principles

- Sources of Variation
- Misclassification
- Sensitivity, Specificity and Predictive Value
- Disease Prevalence and Predictive Value of a Test

Sources of Variation

- Within patient variability (Day to day)
- Measurement Error
  - Instruments
  - Calibrations
  - Reading or administration errors
  - Experience of person taking measurements
  - Subject experience with measurement (learning effects)
- Between subject variability
  - Covariates

Between Subject Sources of Variation

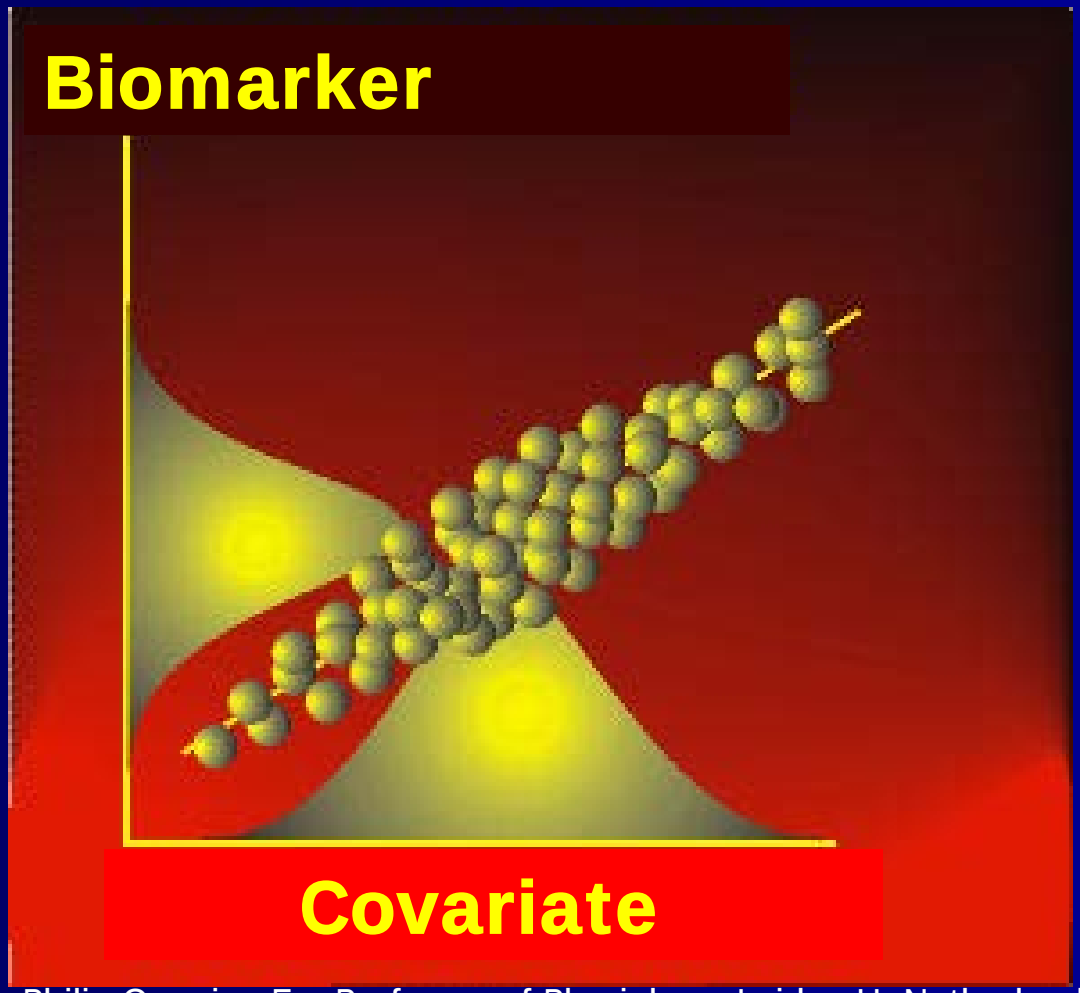
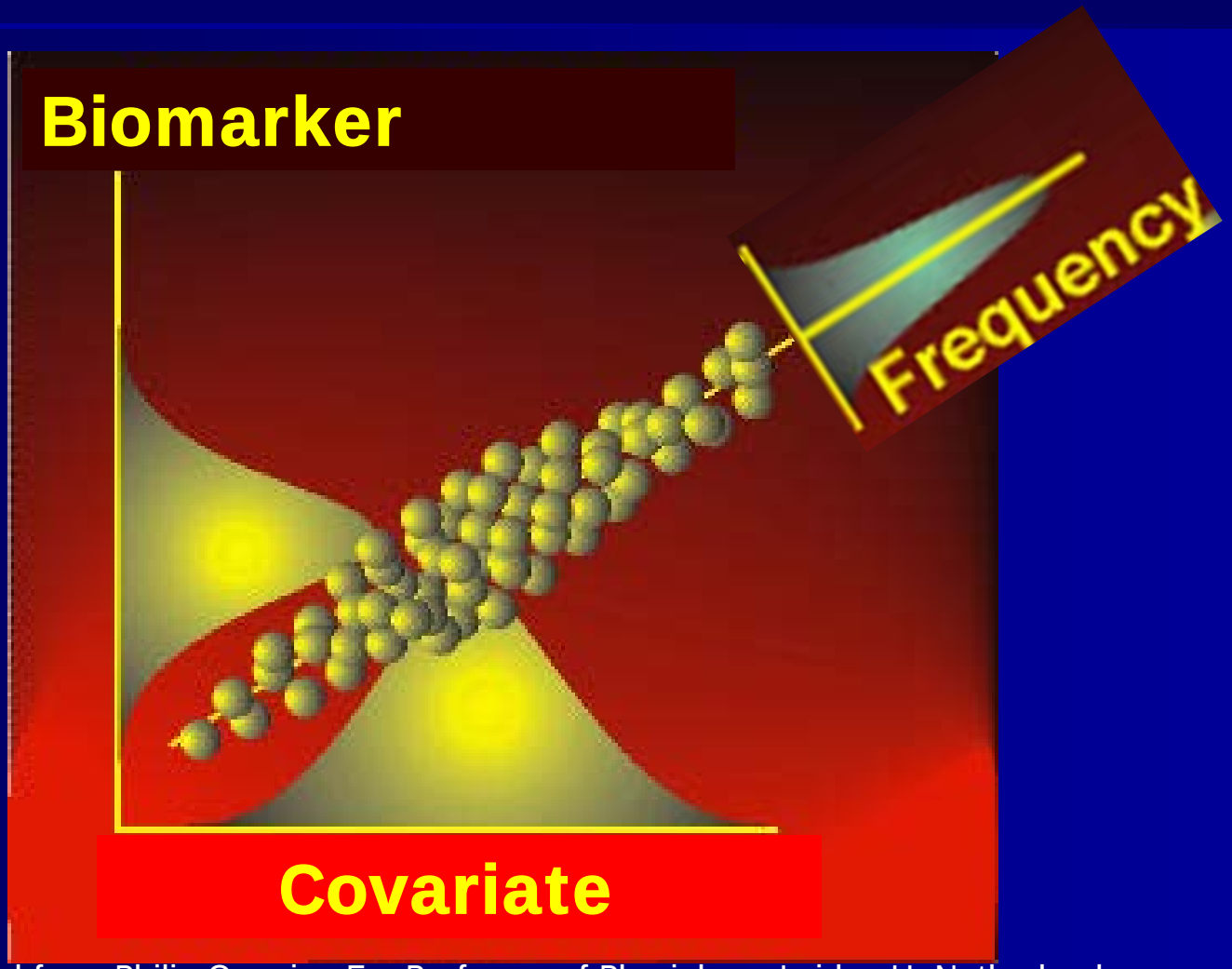


Figure from Philip Quanjer, Em Professor of Physiology, Leiden U, Netherlands www.spirxpert.com

Between Subject Sources of Variation Can Be Reduced



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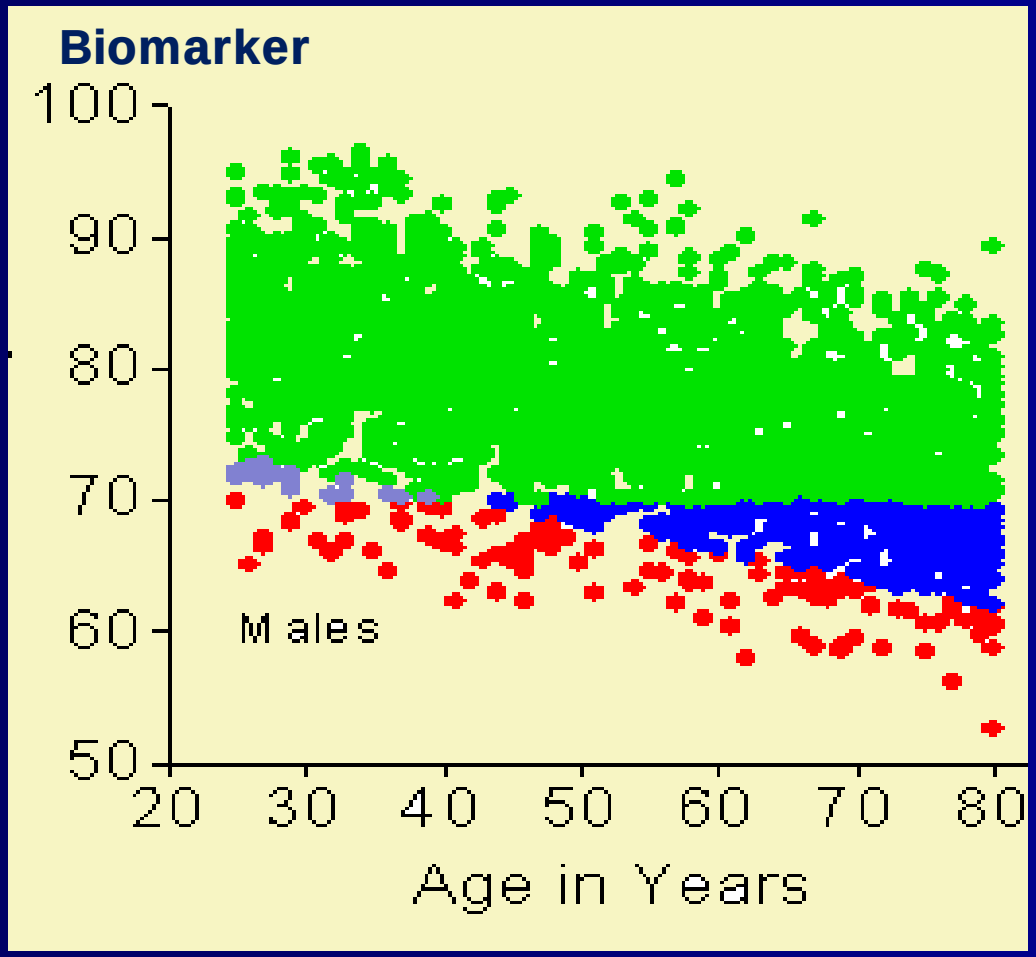
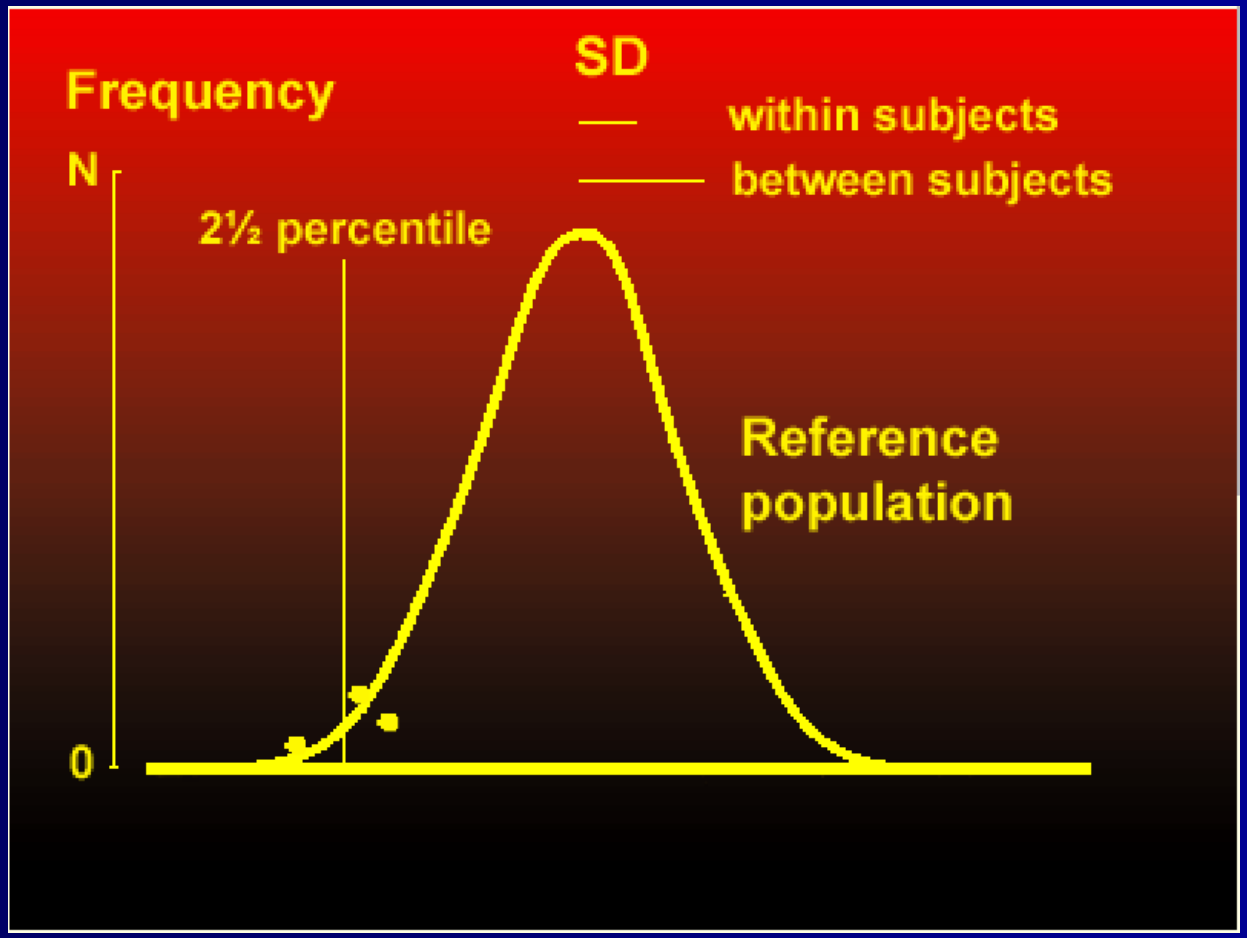
Ignoring an Important Covariate Results in Misclassification



- Correctly classified as Normal
- Normal, classified as Abnormal without covariate
- Correctly classified as Abnormal
- Abnormal, classified as Normal without covariate

Figure adapted from Philip Quanjer, Em Professor of Physiology, Leiden U, Netherlands www.spirxpert.com

Random Error Results in Misclassification



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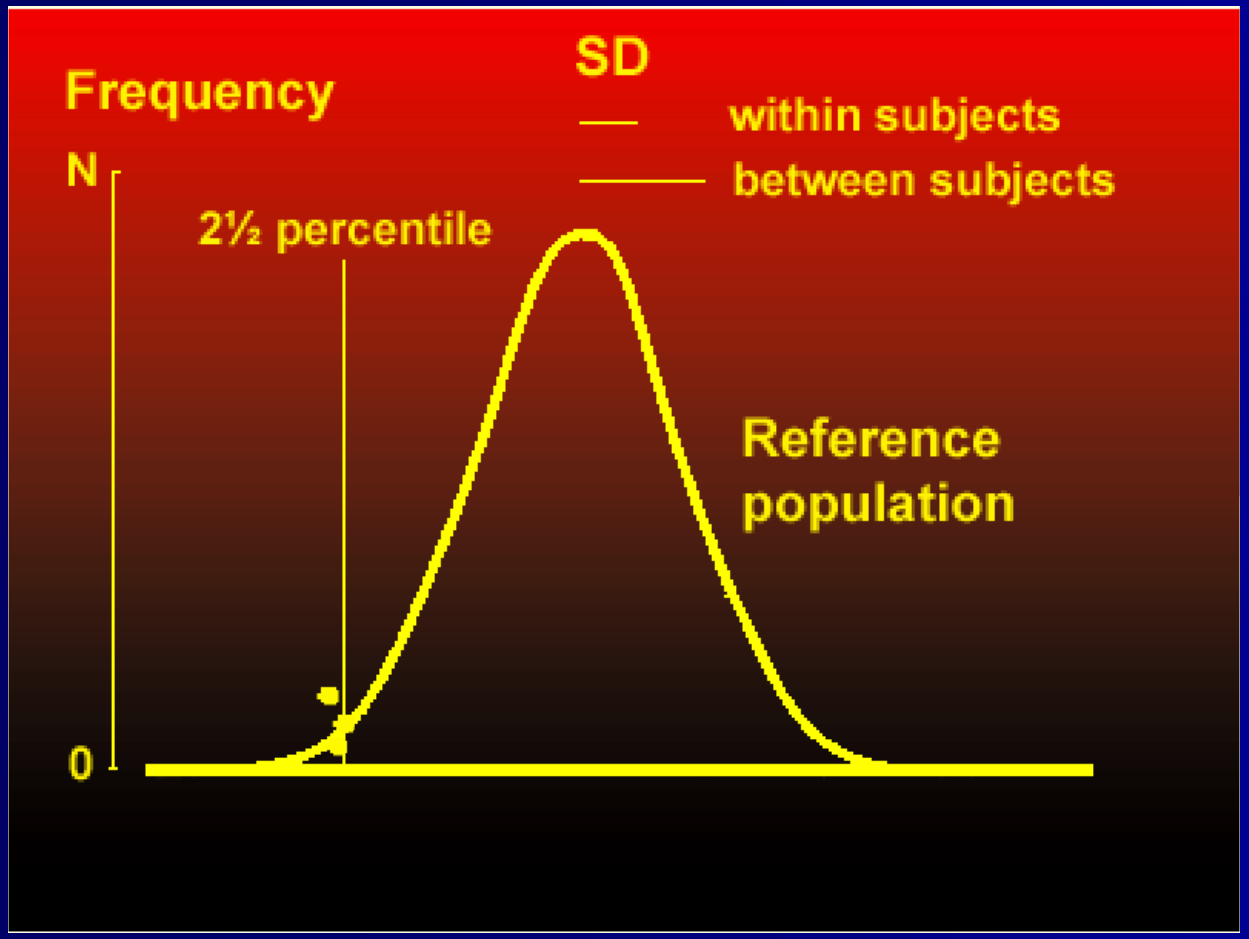

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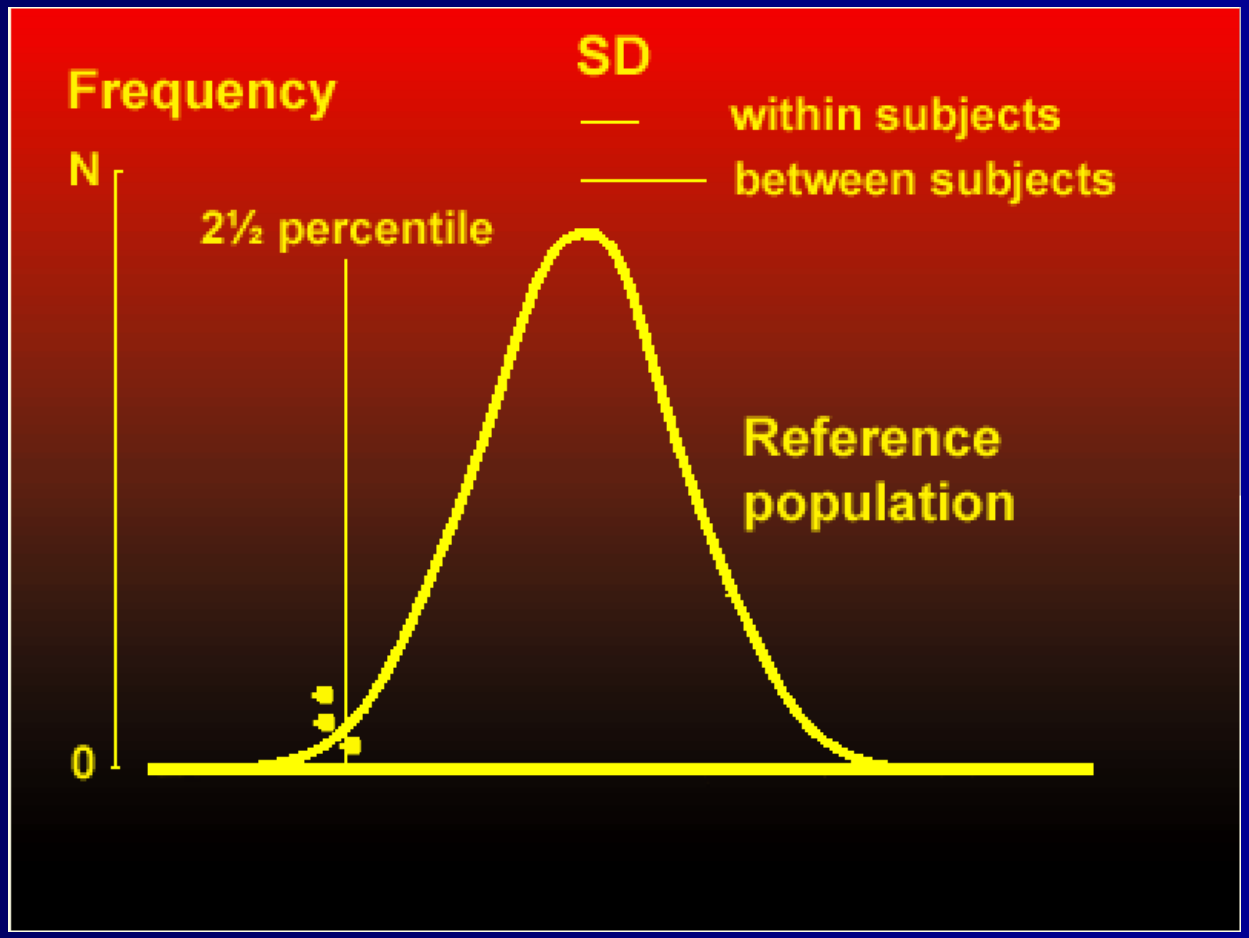

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Misclassification Rate Depends on Disease Prevalence

- Few tests are inherently dichotomous
- Continuous traits are used to categorize individuals
- This may result in substantial variation of the same diagnostic test in different populations
- Also depends on measurement error

Brenner H. and Gefeller O., “Variation of sensitivity, specificity, likelihood ratios and Predictive values with disease prevalence” Statistics in Medicine 16: 981-91, May 1997

Misclassification Rate Depends on Ratio of Between to Within Patient Variability and Prevalence

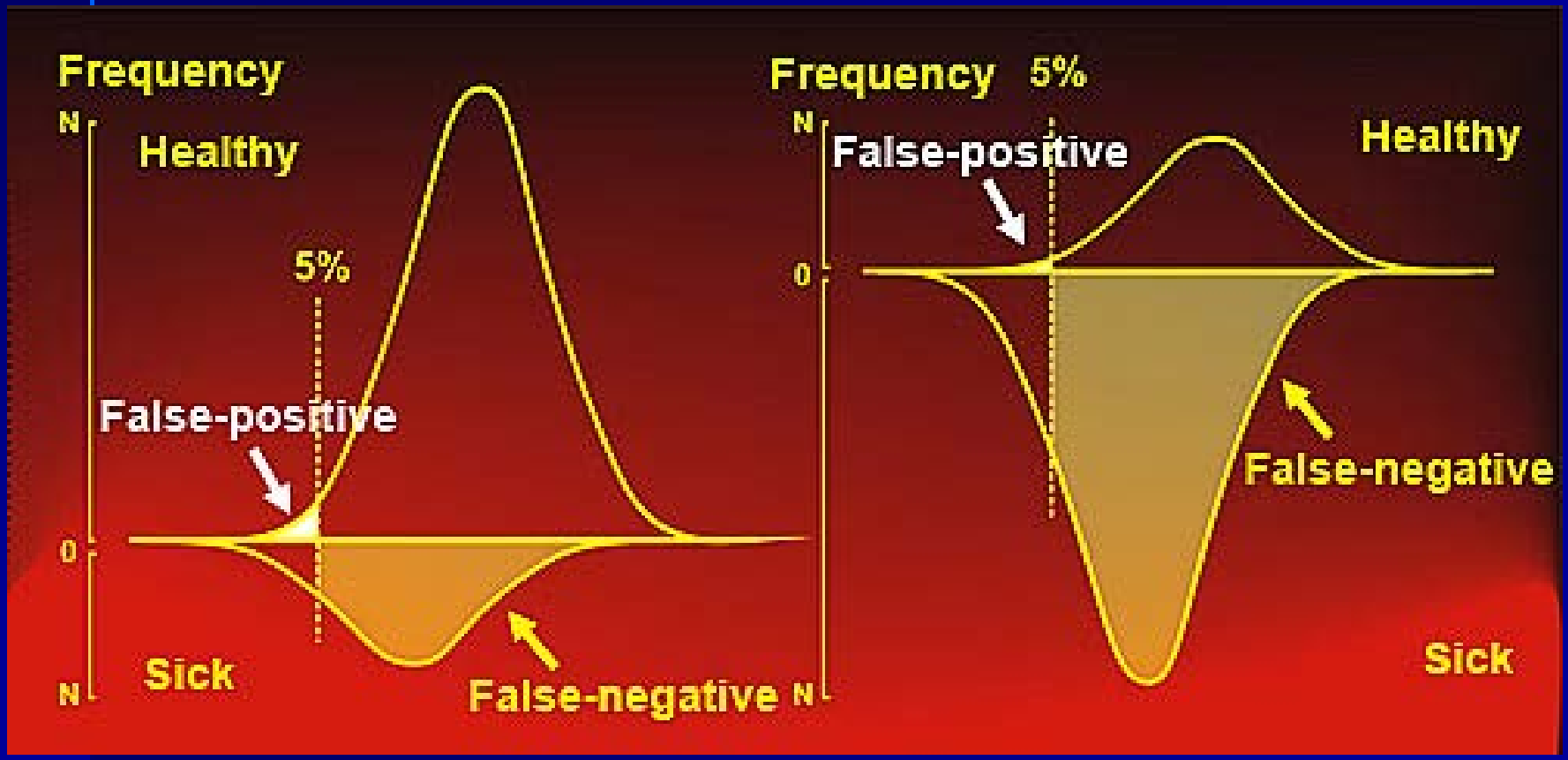
Reference population with 2.5% abnormal observations				
Mean outcome measure	3500	3500	3500	3500
SD between subjects	350	350	350	350
SD within subjects	105	105	140	140
Disease prevalence %	10	30	10	30
Undetected Abnormal Cases %	2.6	7.8	3.5	10.5

- In early AD, within-patient variability is larger, resulting in more misclassification

Sensitivity, Specificity and Predictive Value

- Must be calculated against a “gold standard”
- In prodromal AD, the “gold standard” is future diagnosis with AD
- Other standards: Amyloid Imaging, future clinical decline, post-mortem plaque load
- Level of evidence required depends on risks and benefits

Predictive Value of a Test Varies with Prevalence



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Application to AD Biomarkers – Ideal Scenario

Diagnosis -- Prognosis -- Prediction

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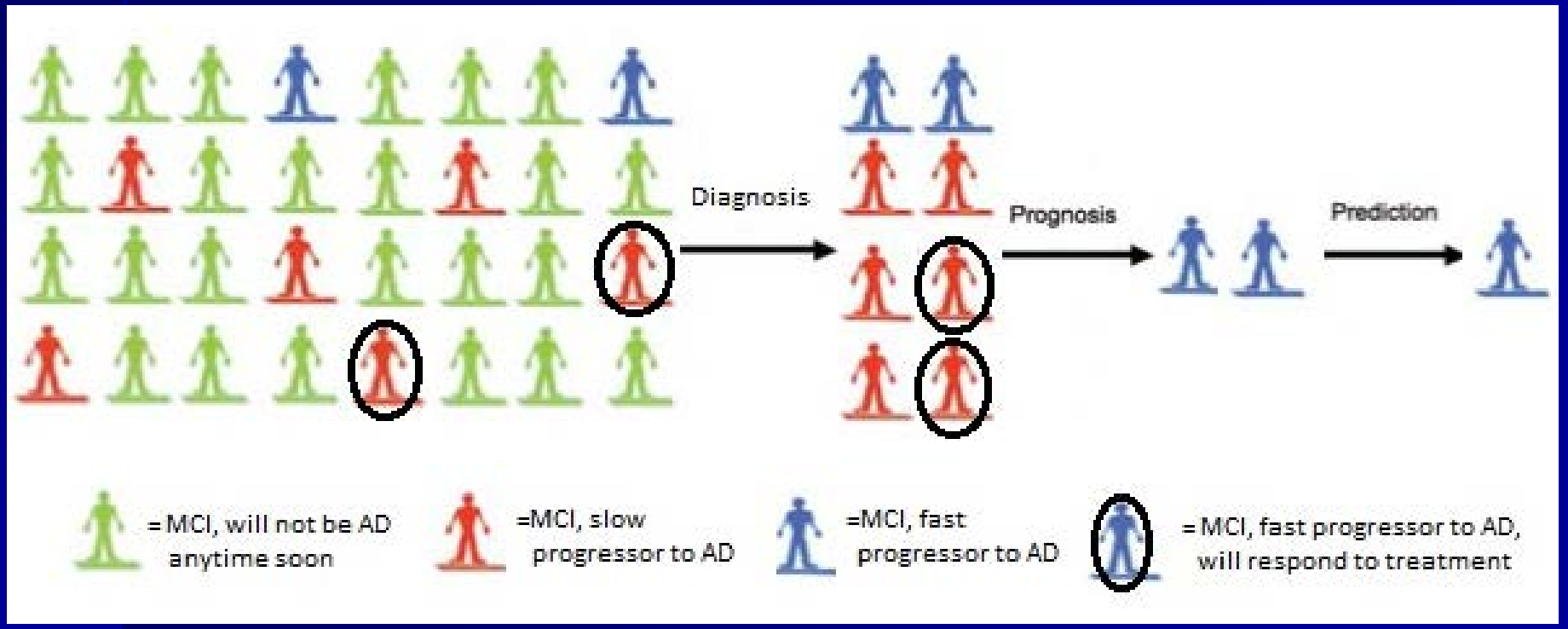
What if slow decliners respond better to treatment?

Diagnosis -- Prognosis – Prediction?



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Conclusions

- Biomarker Qualification requires estimation of and reduction in sources of variability
- Composites, repeated measurements and covariates may reduce variability
- Prevalence must be considered
- Biomarker validation depends on the risk/benefit of classification within the specified context of use