Potential Roles and Limitations of Biomarkers in Alzheimer's Disease

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Biomarkers and Disease

– Natural history
– Risk prediction
– Phenotype definition
– Clinical and biological heterogeneity
– Diagnostic or screening tests
– Response to treatment
– Prognosis

Use of Biomarkers in Epidemiology and Clinical Medicine

Traditional

Exposure → Disease

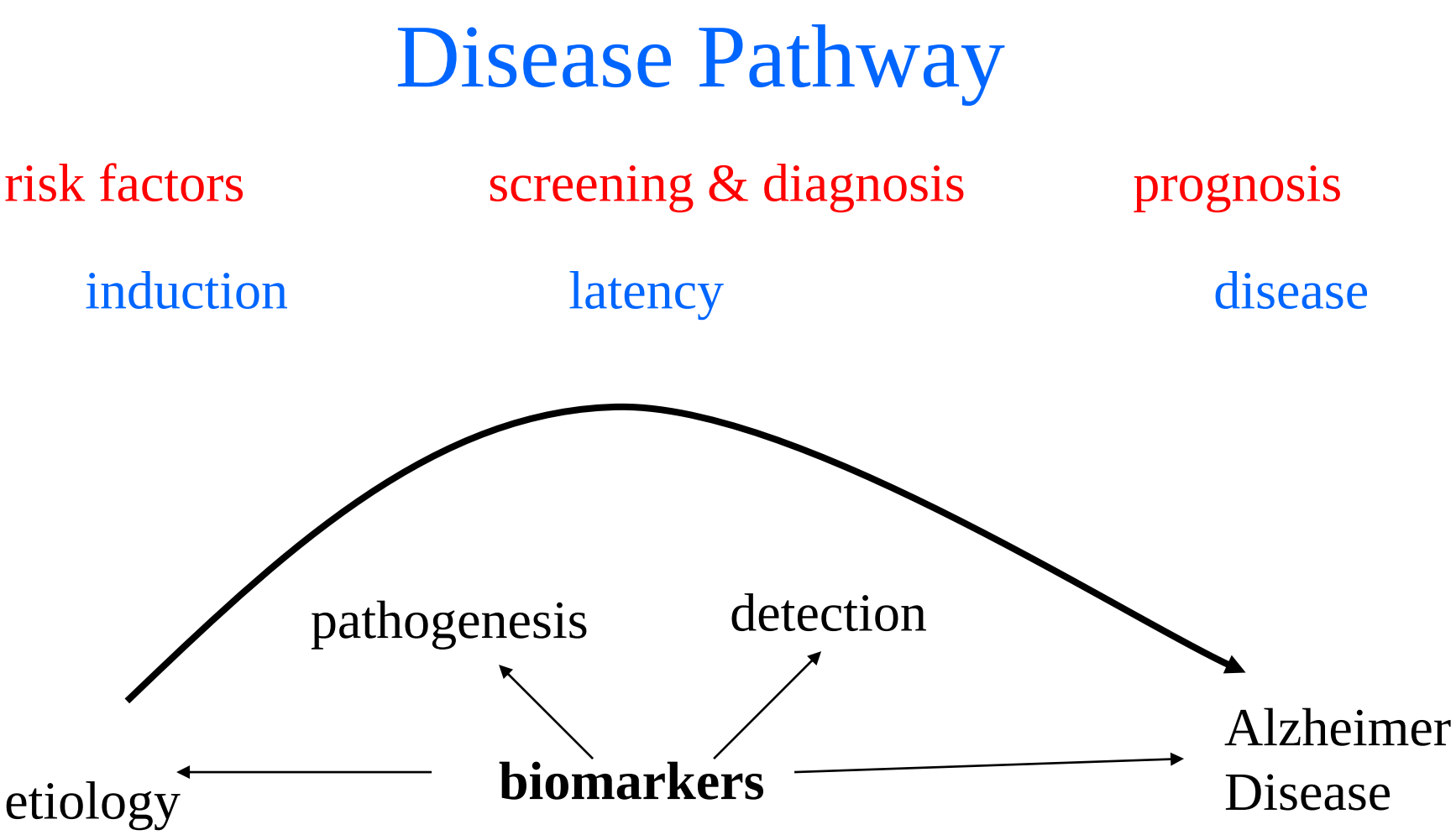
Biological or Molecular Epidemiology

Markers of Exposure → Biomarkers of Disease

Exposure → dose → biological effect

Altered structure/ function → clinical diagnosis → prognosis

Disease Pathway



Steps to Develop Biomarker

selection of type: risk factor vs. disease surrogate

validity of relation to disease

field methods

dose-response

modifiers

sensitivity & specificity

population variation

Risk or Predictors

Temporal Relationship

Past **Present** **Future**

Case-control

Biomarker Disease

“odds of exposure”

Cohort Study

Biomarker Disease

“risk of disease”

Exposure-Biomarker-Disease Association

1. $IM_1 \rightarrow D$

2. $IM_1 \rightarrow D$, $IM_2 \rightarrow D$

One or two intermediate biomarkers sufficient to cause disease

3. $E_1 \rightarrow IM_1 \rightarrow D$, $E_2 \rightarrow IM_2 \rightarrow D$

4. $E_1 \rightarrow IM_1 \rightarrow D$, $E_1 \rightarrow IM_2 \rightarrow D$, $E_2 \rightarrow IM_2 \rightarrow D$

5. $E \rightarrow U \rightarrow D$, $U \rightarrow IM_1$

Exposures mediated via intermediate biomarker(s) or exposure is related to an unknown event associated with biomarker

Strategy to Validate Biomarkers of Risk

- Select candidates relevant to disease pathway
- Identify and quantitate the association between the maker and the disease
- For intermediate markers consider attributable proportion

	Disease	
Biomarker	yes	no
Present	A	B
Absent	C	D

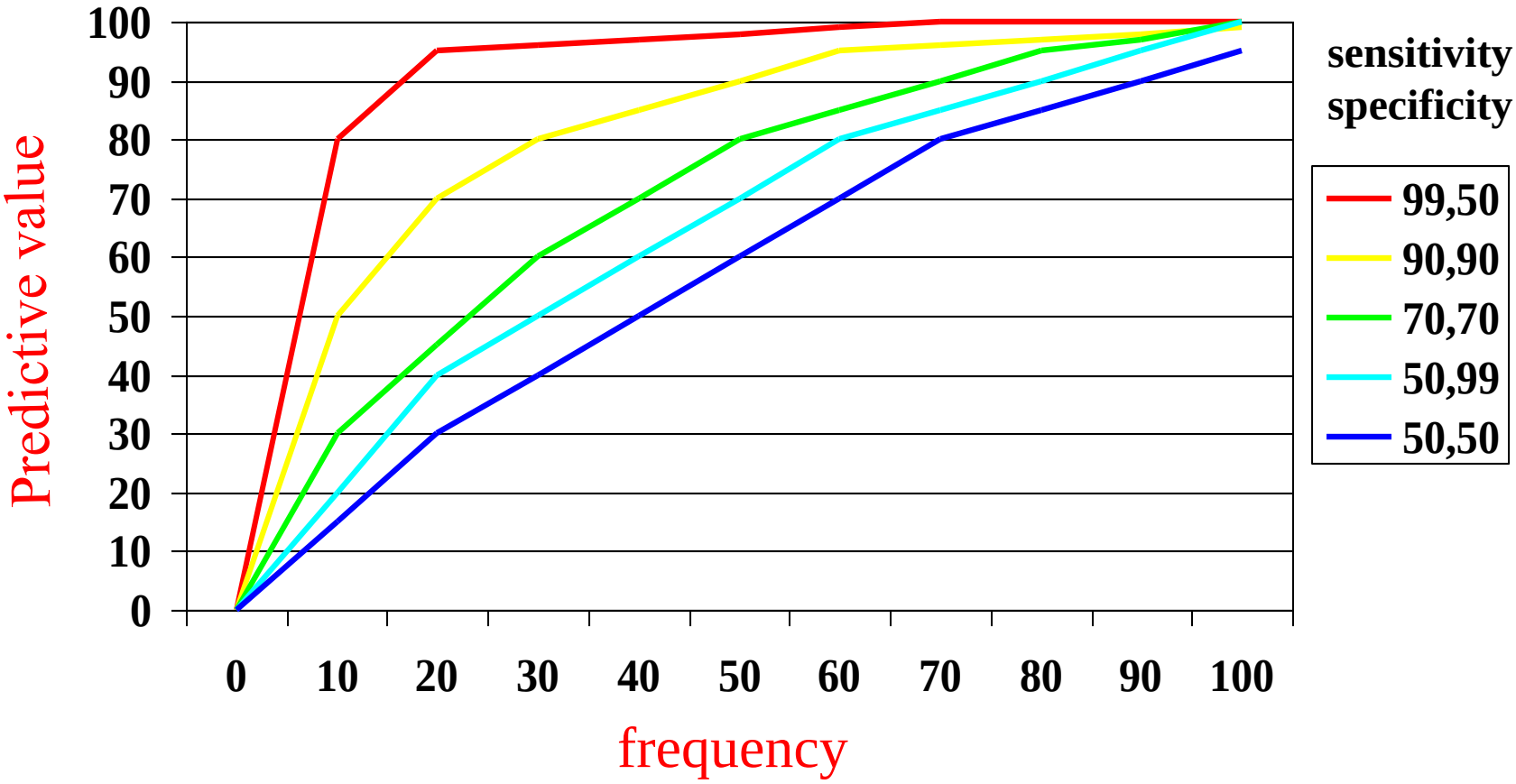
Sensitivity (S) = A/A+C

RR= [A/(A+B)]/[C/(C+D)]

Attributable proportion =

S(1-1/RR)

Relation Between Predictive Value and Frequency of Biological Marker



Screening & Diagnosis

Diagnostic & Screening Tests

Sensitivity	=	a/a+c	(true positives/patients)
Specificity	=	d/b+d	(true negatives/healthy)
*PPV	=	a/a+b	(true positives/trait present)
*NPV	=	d/c+d	(true negatives/trait absent)

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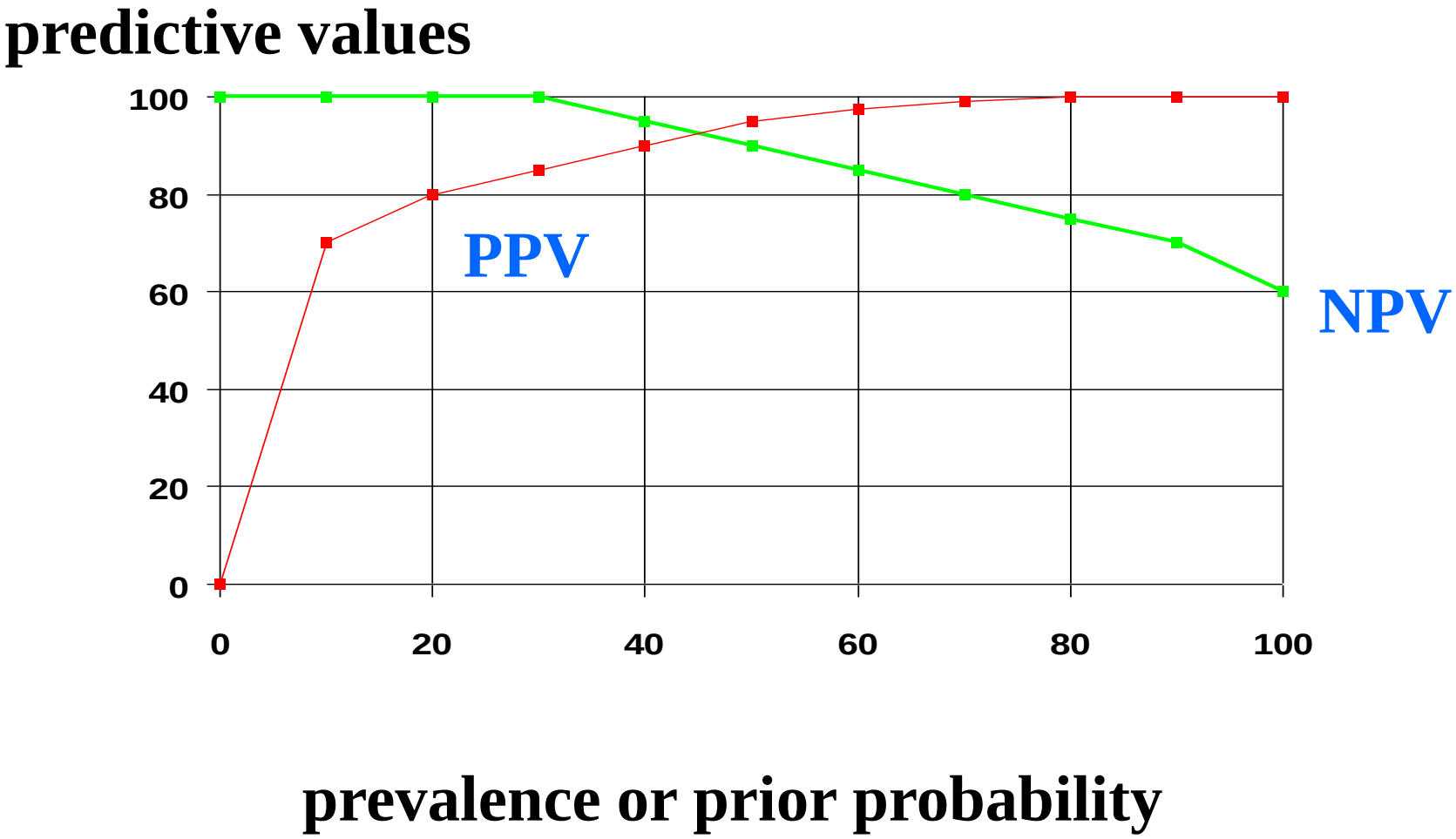
*Prior probability	=	a+c/N (patients/total population)

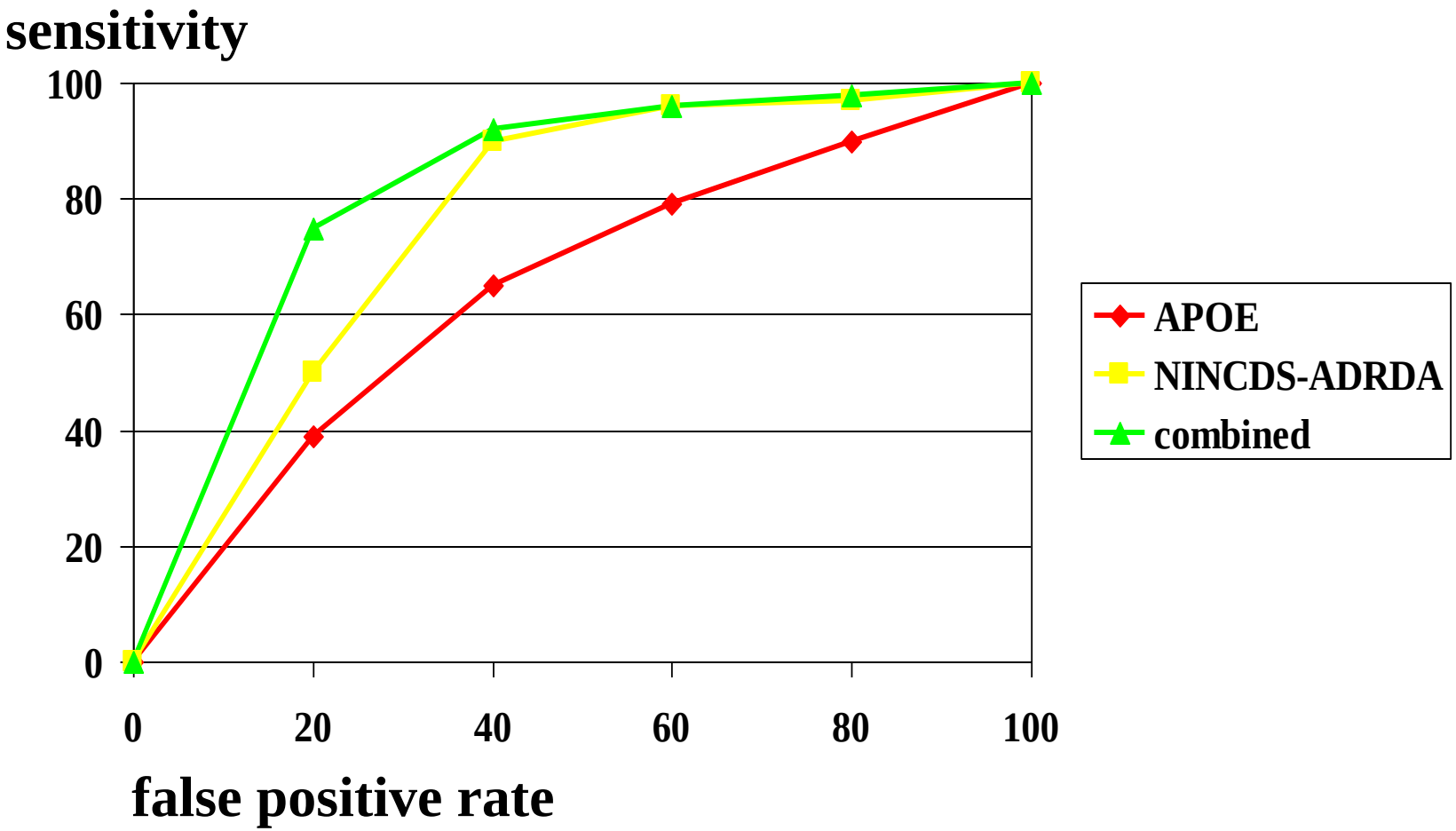
Relation Between Prior Probability and Predictive Values for a Test (90/90)



Evaluation of Diagnostic Tests

- Receiver operating characteristic (ROC)
  - Estimates probabilities of decision outcomes
  - Provides an index of the accuracy decision criterion
  - A measure of detection and misclassification
  - Efficacy = practical (or “added”) value

Utility of APOE Genotype in Diagnosis of Alzheimer's Disease



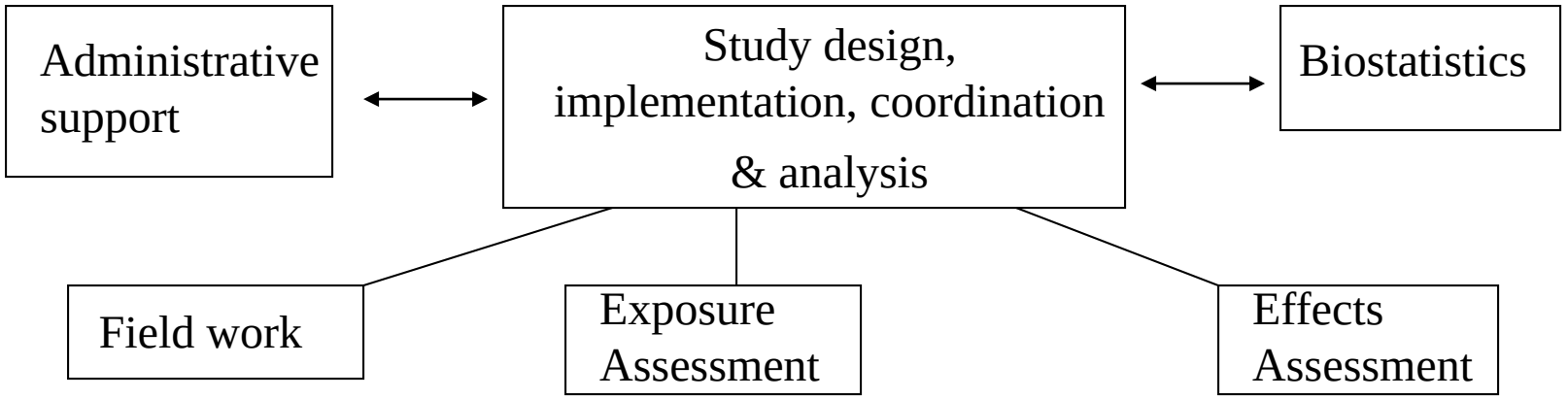
Requirements for Screening Tests

- Test must be quick, easy and inexpensive
- Test must be safe, acceptable to persons screened and physicians or health care workers screening
- Sensitivity, specificity and predictive values must be known and acceptable to medical community
- Adequate follow-up for screened positives with and without disease

Prognosis

- Same rules apply:
  - Sensitivity and specificity
  - Validity of outcome and exclusion of confounders
  - Relation between stage of disease and marker

Biomarkers: What Is Needed?



Interviewers

Specimen collectors

Field lab

Data management

Laboratory Manager

Technicians

Specimen banker

Registry

Laboratory

Specimen banker

Collaborating investigators, institutions, etc

Registry and database

Measurement Errors

- Source
  - Donor problem
  - Collection equipment
  - Technician
  - Transport/handling
  - Storage
  - Receipt and control errors (e.g.Transcription)
- Solutions
  - Procedures manual
  - Document storage
  - Monitor specimens for degredation
  - Maintain records
  - Quality control program

Bias

- Sources
  - Specimen unrelated to exposure or disease
  - Differential availability related to exposure or disease
  - Specimen acquisition, storage, analysis or procedures related to exposure or disease
- Solutions
  - High response rate rate
  - Document procedures to monitor selection bias
  - Keep track of specimen usage
  - Aliquot & use small portions
  - Use reviewed by objective panel

Confounding

- Sources
  - Failure to identify potential intermediate factors or related biomarkers (e.g. BMI, use of laboratory kits)
  - Failure to adjust for confounders in the analyses
- Solutions
  - Use data on confounders in designing study
  - Collect relevant data on acquisitions, transport, storage and laboratory personnel changes
  - Discuss confounders with biostatistician

Biomarkers

Advantages

- objective
- precision
- reliable/valid
- less biased
- disease mechanism
- homogeneity of risk or disease status

Disadvantages

- timing
- expensive
- storage
- laboratory errors
- normal range
- statistics
- ethical responsibility

It’s the Controls, Stupid!