

Roberta B. Ness, MD, MPH

Dean and M. David Low Professor in Public Health

BIOMARKERS: WHAT ARE THE METHODOLOGICAL ISSUES?



THE UNIVERSITY *of* TEXAS
SCHOOL OF PUBLIC HEALTH

Definition of a Biomarker or Surrogate

Biomarker:

- ž Cellular, biochemical or molecular alterations measurable in human samples

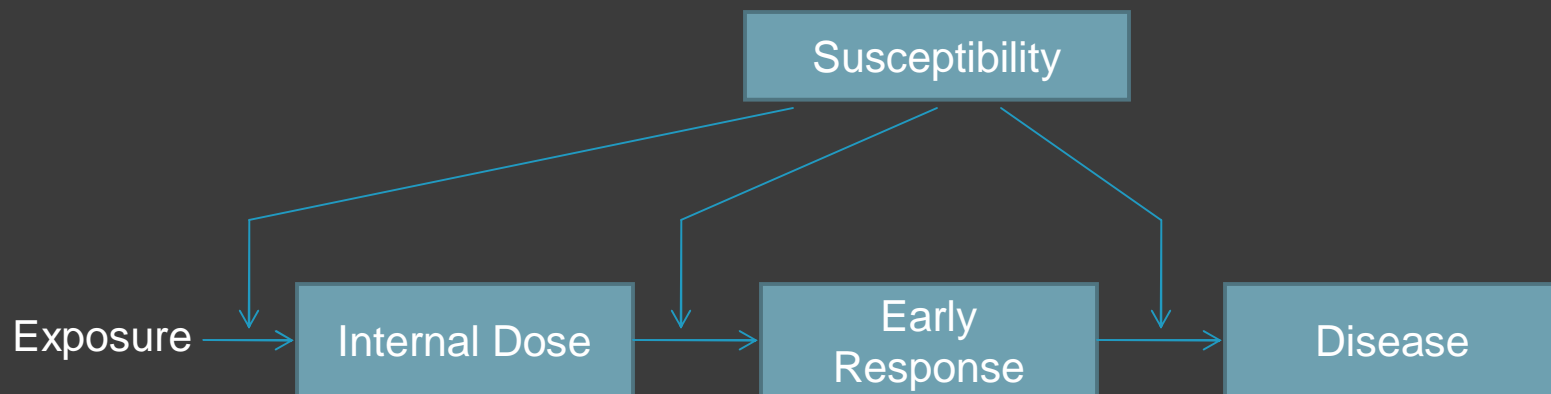
Surrogate:

- ž Substitute for a clinically meaningful endpoint (feel good, function better, live longer)
- ž Biomarker changes as internal dose or response to exposure changes
- ž Surrogate changes as endpoint changes

Ref: Temple RJ: A Regulatory Authority's Opinion About Surrogate Endpoints. In WS Nimmo and GT Tucker (eds.) Clinical Measurement in Drug Evaluation. Wiley, 1995.

Ref: Hulka BS: Biological Markers in Epidemiologic Research, *Archives of Environmental Health*, March/April 1988 [Vol. 43(No.2)]

Markers measure a variety of steps along an exposure - disease pathway

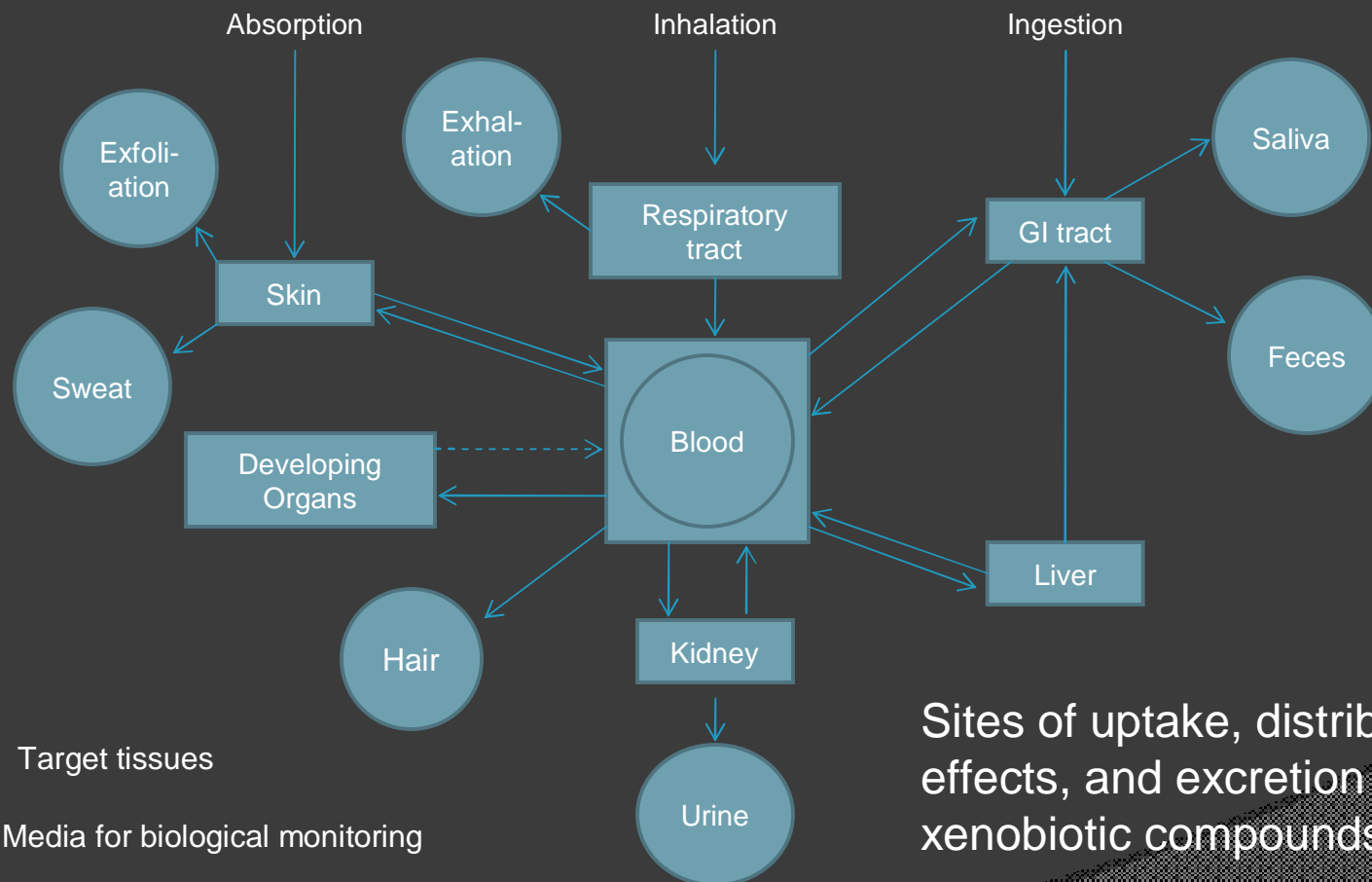


The relationship of biological markers to exposure and disease

Biomarker Persistence

- Highly transient markers may be too fleeting to be useful
- Less transient markers measure current, but not past exposures unless the level of repeated exposures is consistent over time

Sample Markers: Biomarkers May Not Be Evenly Distributed



Sites of uptake, distribution effects, and excretion for xenobiotic compounds.

Measures of Association

	T good	T poor	
ž S Good	a	b	a + b
ž S Poor	c	d	c + d
ž Total	a + c	b + d	N

ž Sensitivity $SE = a / (a+c)$

ž Specificity $SP = b / (b+d)$

ž Positive Predictive Value (PPV) = $a / a+b$

ž Negative Predictive Value (NPV) = $d / c+d$

To be useful...

- Biomarker or surrogate must have both SE and SP close to 1.0
- Biomarker or surrogate must have PPV close to 1.0
- However, “association does not a surrogate make.” (Fleming and DeMets, 1996)

Surrogate Response Variables

ž Requirements (Prentice, 1989)

T = True Clinical Endpoint

S = Surrogate

Z = Treatment

ž $H_0: P(T|Z) = P(T | S,Z) \quad P(S|Z) = P(S)$

ž Sufficient Conditions

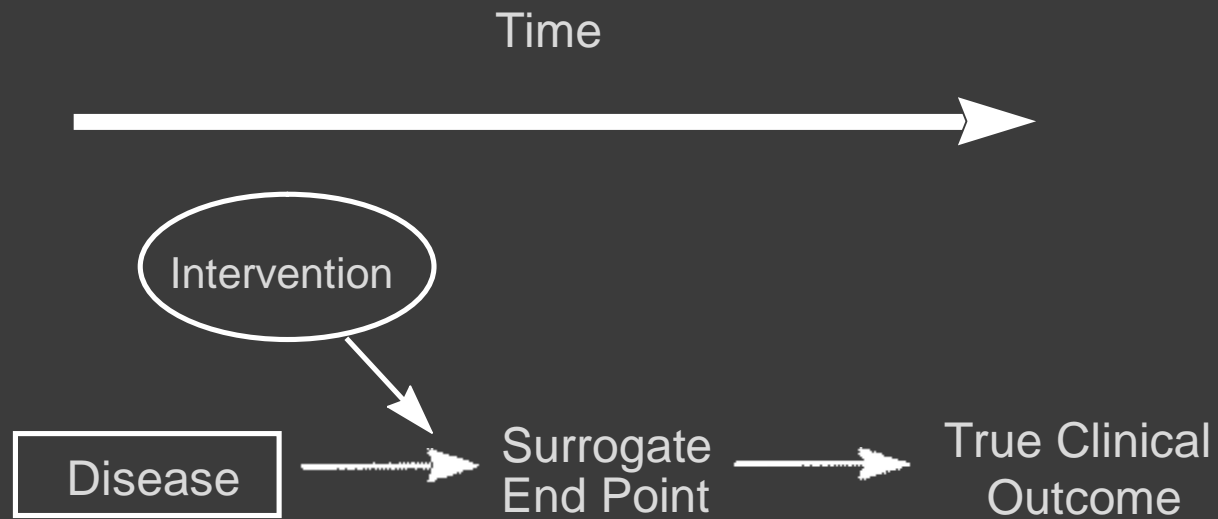
1. S is informative about T

$$P(T|S) = P(T)$$

2. S fully captures effect of Z on T

$$P(T|S,Z) = P(T|S)$$

The setting that provides the greatest potential for the surrogate endpoint to be valid.



Reprinted from *Ann Intern Med* 1996; 125:605-13

Time



Reasons for failure of surrogate end points:

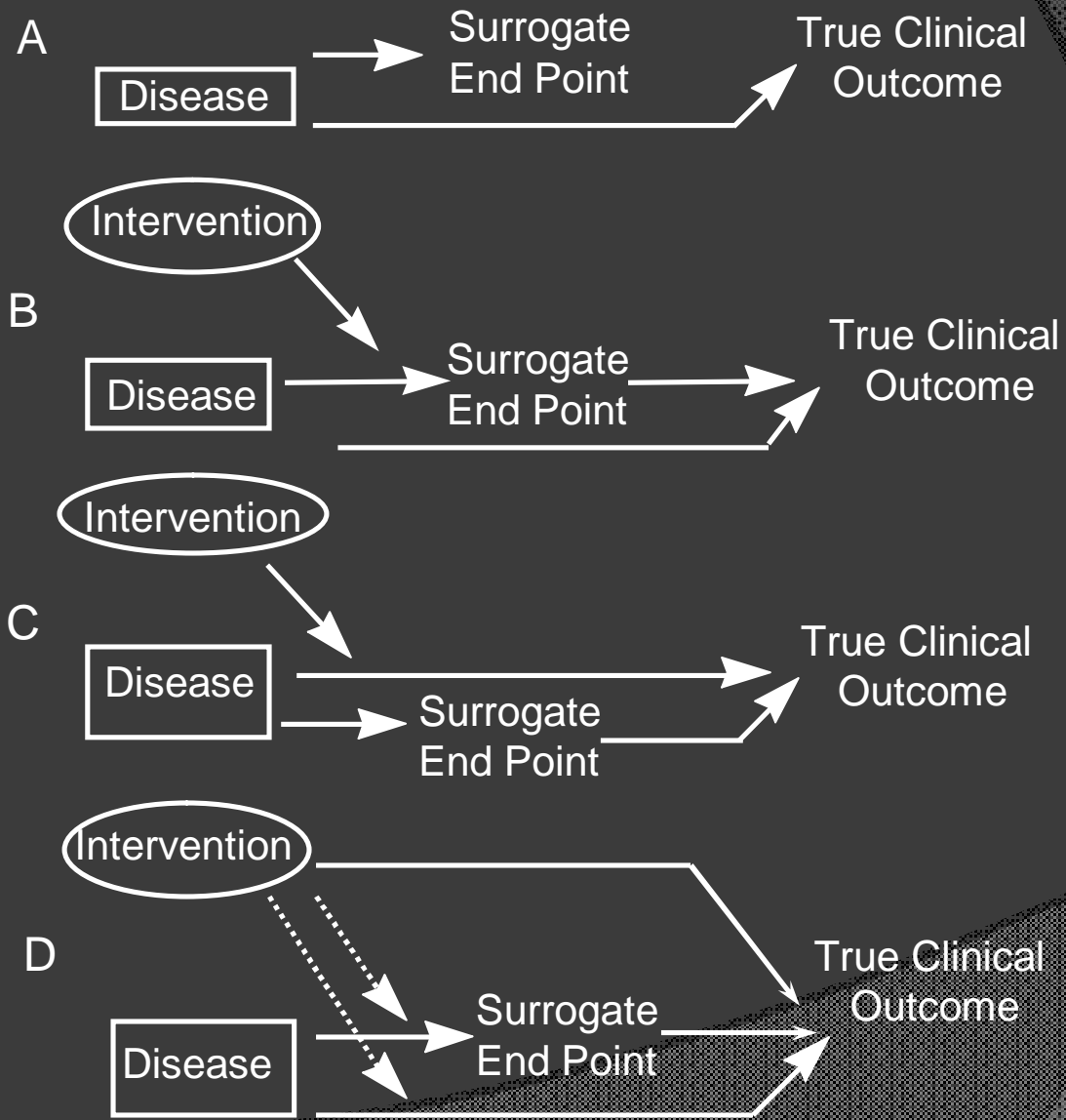
A. The surrogate is not in the causal pathway of the disease process.

B. Of several causal pathways of disease, the intervention affects only the pathway mediated through the surrogate.

C. The surrogate is not in the pathway of the intervention's effect or is insensitive to its effect.

D. The intervention has mechanisms for action independent of the disease process.

Dotted lines = mechanisms of action that might exist.



To be useful...

- Surrogate must be predictive of clinical outcome
- All effects of intervention on clinical outcome must be captured by the surrogate
- Implies that biological mechanism and pathway of action is known

Validation or Evaluation of Potential Surrogates?

- **Validation is tough, perhaps not possible**
- **Evaluation for usefulness**
 - **Correlation consistency of surrogate across studies & populations**
 - **Correlation consistency of change in surrogates across studies and populations**
 - **Understanding of biology and role of surrogate in mechanism pathway**
 - **Understanding new intervention**

Regulatory Approval of Drugs Using Surrogates That:

- ž Lower cholesterol without evidence of survival benefit
 - ž Lower blood pressure without evidence of reducing stroke, MI, CHF, or mortality rates
 - ž Increase bone density without evidence of decreased fractures in osteoporosis
 - ž Increase cardiac function in CHF without improving survival
- Decrease rates of arrhythmias without evidence of improving survival

Some "Surrogate" Failures

(Fleming & DeMets, 1996)

- ž PFT for COPD patients and nocturnal oxygen
- ž Arrhythmia suppression
- ž Cardiac function in CHF / inotropic drugs
- ž Cardiac function in CHF / beta-blockers
- ž Bone density in osteoporosis / sodium flouride
- ž Lipid reduction for post menopausal women / HRT
- ž etc

Years of Life Saved by Using HRT

<u>Variable</u>	<u>Life Expectancy</u>	<u>Net Change in Life Expectancy</u>		
		Estrogen	E+P	E+P
White woman, 50 years old				
No risk factors	82.8	+0.9	+1.0	+0.1
With hysterectomy	82.8	+1.1		
With history of coronary heart disease	76.0	+2.1	+2.2	+0.9
At risk for coronary heart disease	79.6	+1.5	+1.6	+0.6
At risk for breast cancer	82.3	+0.7	+0.8	-0.5
At risk for hip fracture	82.4	+1.0	+1.1	+0.2

Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. Ann Int Med 1992;117:1016-1040.

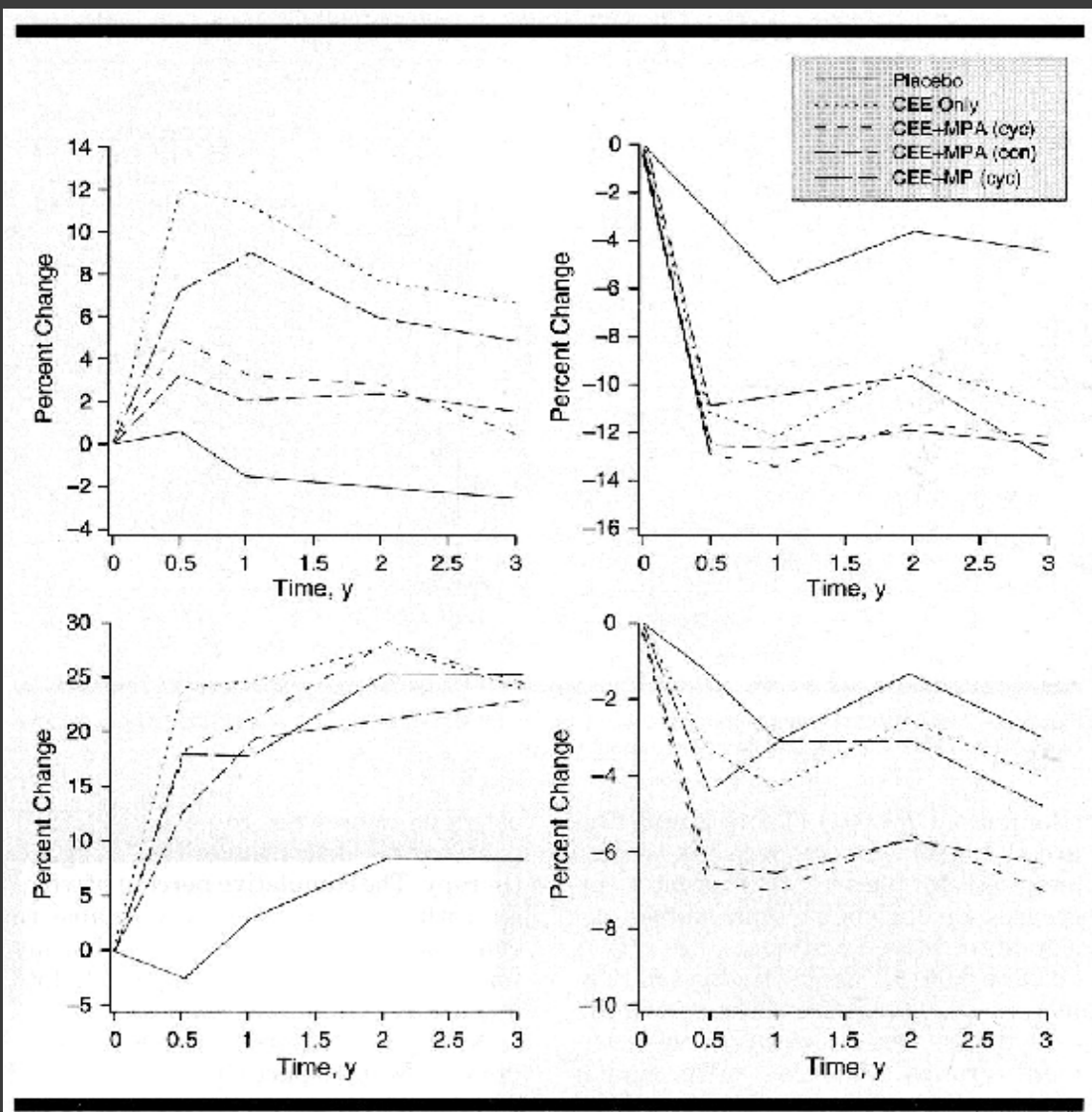


Figure 1-Mean percent change from baseline by treatment arm for high-density lipoprotein cholesterol (top-left), low-density lipoprotein cholesterol (top right), triglycerides (bottom left), and total cholesterol (bottom right).

The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. JAMA 1995;273:199-208.

Women's Health Initiative (2002)

Absolute Excess Risk per 10,000 women

⊕ 7 CHD Events

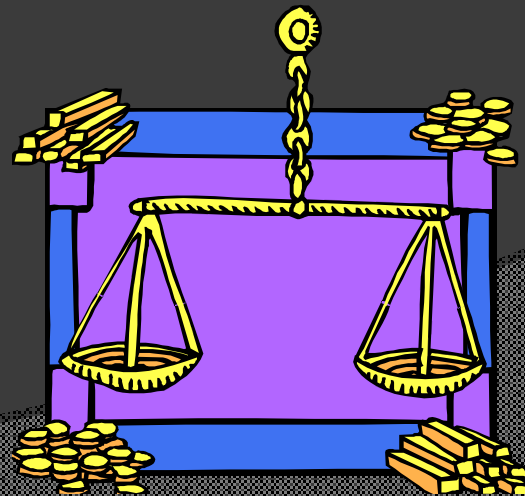
⊖ 6 Colorectal Cancers

⊕ 8 Strokes

⊖ 5 Hip Fractures

⊕ 8 PEs

⊕ 8 Breast Cancers



Cardiac Arrhythmias

- Cardiac arrhythmias associated with sudden death
- Class of drugs developed to suppress arrhythmias
- FDA approved for high risk patients
- “Off-label” use increased

CAST

Early Termination in 2 Drug Arms

	Drugs	Placebo
Sudden Death	33	9
Total Mortality	56	22

From: DeMets

Lessons Regarding Biomarkers

- Biomarker and surrogate endpoints do not always concur with “hard endpoints”
- Biology may be incompletely reflected in biomarkers measured
- Risk group may vary: biomarkers may be useful in one group and not another

How Can Biomarkers be Used to Improve Patient Care?

- **Improve global risk assessment, particularly in intermediate-risk patients**
- Guide selection or intensity of therapy
- Provide target of therapy if risk factor and not just marker

Lessons about Biomarkers

- Failure to account for missing data can be a major limitation
- Multiple biomarkers are better than one
- Biomarkers are just patient characteristics subject to multiple comparison problems
- Understanding biomarkers can only happen if successes and failures are shared
- The human brain is not configured to deal with probabilistic assessments
 - Pictures and stories dominate over probabilities
 - A massive educational effort is needed