Role of Surrogate Outcome Measures in Clinical Trials

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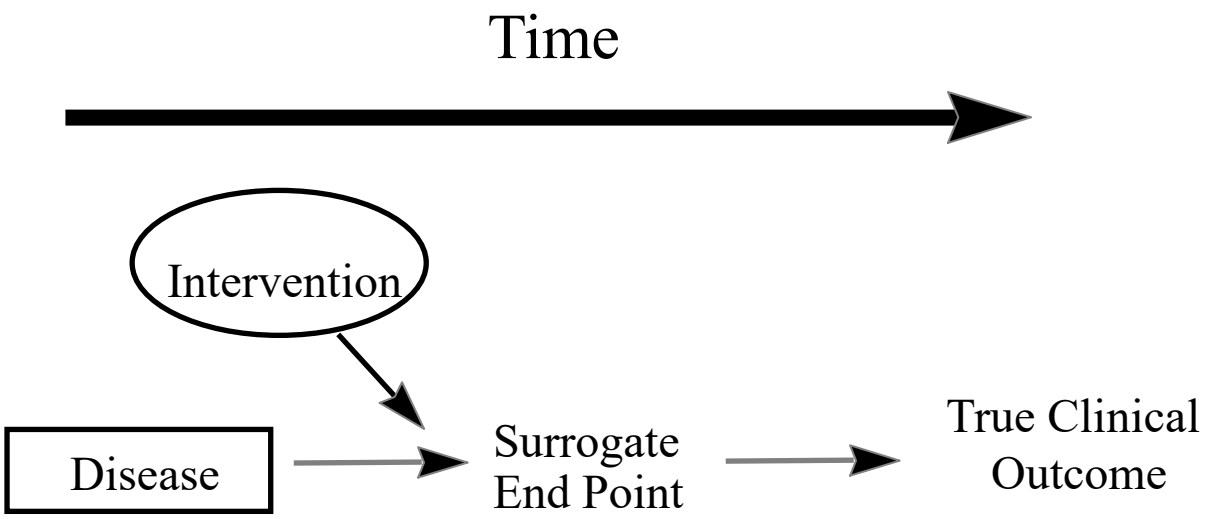
Fleming TR and DeMets DL: Surrogates endpoints in clinical trials. Are we being misled?

Annals of Internal Medicine 1996.

Surrogate Outcome Measures

- Used as alternative or substitute for clinically relevant response
- Surrogate must be
  - Be predictive of clinical outcome
  - Capture all effects of intervention on clinical outcome
- Correlation is not causal
- May be other unfavorable effects
- Surrogate may correlate with one clinical endpoint, but not others



The setting that provides the greatest potential for the surrogate endpoint to be valid. Reprinted from *Ann Intern Med* 1996; 125:605-13.

Reasons for failure of surrogate end points:

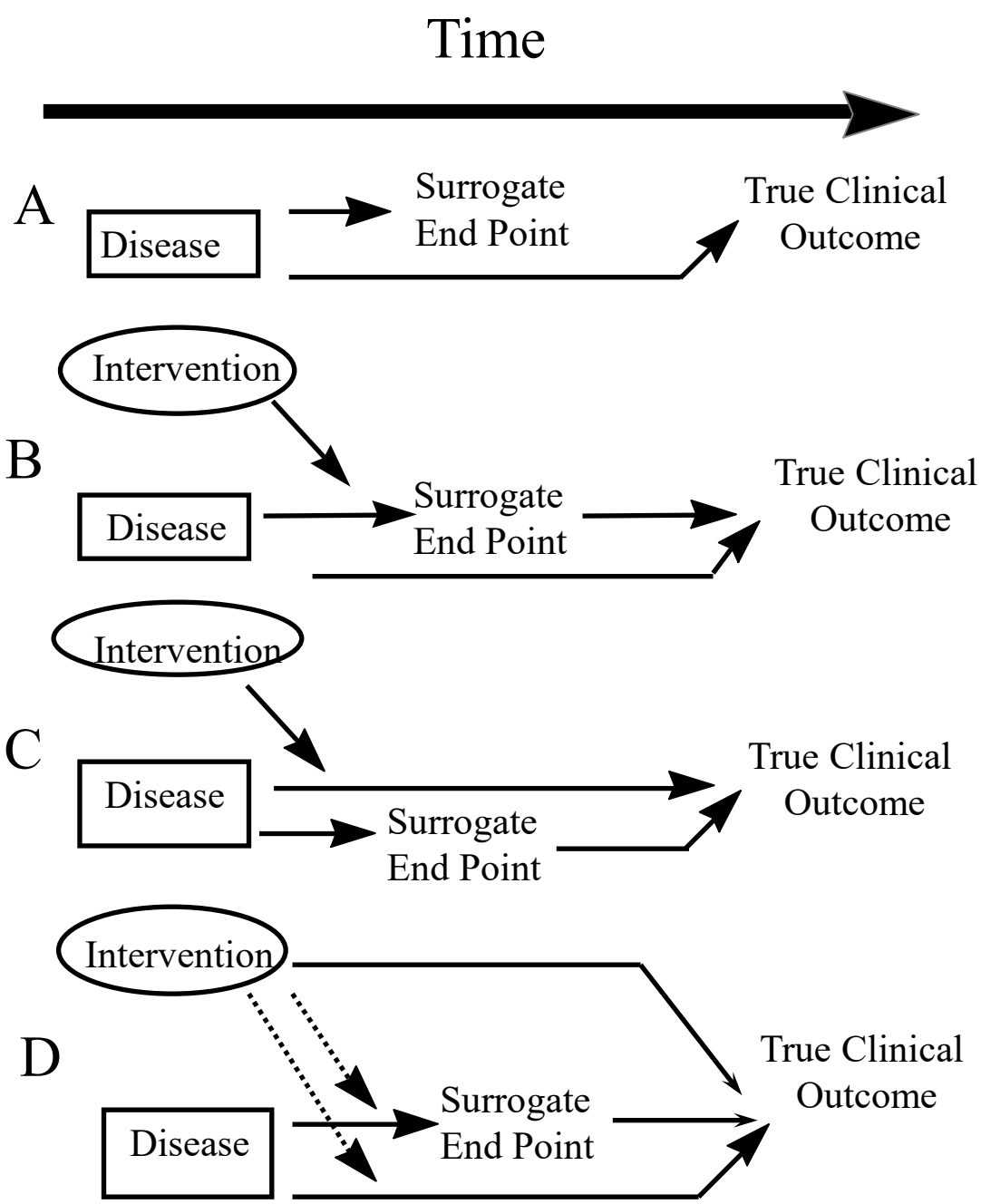
A. The surrogate is not in the causal pathway of the disease process.

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.



Cases of "Surrogates" Failures

- Lowered cholesterol without evidence of survival benefit / CDP
- Decreased rates of arrhythmias (PVCs) but reduced survival /CAST
- Increased bone density but increased fractures in osteoporosis/Mayo
- Increased cardiac function in CHF without improving survival / PROMISE, PROFILE
- Lower glucose & glycosylated hemoglobin with no benefit on survival /ELIXA
- Increased serum beta carotene but increased lung cancer mortality/ATBC, CARET
- Used HRT but increased cancer & heart disease/WHI
- Increased CD4 counts but no effect on AIDS / ACTG
- Tight control in diabetes had increased microaneurism but had long term clinical benefit /DCCT

Concluding Remarks on Surrogates

- Surrogates play an important role in Phase I, II, and Pilot Phase II studies.
- Results for Phase III very mixed
- Treatments may affect more than one mechanism.
- "Surrogates" do not reliably predict treatment effect on clinical outcome.
- Success for one drug in a class does not guarantee success for the next drug in same class
- Success in one class does not guarantee the next
- Reliance on "surrogates" should be minimized.
- If necessary, recognize what is known & what is not but willing to take a risk