Statistical Considerations for Surrogate Endpoints

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Minimal Residue Disease in AML Workshop

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*The views expressed in this presentation are those of the presenters and do not necessarily represent those of the U.S. Food and Drug Administration.

Outline

- Type of Endpoints
- Use of Surrogate Endpoints
- Evaluating a potential surrogate endpoint

Acknowledgement: Thanks to Dr. Thomas Fleming for the use of some slides

Types of Endpoints

- Clinical Benefit Endpoint
  - …a direct measure of how a patient “functions, feels or survives”…Robert Temple, FDA
- Surrogate Endpoint
  - "a biomarker intended to substitute for a clinical endpoint" - NIH
- A Correlate
  - A post-baseline measurement that is prognostic of clinical outcome

Uses of Surrogate endpoints

- Analyses on surrogate endpoints can be used to
  - draw ***conclusions*** of effects on a clinical benefit endpoint
  - *reasonably likely* ***predict*** clinical benefit

Property of a Surrogate

- *Effect of the Intervention*
  on the Clinical Endpoint

  is reliably predicted by the

  Effect of the Intervention
  on the Surrogate Endpoint

Fleming and DeMets (1996)

Support for surrogates

Table 1. Support for Surrogates

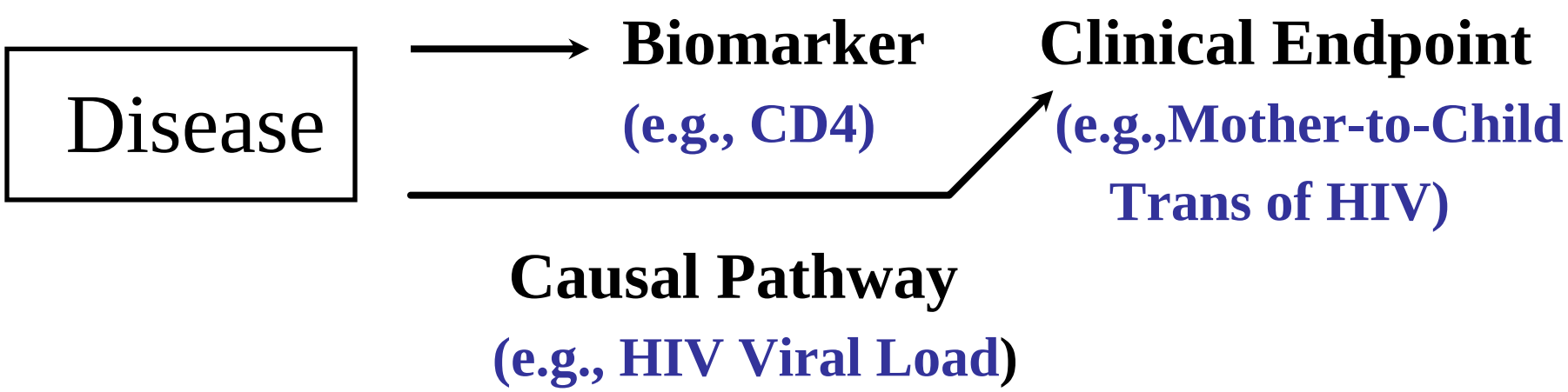
Factor	Favors Surrogate	Does Not Favor Surrogate
Biological plausibility	Epidemiologic evidence extensive and consistent Quantitative epidemiologic relationship Credible animal model shows drug response Well-understood disease pathogenesis Drug mechanism of action well understood Surrogate relatively late on biological path	Inconsistent epidemiology No quantitative epidemiologic relationship No animal model Pathogenesis not clear Novel actions not previously studied Surrogate remote from clinical outcome
Success in clinical trials	Effect on surrogate has predicted outcome with other drugs of same pharmacologic class (supports surrogate in class) Effect on surrogate has predicted outcome in several classes (supports more general use)	A negative outcome without clear explanation Inconsistent results across classes
Risk-benefit, public health considerations	Serious or life-threatening illness and no alternative therapy Large safety database Short-term use Difficulty of studying clinical end point (rare, delayed)	Nonserious disease and alternative therapy with different pharmacologic action known to affect outcome Little safety data Long-term use Easy to study clinical end point (short-term study) Long-delayed, small effect in healthy people

Temple 1999 JAMA

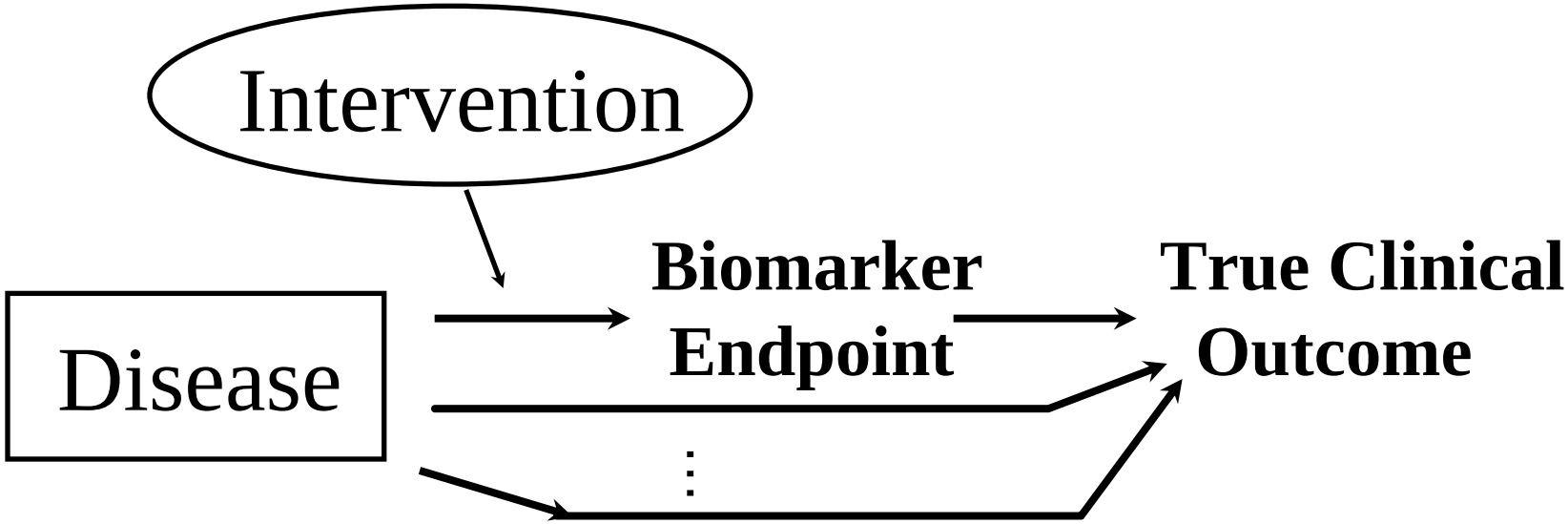
Evaluating a marker for a surrogate endpoint

- Understanding of the disease process
  - Is the marker on a pathway towards (meaningful) benefit
- Results from many randomized trials
  - Do treatment effects on the marker correspond to treatment effects on the clinical benefit endpoint

Biomarker not in Causal Pathway of Disease Process

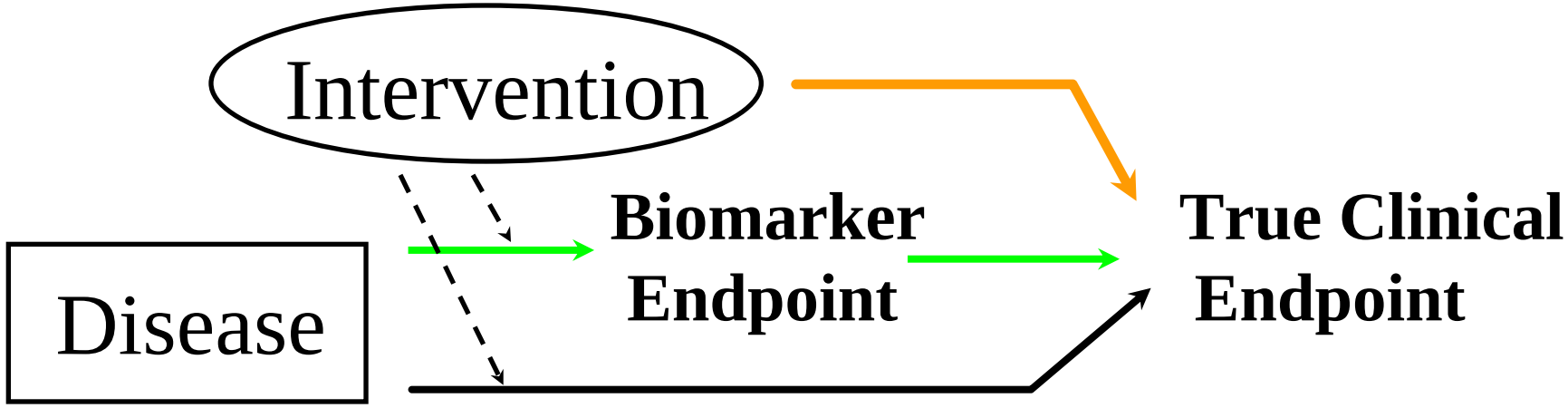


Intervention affects one of multiple pathways



Large effects on the biomarker may correspond with small effects on clinical outcome

Interventions having Mechanisms of Action Independent of the Disease Process



Off target effects have a detrimental impact on clinical outcome

Prentice's Criteria

- To be a direct substitute for a clinical benefit endpoint on inferences of superiority and inferiority
  - The surrogate endpoint must be correlated at a patient-level with the clinical outcome (independent of treatment)
  - The surrogate endpoint must fully capture the net effect of treatment on the clinical outcome
    - Model for clinical outcome: treatment parameter = 0 when adjusting by the surrogate endpoint

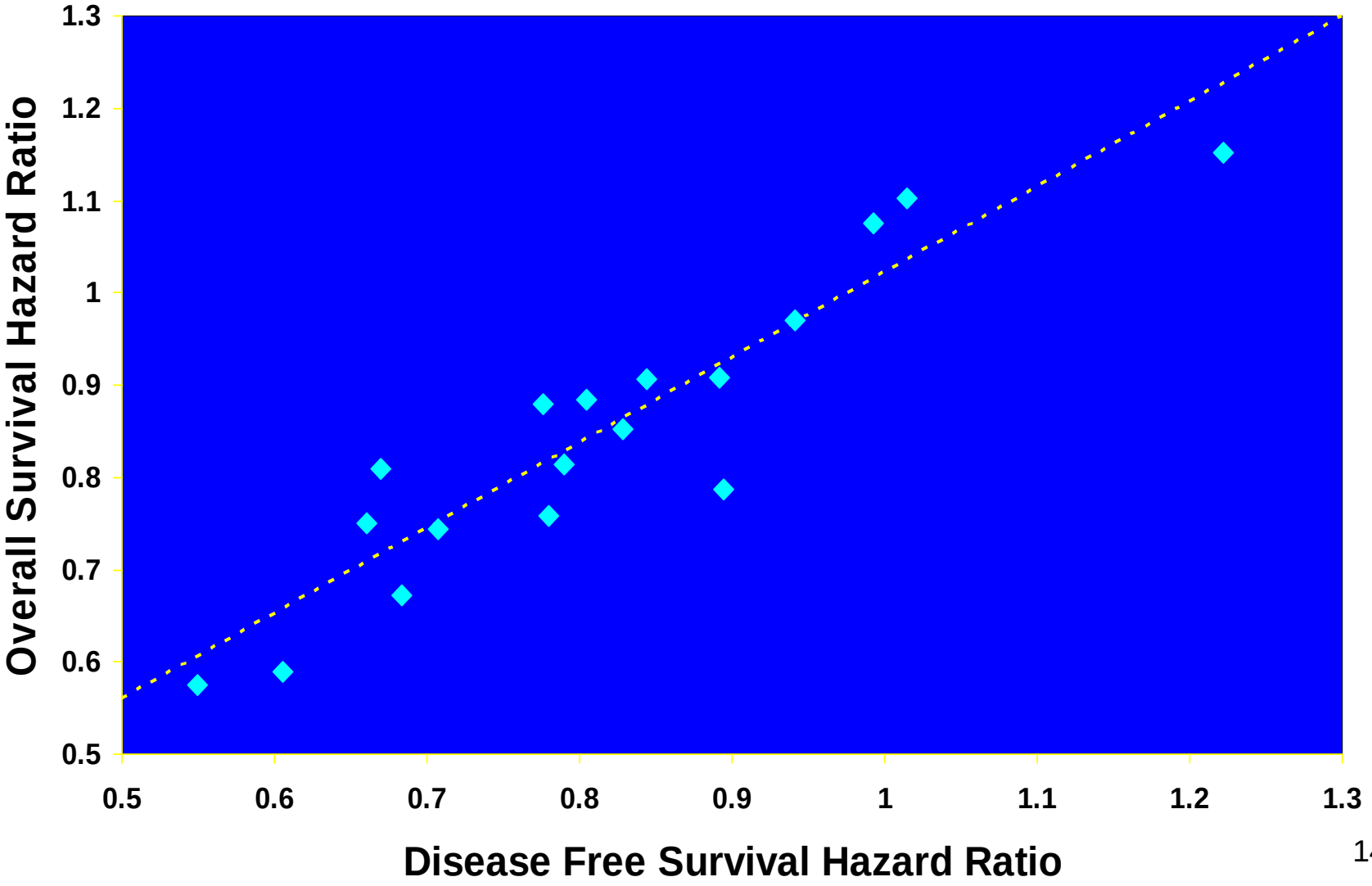
Prentice's Criteria

- Model for clinical outcome: treatment parameter = 0 when adjusting by the surrogate endpoint
  - Needs to be shown; not failing to disprove
  - Minimally need a high-level confidence that the true value of the treatment parameter is close to zero
  - Different consequences for whether the true parameter is positive or negative

Assessing the reliability of a surrogate endpoint

- Determine the pattern relating observed effects on the surrogate endpoint to observed effects on the clinical benefit endpoint
- Assess the amount of deviation from that pattern

Colorectal Adj.: Hazard Ratios for **DFS** vs. **Overall Survival**



Landmark analyses

- Potential Surrogate evaluated at a landmark
  - Chosen landmark picks up effects of therapy
- How does the use of the potential surrogate at the chosen landmark predict the final analysis of the clinical endpoint relative to other comparisons?