

# Surrogate Markers

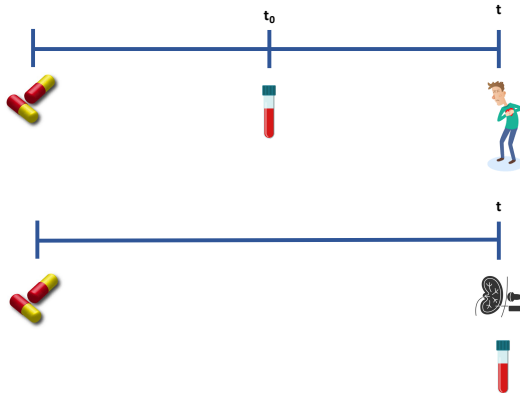
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# What is a Surrogate Marker?

⇒ **Replace** the primary outcome

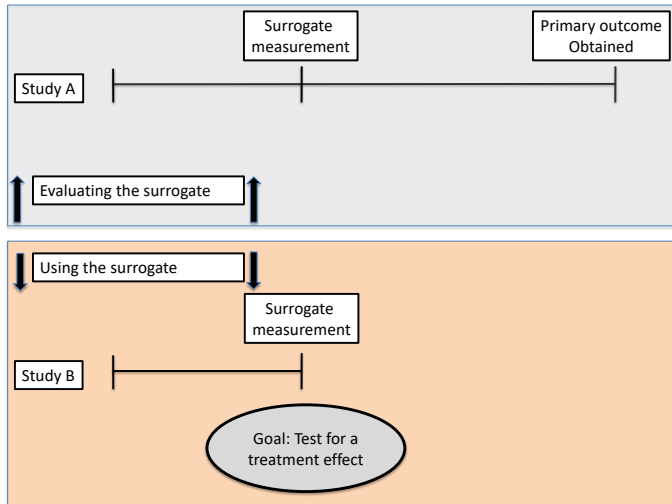


# Promise of Surrogate Markers



- A surrogate marker would potentially allow researchers to make conclusions sooner and/or less cost
- $\Rightarrow$  accelerate treatment decision-making

Goal: **evaluate** surrogate markers and **use** them to make decisions about treatments



# Not the same as:



- Gaining statistical efficiency
- Prediction
- Mediation
- Treatment effect on the surrogate marker

- U.S. Food and Drug Administration's (FDA) Accelerated Approval Program
  - Allows for drugs to be approved based on demonstrated effectiveness on a surrogate marker
  - "A surrogate endpoint is a marker[...] that is not itself a direct measurement of clinical benefit, and (A) is **known to predict clinical benefit** and could be used to support traditional approval of a drug or biological product; or (B) is **reasonably likely** to predict clinical benefit and could be used to support the accelerated approval of a drug or biological product."

# Regulatory Examples

- FDA originally approved a new drug, Jardiance, for people with Type 2 diabetes based on results showing that the drug lowered blood glucose levels, a surrogate marker
- Two years later  $\Rightarrow$  approved the drug based on subsequent results showing that the drug reduced the risk of cardiovascular death



# Regulatory Examples

## What you should know about aducanumab (brand name Aduhelm)

FDA approval of aducanumab for mild Alzheimer disease is controversial. Although the drug reduces plaque in the brain, experts are uncertain whether this is linked to improved patient symptoms and quality of life.



### The bottom line on FDA approval

In clinical trials, aducanumab reduced visible plaque in the brain, which is considered a **surrogate outcome** (a test result with no direct patient benefit).

Aducanumab did NOT have a noticeable effect on **patient outcomes** (something directly felt or experienced by the patient such as improvement in symptoms or quality of life).

From: Woloshin, S., & Kesselheim, A. S. (2022). What to know about the Alzheimer drug aducanumab (Aduhelm). *JAMA Internal Medicine*.





**Prentice criterion** for a valid surrogate marker requires that a test for treatment effect on the surrogate marker is also a valid test for treatment effect on the primary outcome of interest (Prentice, 1989)



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⇒ Lack of agreement on a single method to validate a surrogate marker

*Annual Review of Statistics and Its Application*

## Surrogate Endpoints in Clinical Trials

Michael R. Elliott<sup>1,2</sup>

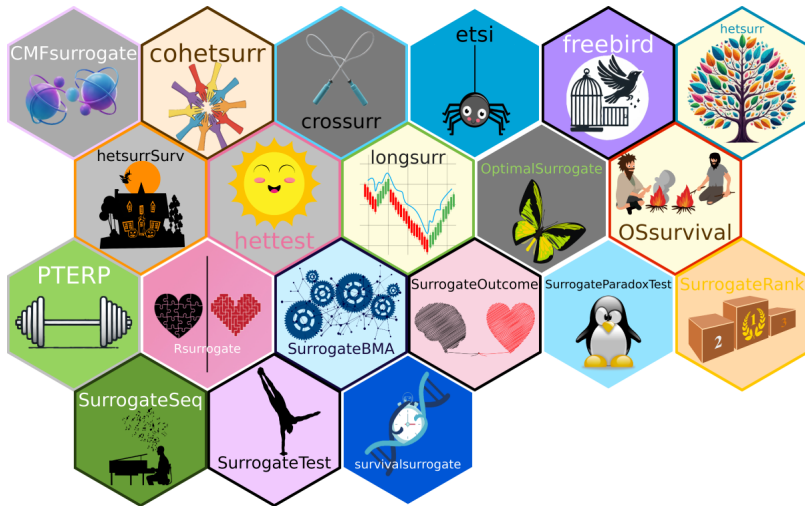
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<sup>2</sup>Survey Methodology Program, Institute for Social Research, Ann Arbor, Michigan, USA

# Surrogate markers

- Not restricted to randomized clinical trials
- Causal estimands, identifiability assumptions, confounding, heterogeneity, interference, generalizability, transportability (shifts)





Information: [www.surrogatemarkers.com](http://www.surrogatemarkers.com)



## Which one?

It can be difficult to know which package/software to use for your particular setting. We are actively working on guidance to help you understand which software is appropriate for you.

HELP ME CHOOSE A PACKAGE

Thank you!