



Appropriate validation of (predictive) biomarkers

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BEST Definition of Biomarker

A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers. *A biomarker is not an assessment of how an individual feels, functions, or survives.*

**Expand to measurement types beyond biochemical
Not specific to therapeutics development
Distinguished from *clinical outcomes***

Different biomarker types

- **Descriptive or biologic**
- **Surrogate (trial-level)**
- **Pharmacodynamic**
- **Prognostic**
- **Predictive**

Application of biomarker

- Descriptive or biologic: phase 1/2
- Surrogate: any phase
- Pharmacodynamic: preferred phase 1/2
- Prognostic: when there is a need to identify risk/benefit for triage
- Predictive: personalization of therapy

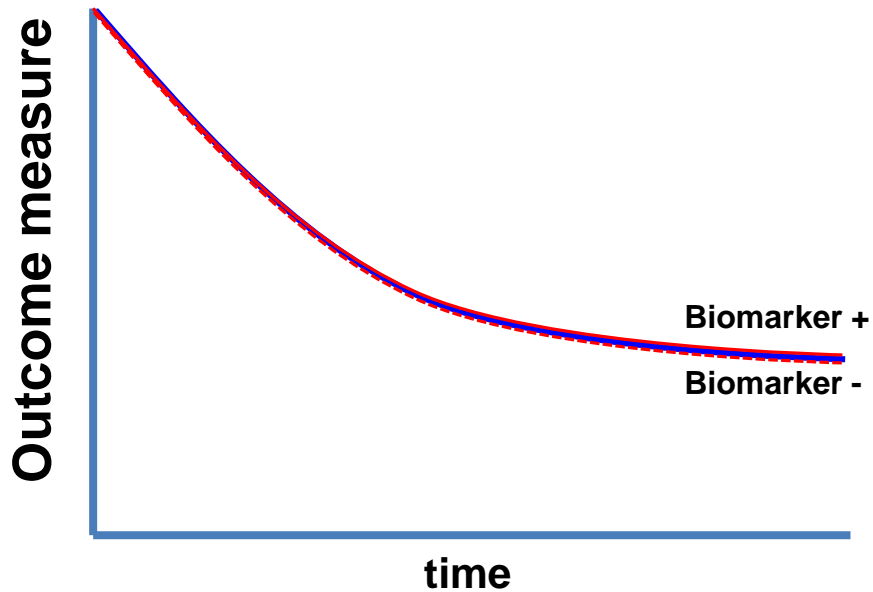
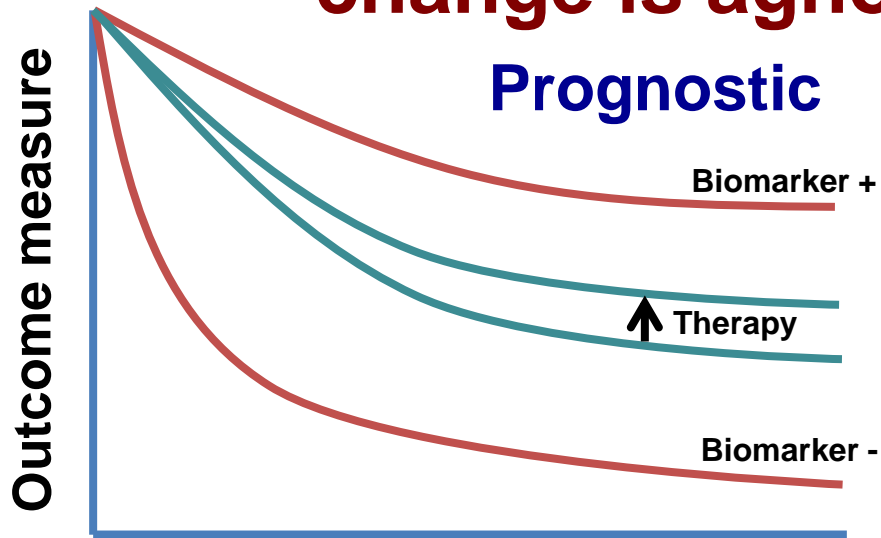
Confounders of biomarker development

- Descriptive or biologic: quality metrics of sample acquisition, processing, storage, and use
- Surrogate: quality metrics of sample acquisition, processing, storage, and use & validity of endpoint against which surrogate is compared
- Pharmacodynamic: quality metrics of sample/use
- Prognostic: quality metrics of sample/use and associated clinical data, power of observations
- Predictive: quality metrics of sample/use and associated clinical data, power of observations, & treatment/outcome interaction

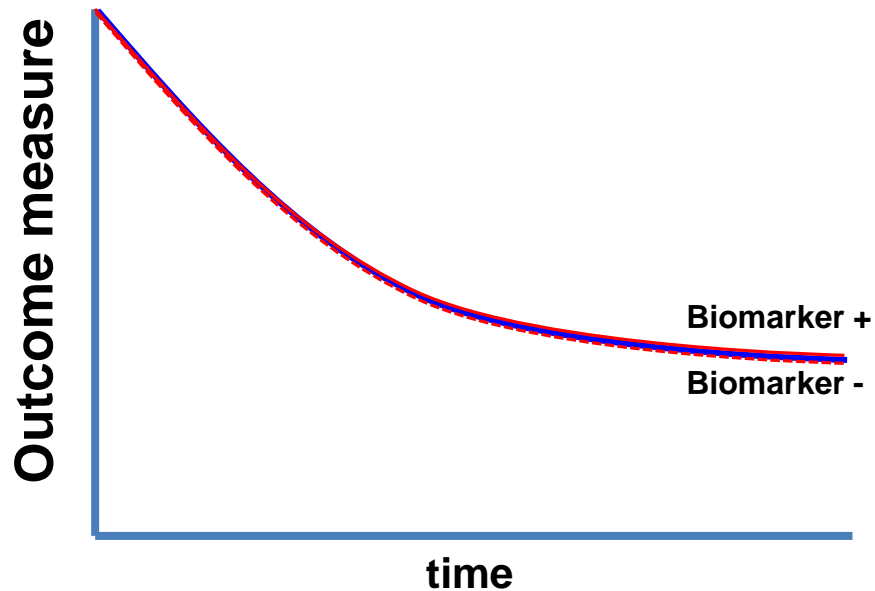
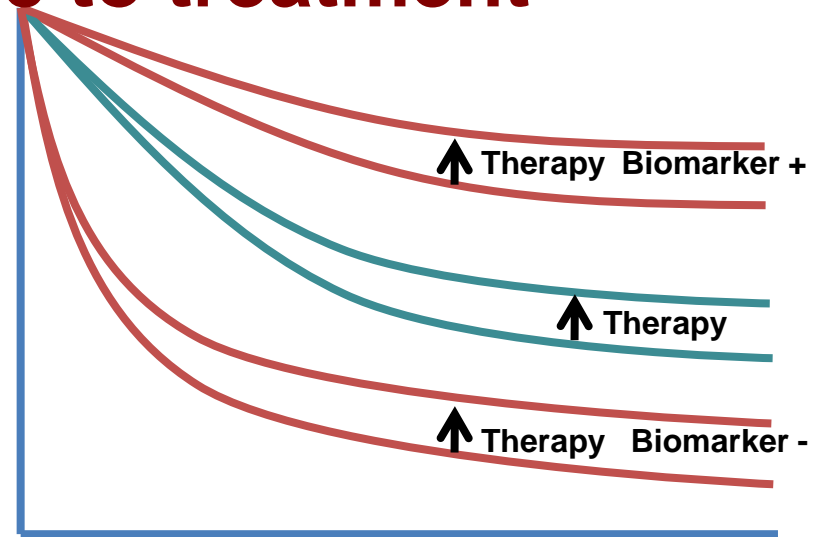
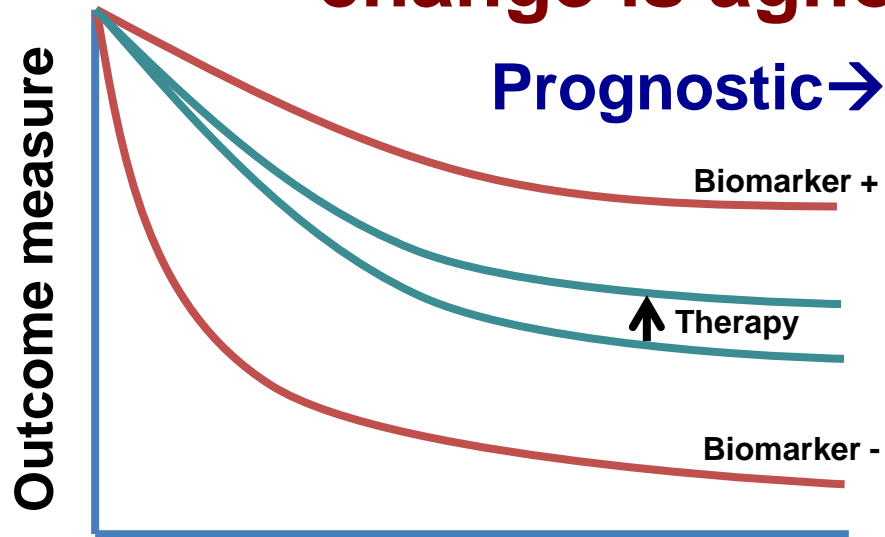
Prognostic and predictive:
the most confused of the biomarkers

Prognostic biomarkers: Outcome, biology, change is agnostic to treatment

Prognostic



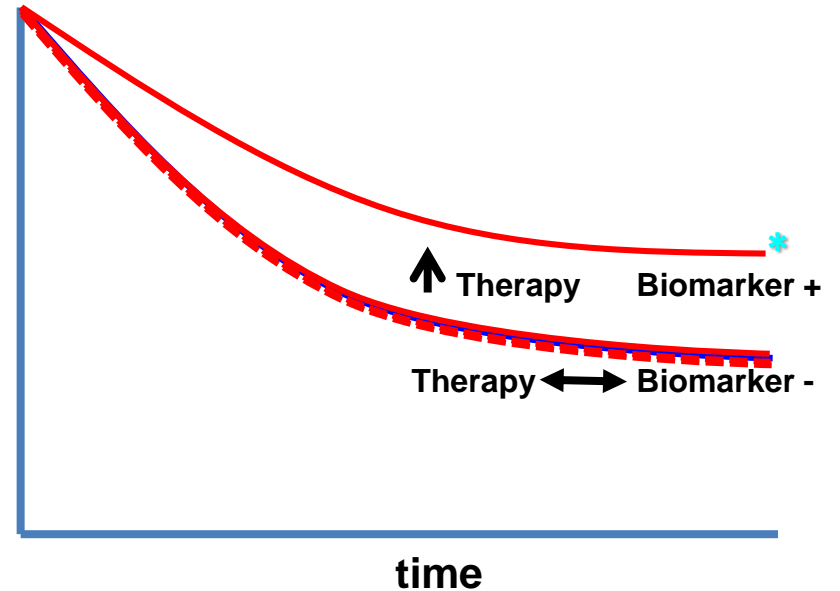
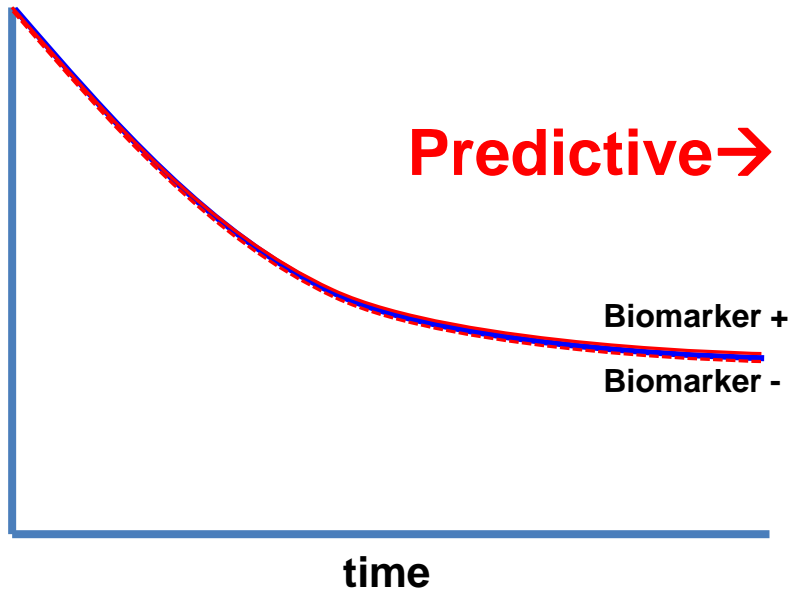
Prognostic biomarkers: Outcome, biology, change is agnostic to treatment



Predictive biomarker: Selection, Change as a function of treatment

Outcome measure

Outcome measure



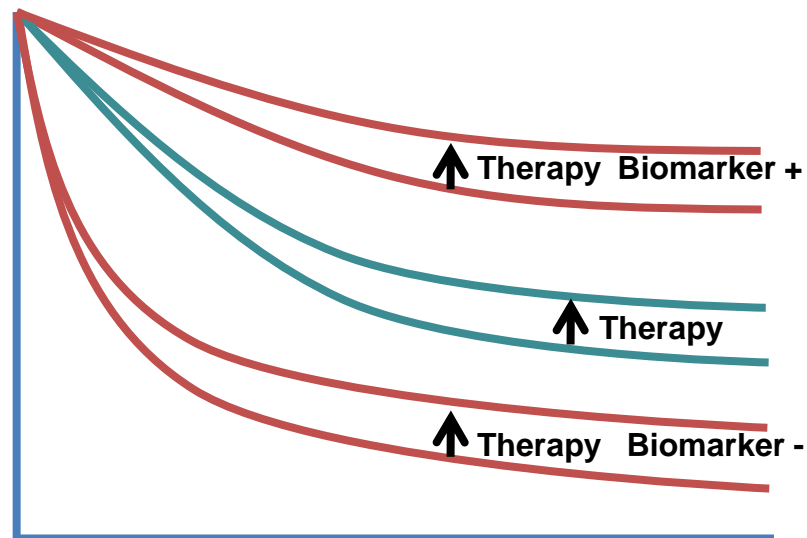
*can also negatively predict

Predictive Biomarker:

Definitions and Uses

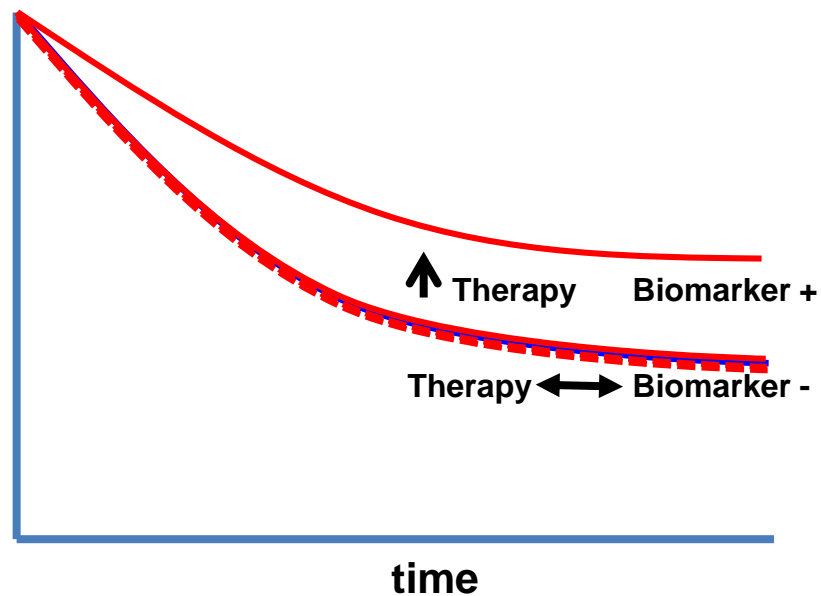
Outcome measure

Prognostic →



Outcome measure

Predictive →



Points for discussion

Variables requiring optimization/validation

Steps for validation

Statistical concerns

Use validated biomarkers in trial design

How

When

