Biomarkers in Drug Development

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BEST Resource: Biomarkers, EndpointS, and Other Tools

- A glossary of terminology and uses of biomarkers and endpoints in basic biomedical research, medical product development, and clinical care
- Created by the NIH-FDA Biomarker Working Group
- Publicly available at http://www.ncbi.nlm.nih.gov/books/NBK326791/
- BEST harmonizes terms and definitions and addresses nuances of usage and interpretation among various stakeholders, including:

  - Biomedical scientists
  - Translational and clinical researchers
  - Medical product developers
  - Patient/disease advocacy groups
  - Government officials
  - Clinicians

What is a Biomarker?

BEST (Biomarkers EndpointS and other Tools) Definition

- 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.
- Types: Molecular, histologic, radiographic, or physiologic
- Biomarkers may measure disease presence or status, or measure aspects of response to treatment
- A biomarker is not an assessment of how a patient feels, functions, or survives.

https://www.ncbi.nlm.nih.gov/books/NBK326791/

Types of Biomarkers

- Diagnostic
- Monitoring
- Response/Pharmacodynamic
- Predictive
- Prognostic
- Safety
- Susceptibility/risk

Biomarker Examples*

Susceptibility

Will I develop the disease?

ApoE4→Alzheimer's disease

Safety

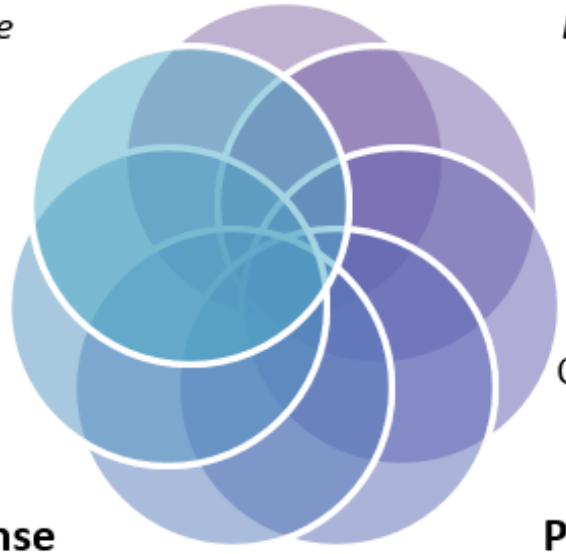
Am I having an adverse event?

ALT→Hepatotoxicity

Diagnosis

Do I have the disease?

SMN1 gene→spinal muscular atrophy



Monitoring

Status of disease or drug exposure?

MRI→MS

Prognosis

Will I live longer?

CAG length→Huntington's disease

PD/Response

Did treatment work?

Serum TTR→hATTR amyloidosis

Prediction

Response to treatment (good or bad)?

HLA-B*1502→risk of SJS with CBZ

* Defined by BEST; other types exist; functions are not mutually exclusive

Biomarkers Throughout Development

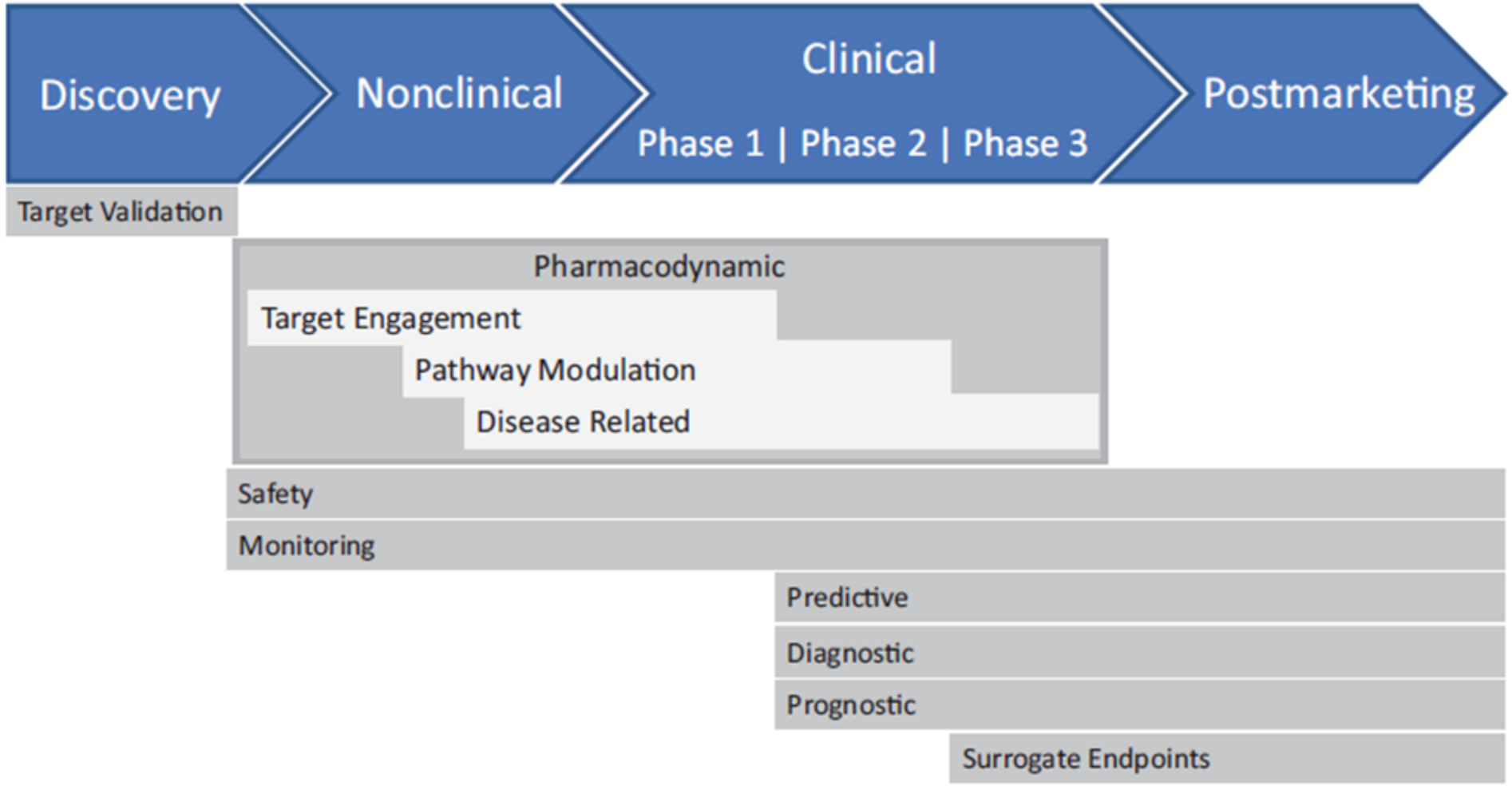


Figure: Atkinson's Principles of Clinical Pharmacology

Uses of Biomarkers in Drug Development

- Proof-of-concept
- Diagnostic
- Enrichment (predictive/prognostic)
- Monitoring
- Efficacy
  - Primary endpoint (surrogate endpoint)
  - Secondary or exploratory endpoints (supportive)

Surrogate Endpoints

- Surrogate endpoint - An endpoint that is used in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives.
  - ***Validated surrogate endpoint -*** An endpoint supported by a clear mechanistic rationale and clinical data providing strong evidence that an effect on the surrogate endpoint predicts a clinical benefit. Therefore, it can be used to support traditional approval without the need for additional efficacy information.
  - ***Reasonably likely surrogate endpoint -*** An endpoint supported by clear mechanistic and/or epidemiologic rationale but insufficient clinical data to show that it is a validated surrogate endpoint. Such endpoints can be used for accelerated approval for drugs or expedited access for medical devices.

Source: BEST

Biomarkers used for accelerated approval

- Use of reasonably likely surrogate endpoints for accelerated approval
- Primarily used when it would require a prolonged period to assess clinical benefit
- Recent examples:
  - NfL used as reasonably likely surrogate for accelerated approval of tofersen for SOD1-ALS
  - Reduction in amyloid beta plaque for accelerated approval of lecanemab for Alzheimer's disease

Regulatory Considerations

- Do biomarkers need to be “Qualified” to be used in a drug development program? **NO!!!!**
- The specific context of use drives the extent of evidence needed
- The most common pathway to integrate biomarkers into drug development is using them within the context of a specific drug development program
- FDA does offer a Biomarker Qualification Program (BQP) that may be considered in some circumstances, but it is not required for the use of biomarkers in drug development
  - Qualified drug development tools (e.g., biomarkers, COAs) have been demonstrated to reliably support a specified manner of interpretation (context of use) and application in drug development; typically for use in multiple drug development programs without additional FDA review.

Evidence to Support the Biomarker

- Regardless of the pathway chosen for review of the biomarker, good scientific evidence is needed
  - Biological rationale for use of the biomarker (if known)
  - Assay considerations (analytical validation and understanding of potential sources of variability in the measurement)
  - Characterization of the relationship between the biomarker, the outcome of interest, and the treatment (where applicable) required for the proposed context of use (clinical validation and understanding the potential sources of bias)
  - Type of data available to assess the strength of association of the biomarker with its proposed outcome: retrospective or prospective, registry data, and/or randomized controlled trial (RCT) data