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Introduction to clinical biomarker development

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Rachael Hawtin

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What is a biomarker?

A characteristic (e.g., molecule) that is objectively measured to evaluate:

- Healthy biologic processes – establish a healthy baseline
- Pathologic processes – distinguishes disease from healthy
- Biologic responses to a therapeutic intervention – for example, a characteristic that moves towards healthy under therapeutic pressure

Biomarkers may also serve as an alternative to a clinical endpoint – these are called surrogate biomarkers

Based on FDA definition

Importance of biomarkers in rare diseases

*"In rare diseases, often the **population size and heterogeneity**, the **nature of the disease** and the **limited historical clinical data** can make traditional studies with **clinical endpoints** difficult or impossible to conduct."* *Kakkis et al., Orphanet journal of rare diseases (2015)10:16*

- The nature of rare diseases frequently includes:
  - **Pediatric indications**, in which clinical measures may be more subjective / challenging to capture and some (e.g., MRI, certain wearables, PROs) may not be practical
  - **Long, slow & progressive periods with no clinically evident changes** (e.g., neurodevelopmental disorders (NDD), bone developmental, musculo-skeletal disorders), leading to long clinical studies
  - Leveraging **novel drug mechanisms**, with variable degrees of biological validation
- Relying solely on clinical endpoints of how a patient "feels, functions or survives" can be impractical in these cases

Biomarkers address these challenges, providing **critical insight into the effects of a drug on the underlying disease mechanism**, and **connecting this with the therapeutic response in the individual patient**

Proof of therapeutic mechanism & clinical concept

Biomarkers provide **critical insight into the effects of a drug on the underlying disease mechanism**, and **connect this with the therapeutic response in the individual patient**

- **Proof of mechanism**: The drug is hitting the target with the "expected" effect on the biology / marker
- **Proof of concept**: The mechanism of action of the drug is associated with clinical activity

RARE DISEASE CHALLENGE	BIOMARKER DELIVERABLES
Patient heterogeneity	• Address **unifying underlying pathobiology** on backdrop of **diverse clinical presentation** • **Clarify pathobiology** & association to clinical presentation & response
Pediatric populations: limitations of standard tools (PROs, wearables) Slow, progressive diseases: Long trials to demonstrate clinical outcomes	• **Objective measures** of drug action • Target engagement, PD, **PoM** • **Early evidence** of potential for disease modification • Surrogate endpoints (at a minimum inform **decision-making**
Novel drug mechanisms	• **Accelerated** test of therapeutic hypothesis & **PoC**

Context of use (COU)defines biomarker strategy

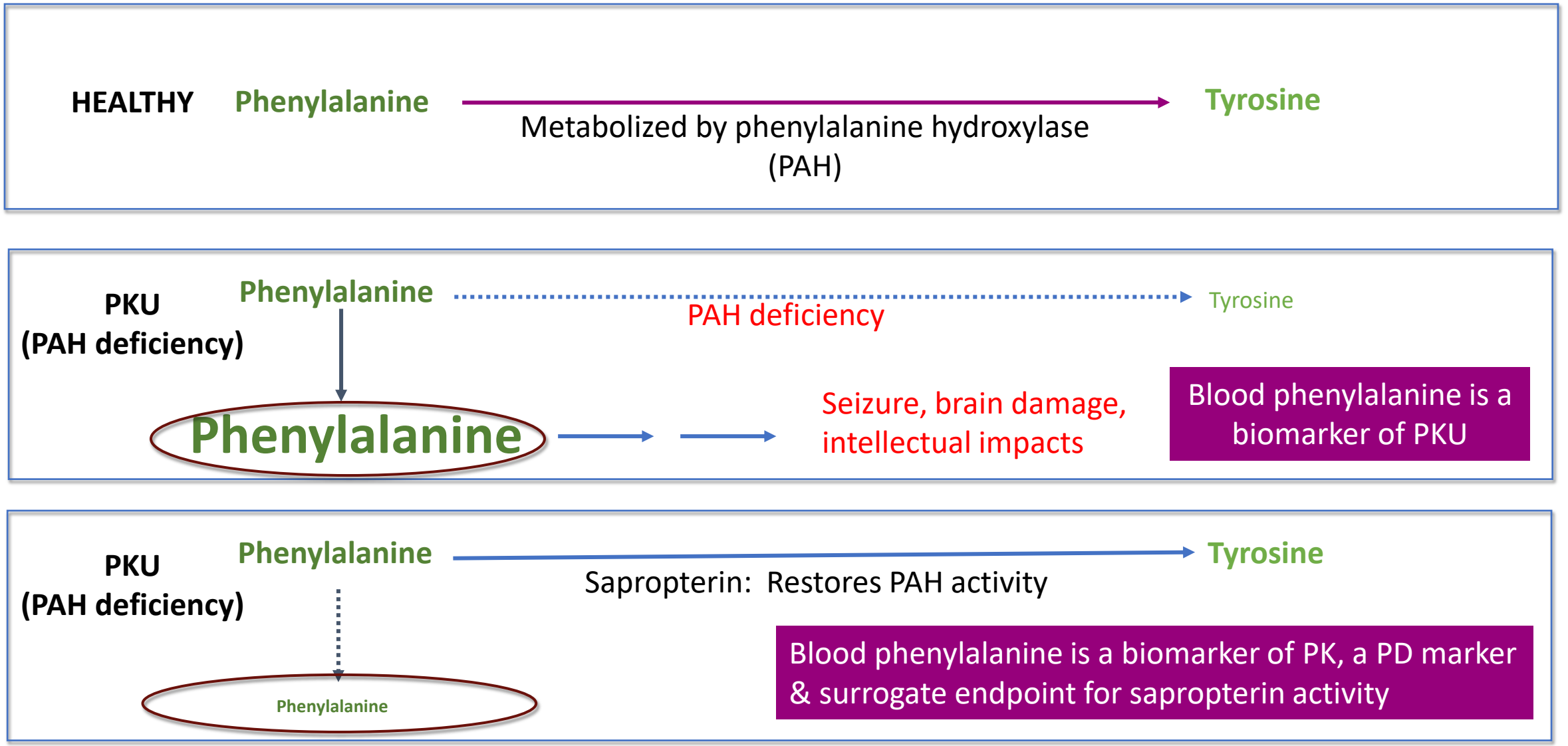
COU encompasses the biomarker category (e.g., pharmacodynamic) and the intended use in a drug development program

Examples of particular use in rare diseases are:

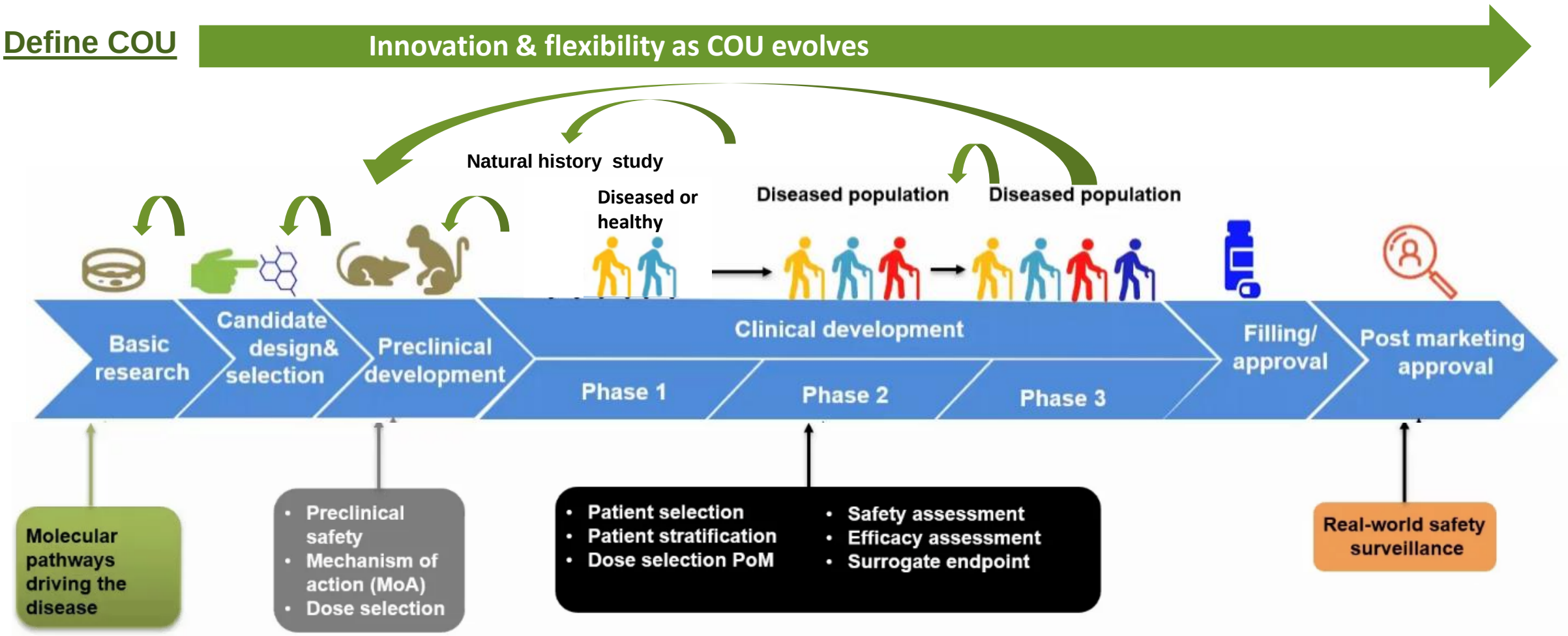
- Inclusion / exclusion criteria for clinical studies
- Support for dose selection in clinical study
- Proof of mechanism - PD response
- Surrogate endpoint
- Stop study treatment due to safety concern

The **same biomarker** may be developed to address **several COU**
(E.g., A PD biomarker may also serve as a surrogate endpoint if the data support this and regulatory requirements can be met)

Example: Phenylalanine biomarker for phenylketonuria (PKU)



Biomarkers are an integral component of drug development



Identify clinical questions & define strategy

Establish feasibility

Preclinical proof of mechanism

Identify clinical sample sources

Clinical proof of concept

Modified from https://www.fda.gov/media

From: AAPS Biomarkers e-course 2022, Module 1

Biomarker needs vary with programs, criteria are constant

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Biomarker Criteria

Kakkis et al., 2016, Nature Biotechnology

1. Biomarker has **direct relationship to important disease process**
2. Changes are specific to changes in the clinical disease biology
3. Stable over time
4. Can be reliably measured with adequate sensitivity & specificity
5. Sampling compartment (e.g., urine) predicts disease compartment/tissue (e.g., difficult to sample organ such as liver)
6. Clinical intermediate endpoints (clinical physiological measures) are relevant to major clinical problem

Biomarkers include a wide range biochemical moieties in a diversity of tissues, and physical measurements

Feasibility, clinical relevance and clinical utility are critical criteria for biomarker development

Early sourcing & careful use of clinical samples is critical

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Sample sourcing through collaboration with patient advocacy groups, consortia and pre-competitive alliances is extremely valuable

ASSAY FEASIBILITY	DISEASE ASSOCIATION	CLINICAL UTILITY	INTERROGATE BIOMARKER IN INTERVENTIONAL STUDY
Research	Pre-IND	Stage 0 / 1	
Interrogate candidate biomarkers identified in preclinical studies-> select those that can be reliably measured	**Identify & select disease-associated biomarker(s) addressing program needs**	**Is biomarker stable in absence of treatment?**	Does biomarker reliably address program needs under therapeutic pressure?
Healthy donor samples	**Disease vs <u>age-matched</u> controls** Single time point Basic clinical annotations	**Does it associate with clinical measurements?** **Longitudinal patient sampling** Clinical annotations critical	Ph1 / 2 test & select -> Ph 3

- Assess feasibility of establishing blood-based biomarkers where possible due to ease of sample access

- Non analyte biomarkers, e.g., Physical scans, wearable-captured data -> engagement with clinicians to establish feasibility & options

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 a: 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

Key elements of biomarker strategies

- Biomarkers are used to establish that a given therapeutic is hitting the target and having the proposed effect on the underlying mechanism of disease pathobiology.
- Biomarkers can transform & accelerate the development of novel, safe therapeutics in rare diseases
- Defining the clinical questions early in the program, & focus on context of use are critical to success
- Essential biomarker criteria address feasibility, clinical relevance and clinical utility
- Biomarker & sample acquisition strategies should be initiated as early as possible
- Biomarker development & qualification is highly cross-functional; collaborative teamwork is critical
- Working together across public-private partnerships and in pre-competitive analyses can significantly accelerate biomarker development in rare diseases

Thank You!

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“Biomarkers” are developed for different applications

Defining the **clinical questions** to meet program needs is critical for framing biomarker strategy

BEST (Biomarkers, EndpointS, and other Tools)
Classification: Range of Biomarker Types

FDA

- **Susceptibility / risk biomarker** (e.g., genetic mutation(s))
- **Diagnostic biomarker** -> confirms presence of disease or condition of interest
- **Prognostic biomarker** -> informs on disease status and progression
- **Monitoring biomarker** -> serial measurement of disease across time

Measures of disease presence & status

- **Predictive biomarker** -> predicts whether a subject will respond to therapy
- **Pharmacodynamic (PD) / Response biomarker, including surrogate endpoints**
  - Proof of mechanism, the biomarker shifts under therapeutic pressure
  - In some cases may be developed to identify clinical benefit before traditional clinical measures
  - Example: Phenylalanine in phenylketonuria
- **Safety biomarker-**> measure of likelihood or presence of a toxic effect

Measure aspects of response to treatment

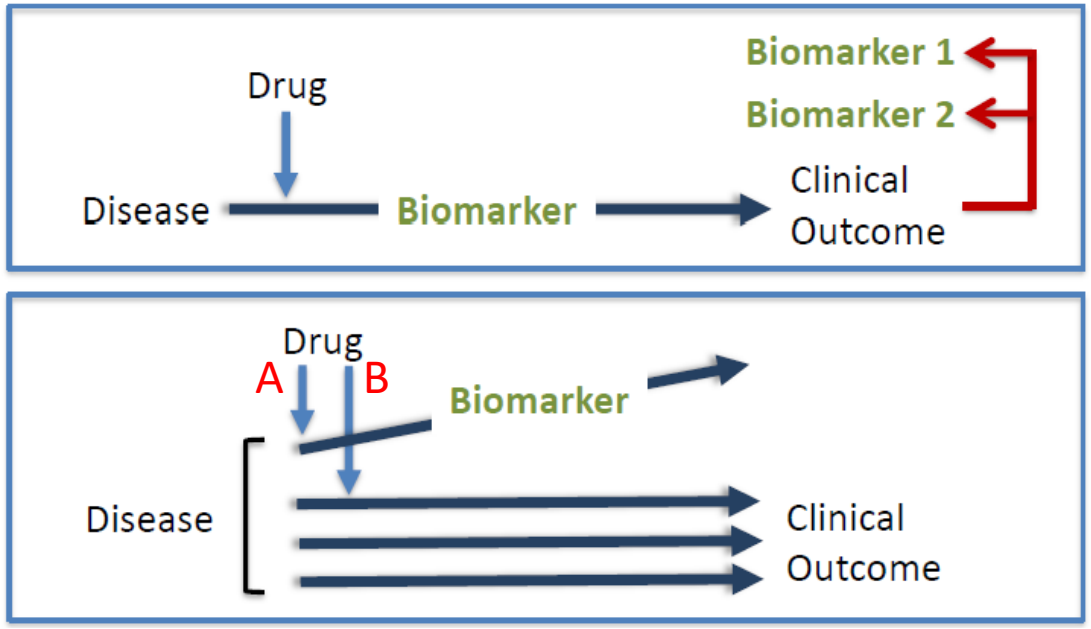
Importance of biomarker association to disease process

The limitations of surrogate endpoints: complex relationships between *disease – biomarker – and clinical outcome*

- Surrogate on **causal pathway** modulated by drug
- Biomarkers may reflect changes induced by **outcome** of disease

A Surrogate ***not* on pathway** of drug MOA so may only indirectly correlate with outcome

B **Multiple disease MOAs** may lead to clinical outcome – and drug may impact only one



Association with the disease biology is critical
(E.g., A urine-based biomarker in a liver metabolic disease must be associated with the disease biology and reflect the liver status +/- therapeutic)