Rare Bootcamp™

Introduction to clinical biomarker strategy

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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

Biomarkers include a wide range of biochemical moieties in a diversity of tissues (matrices), and also include physical measurements

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 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 (PoM)**: The drug is hitting the target with the "expected" effect on the biology / marker
- **Proof of concept (PoC)**: 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**

Biomarker needs vary with programs, criteria are constant

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

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

Context of use (COU) defines biomarker strategy

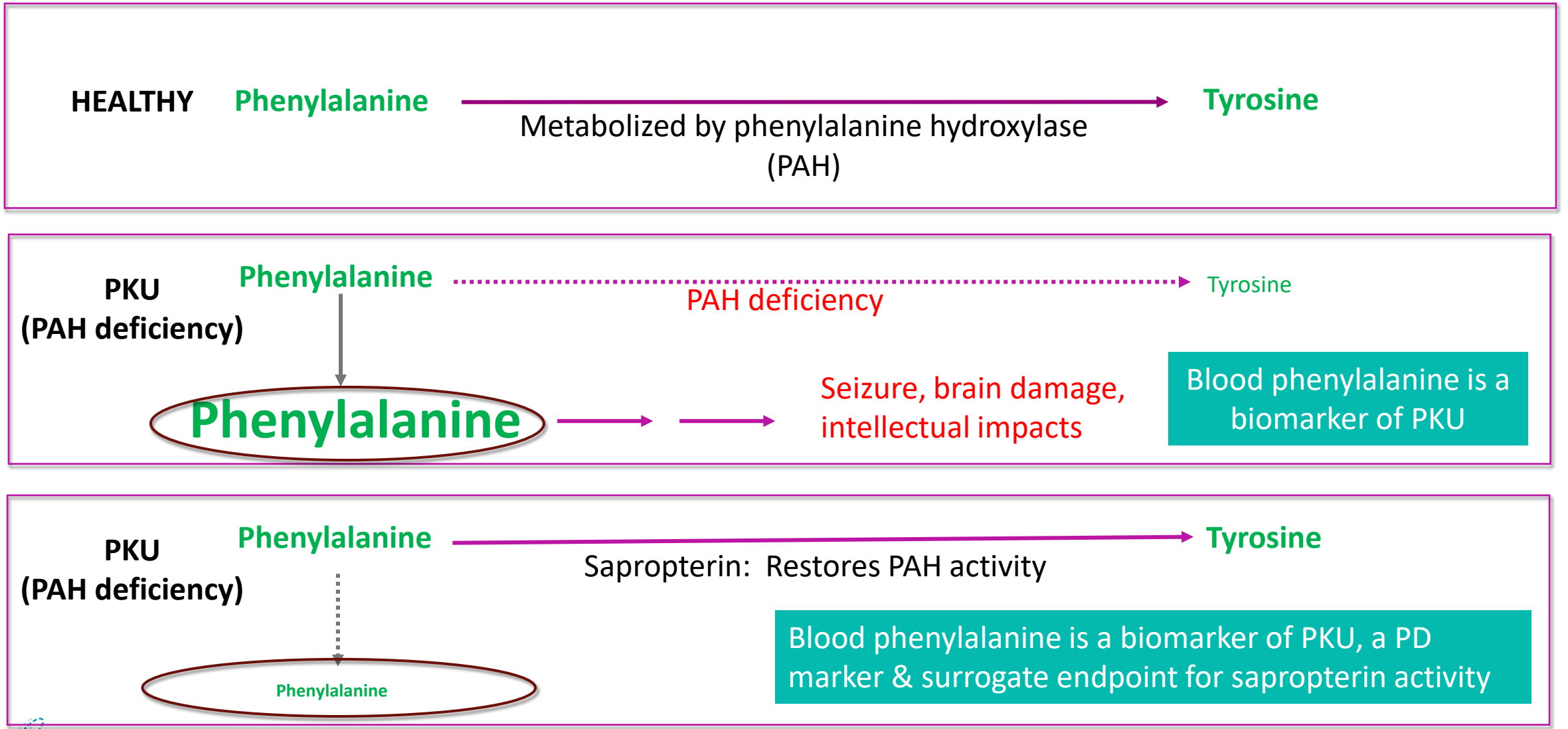
COU encompasses the biomarker category (e.g., pharmacodynamic) and the intended use in a drug development program

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)

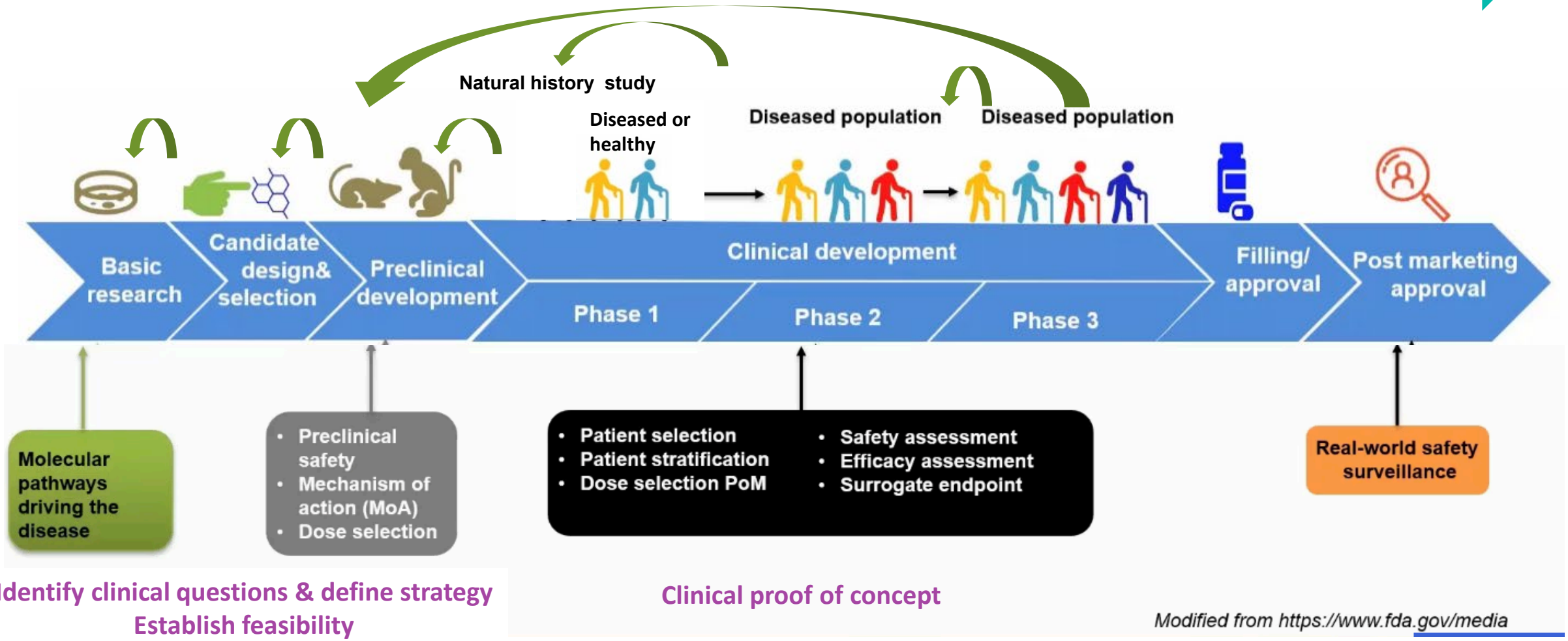
Example: Phenylalanine biomarker for phenylketonuria (PKU)



Biomarkers are an integral component of drug development

Define COU

COU evolves with understanding of biomarker, pathobiology & therapeutic



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

Early sourcing & careful use of clinical samples is critical

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

BIOLOGICAL & ASSAY FEASIBILITY	DISEASE ASSOCIATION	CLINICAL UTILITY	CLINICAL VALIDATION
Nonclinical & healthy donor samples	Single point untreated patient samples vs matched controls	Longitudinal untreated patient samples with clinical annotations	Early phase clinical study samples, baseline vs on-treatment Select biomarker(s) for pivotal study

Establish biomarker association with disease pathobiology & response under therapeutic pressure

Assay development & triage to encompass biomarker strategy in clinical study(ies)

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 can connect a therapeutic target with the underlying disease mechanism and clinical measurements of response
- Biomarkers can 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

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Thank You

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