The Role of Biomarkers in Drug Development: A Regulatory Perspective

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Outline

- Regulatory Framework for Drug Approval
- Role of Biomarkers in Drug Development
- Definitions and terminology
- Multimodal vs Unimodal Biomarkers
- Conclusions

Regulatory Framework for Drug Approval

Under the FD&C Act, for a new drug to be approved for marketing in the United States, FDA must determine that the drug is safe and effective for use under the conditions prescribed, recommended, or suggested in the product's labeling (21 U.S.C. 355(d))

FDA Draft Guidance* – Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products

- Efficacy can be:
  - a measure of how a patient functions, feels, or survives (clinical benefit)
  - a validated surrogate endpoint shown to predict a specific clinical benefit

  Traditional Approval
  - surrogate endpoint or intermediate clinical endpoint that is reasonably likely to predict a clinical benefit

  Accelerated Approval

*https://www.fda.gov/media/133660/download

What is a biomarker?

- **A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathologic processes, or biological responses to a therapeutic intervention, and includes a surrogate endpoint**
- **It can include a molecular, histologic, radiographic, or physiologic characteristic**
- **A biomarker is not an assessment of how an individual feels, functions, or survives (i.e., it is not a clinical benefit)**

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

BEST (Biomarkers, EndpointS, and other Tools)
Categories of biomarkers based on role:

- **Susceptibility / risk biomarker**
- **Diagnostic biomarker**
- **Prognostic biomarker**
- **Monitoring biomarker**
- **Predictive biomarker**
- **Pharmacodynamic/Response biomarker – including surrogate endpoints**
- **Safety biomarker**

Measures of disease presence and status (i.e., disease-focused biomarkers)

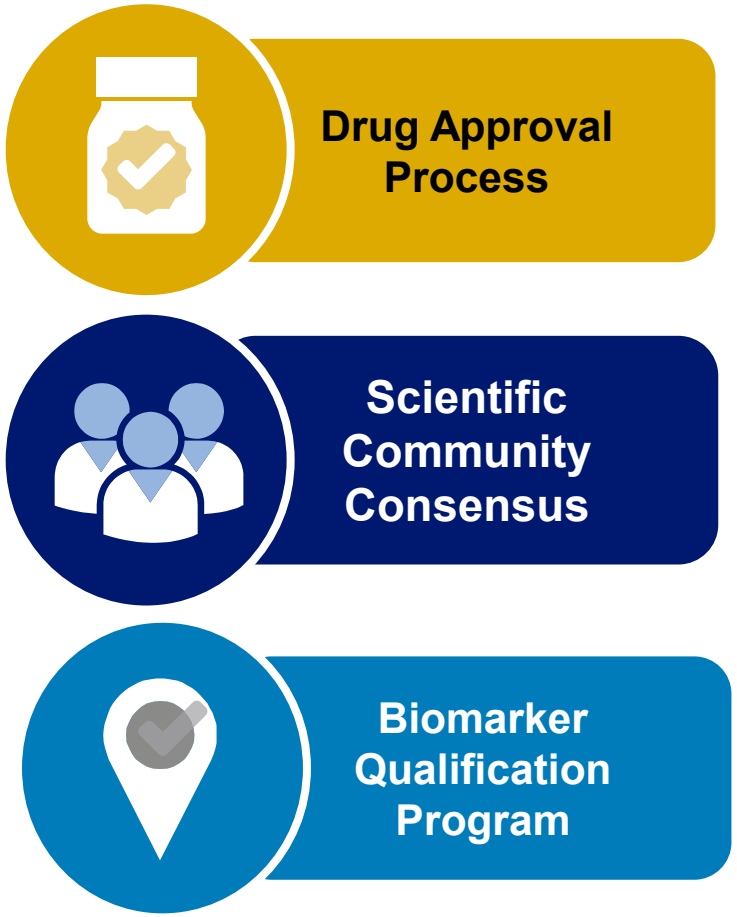
Measure aspects of response to treatment (i.e., treatment-related biomarkers)

Applicable to Unimodal or Multimodal Biomarker

Context of Use

- **The COU is a concise description of the biomarker's specified use in drug development and is generally written to include two components:**
  1. **The BEST biomarker category**
  2. **The biomarker's intended use in drug development**
- **Example:**
  - ***XX is a prognostic biomarker to enrich the likelihood of hospitalizations during the timeframe of a clinical trial in Phase 3 asthma clinical trials***

BIOMARKER INTEGRATION INTO DRUG DEVELOPMENT



Note: These pathways do not exist in isolation and many times parallel efforts are underway within or between pathways. All share common core concepts, are data-driven, and involve regulatory assessment and outcomes based on the available data.

Facilitating Biomarker Development: Strategies for Scientific Communication, Pathway Prioritization, Data-Sharing, and Stakeholder Collaboration; Published June 2016, Duke-Margolis Center for Health Policy

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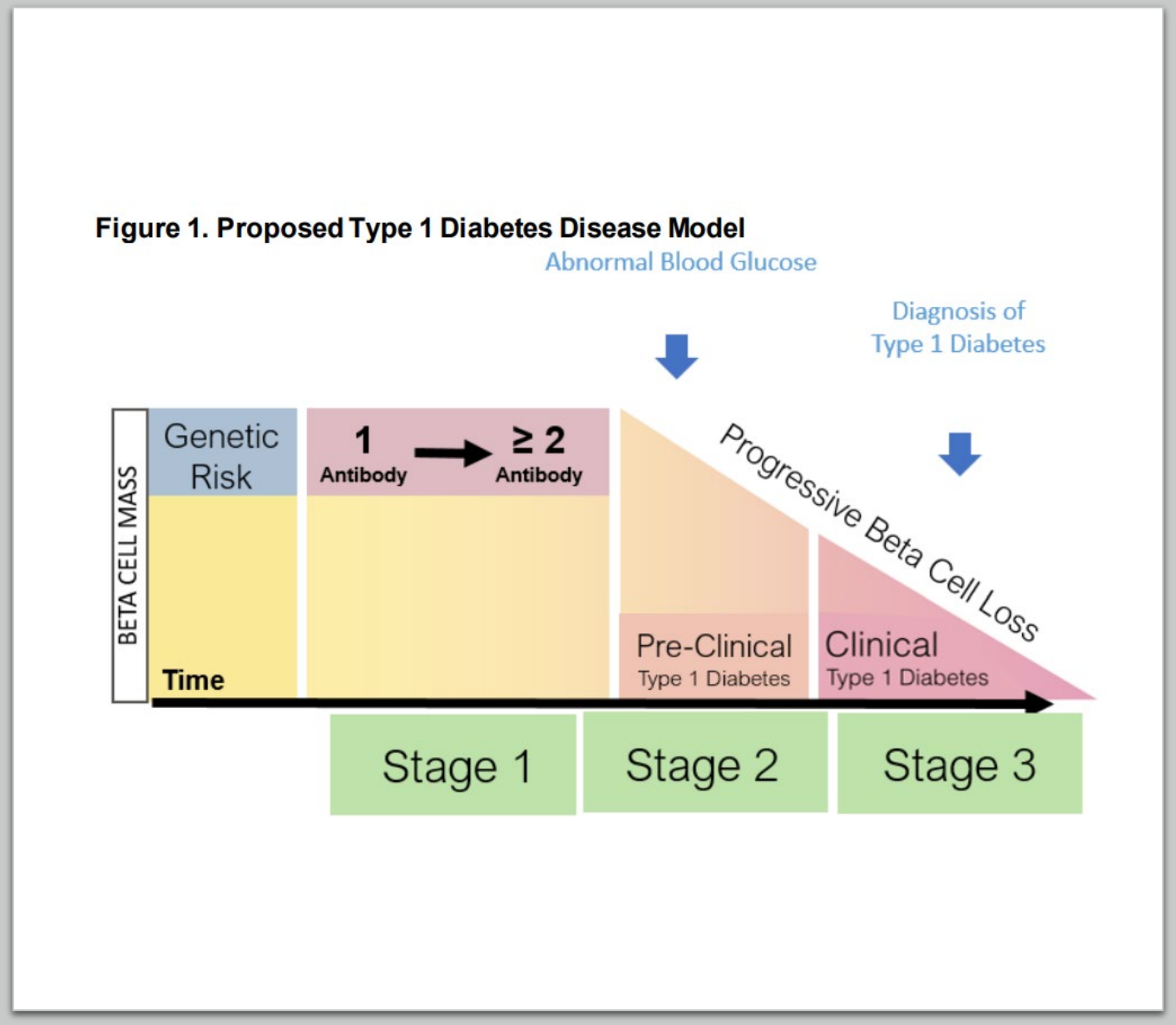
Why Multimodal vs Unimodal Biomarkers

- **Majority of diseases are complex, caused by a combination of genetic, environmental, lifestyle factors, etc. (example: cardiovascular disease)**
- **Many diseases present on a continuum – progressing from pre-clinical or asymptomatic stage to full-blown clinical manifestation (example: Type 1 diabetes)**
- **Disease with a known defect but multiple organs are affected (example: Fabry Disease)**

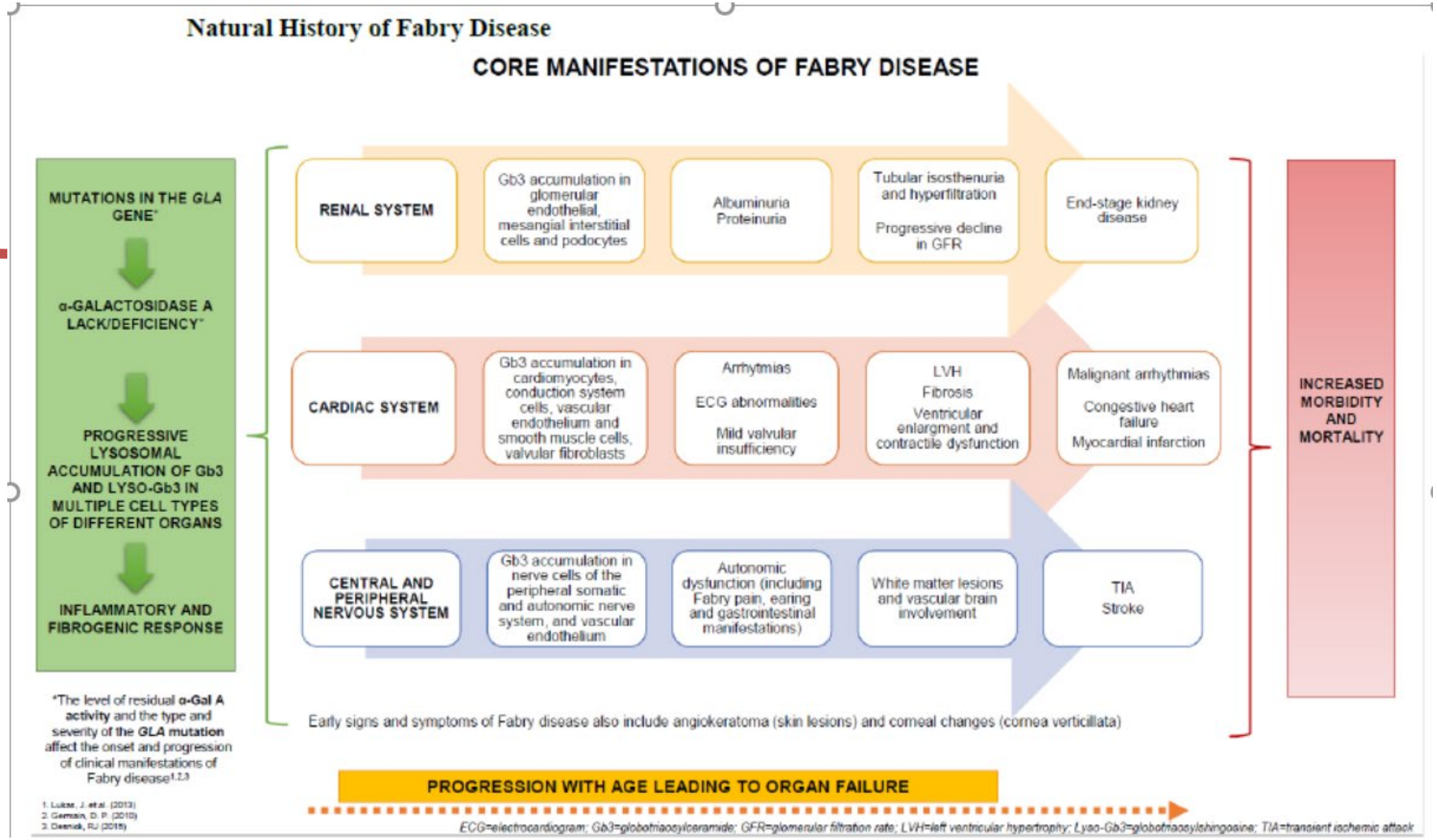
Stages of Type 1 Diabetes

Many diseases present on a continuum – progressing from pre-clinical or asymptomatic stage to full-blown clinical manifestation



Fabry Disease

Mutation of GLA gene encoding alpha galactosidase A affecting multiple organs with clinical variable presentation



WORKSHOP

FDA Public Meeting: Identification of Concepts and Terminology for Multi-Component Biomarkers

MARCH 23 - 24, 2022

A proposed definition…

… a defined characteristic or characteristics that includes features based on two or more measurements evaluated through an algorithm as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions and environmental exposures.

Multimodal Biomarkers – not a novel concept

- Applied in clinical decision making
- Applied in clinical research/medical product development
- Applied in regulatory decision-making
- Regardless of application, critical points for consideration:
  - Analytical validation: establishing that the performance characteristics (e.g., sensitivity, specificity, accuracy, and precision) of a test, tool, or instrument are acceptable
  - Clinical validation: establishing that the test, tool, or instrument acceptably identifies, measures, or predicts the concept of interest
  - Clinical utility: use of the medical product will provide useful information on the diagnosis, treatment or prevention of the disease of interest
  - Qualification: a determination made after FDA review that a test, tool, or instrument and its proposed context of use can be relied upon to have a specific interpretation and application in drug development and regulatory review

Challenges to Consider with Multimodal Biomarkers

Analytical validation – may be more difficult with many measures and different modalities/platform of measurement

Clinical validation – multidirectional change or variable degrees of change across different biomarkers may present challenges to a defined context of use

Qualification – amount of data necessary to qualify multimodal biomarkers more extensive than amount of data necessary to qualify unimodal biomarkers

Clinical Utility – risks, expense, availability of test/measure/instrument, expertise

Biomarker ⟹ Surrogate Endpoint

- Not a direct measure of how a patient ***feels, functions*** *or* ***survives***
- Intended to reflect and predict clinical benefit not measure the outcome
  - Challenges of translating from **indirect measure** to **extent of clinical benefit**
  - Often more limited trial safety exposure with surrogate endpoint – so less precision on "risk"
- And biomarkers may *fail* to predict clinical benefit – *residual risk that strength (or presence) of relationship to clinical endpoint is not valid*
  - Many examples of "sure thing" biomarkers that failed – e.g., HDL-c and failed CVOTs across multiple programs for HDL-raising drugs

Opportunities exist…(avoid one size fits all)

Biomarker Category

- Susceptibility / risk biomarker
- Diagnostic biomarker
- Prognostic biomarker
- Monitoring biomarker
- Predictive biomarker
- Pharmacodynamic/Response biomarker – including surrogate endpoints
- Safety biomarker

Role in Drug Development

Defining the condition/disease
Staging the disease
Predicting course of disease
Modifying course of disease
Identifying targets for intervention
Selecting patients for clinical trials
Dose selection
Monitoring intervention
Measuring outcome of intervention on disease
Assessing risks of intervention….

Closing Remarks

- **Encouraging the identification and use of reliable biomarkers can significantly facilitate development of new, safe, and effective drugs**
- **Qualification of biomarkers is highly resource-intensive and may be challenging for individual stakeholders and FDA**
- **Collaboration between several stakeholders (patient groups, academia, industry and regulators) is necessary to advance promising biomarkers through:**
  - **Enhance data sharing**
  - **Cooperative data generation**
  - **Application of joint expert knowledge and resources**
  - **Sharing information/views at public workshops**
  - **Establishing consensus on definitions and terminology**