Biomarkers in Drug Discovery

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Introduction

- What is Biomarker data?
- Biomarkers in basic research
- How can biomarkers bring value to clinical studies?
- Clinical trials with the biomarker components
- How biomarkers benefit patients after the approval of drugs?

Biomarker

- FDA/NIH 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*"

- Key attributes
  - Measurable
  - Indicator of a biological phenomenon
  - (Potentially) Actionable

History of Biomarkers

- Examination of livers (4000 BC)
  - Sumerians and Babylonians
- Examination of urine of pregnant woman (1)
  - Wheat and barley (wheat=male, barley=female)
  - Predictive value 70% (1963)
- Ancient assessment of Diabetes
  - Ants attracted to the urine of the patient
- Modern method for Diabetes
  - Dipstick - sugar

Types of Biomarker

- Molecular
  - Transcriptional Signature
  - Gene mutation/SNPs
  - Serum glucose
- Histological
  - Excision or Wedge Biopsy
  - Bone marrow aspiration
- Radiographic
  - CT Scan of lung
  - MRI of brain
- Physiological characteristics
  - Blood Pressure

Categories of Biomarkers

- Based on the properties and utility
- BEST resource identify following categories
  - Susceptibility/risk biomarker
  - Diagnostic biomarker
  - Monitoring biomarker
  - Prognostic biomarker
  - Predictive biomarker
  - Pharmacodynamic/response biomarker
  - Safety biomarker
- Some biomarkers may fall under more than one categories

Pharmacodynamic/Response Biomarkers

- Shows a biological response following an exposure to a drug
- Link between the biomarker and clinical outcome
- Proof-of-concept clinical study: Pharmacological response
- Help guide dosing of a drug or continuation of a therapy
- Examples:
  - Serum LDL in hypercholesterolemia treated with drugs such as Lipitor
  - Blood pressure in hypertensive subjects treated with Valsartan®
  - Viral load in HIV subjects treated with HAART

Prognostic Biomarkers

- Identify likelihood of a clinical event in a subject with a disease
- Prognostic association may vary based on clinical settings
- Clinical Studies
  - Eligibility criteria
  - Enrichment factor
- Newer prognostic biomarkers – Genetic/Genomic
  - Molecular indicators
  - Transcriptional signature
- Examples
  - Increasing PSA in likelihood of prostate cancer progression
  - TP53 mutations associated increased death in CLL

Predictive Biomarker

- Identify subjects more likely to respond to a drug
- Response
  - Better symptomatic benefit
  - Improved survival
  - Adverse Event
- Predictive enrichment of study population
  - Subject selection
  - Stratification
- Targeted therapy
  - Best therapeutic regimen

Diagnostic Biomarkers

- To detect or confirm presence of a disease
- To identify individuals with a subtype of the disease
- Clinical trials
  - Patient selection
- Clinical practice
  - Determine the choice of for targeted therapy
- Metrices to assess accurace and precision
  - Sensitivity and Specificity
  - PPV and NPV

Why is Biomarkers used in Clinical Research?

- Significant role in translation medicine
  - Surrogate Endpoint for clinical measures
    - Accelerated approval
  - Integrative analysis
    - Genetic/genomic platforms
    - Clinical trials
    - Post-market safety surveillance data
  - Patient care
    - Diagnosis of the disease

Surrogate Endpoint

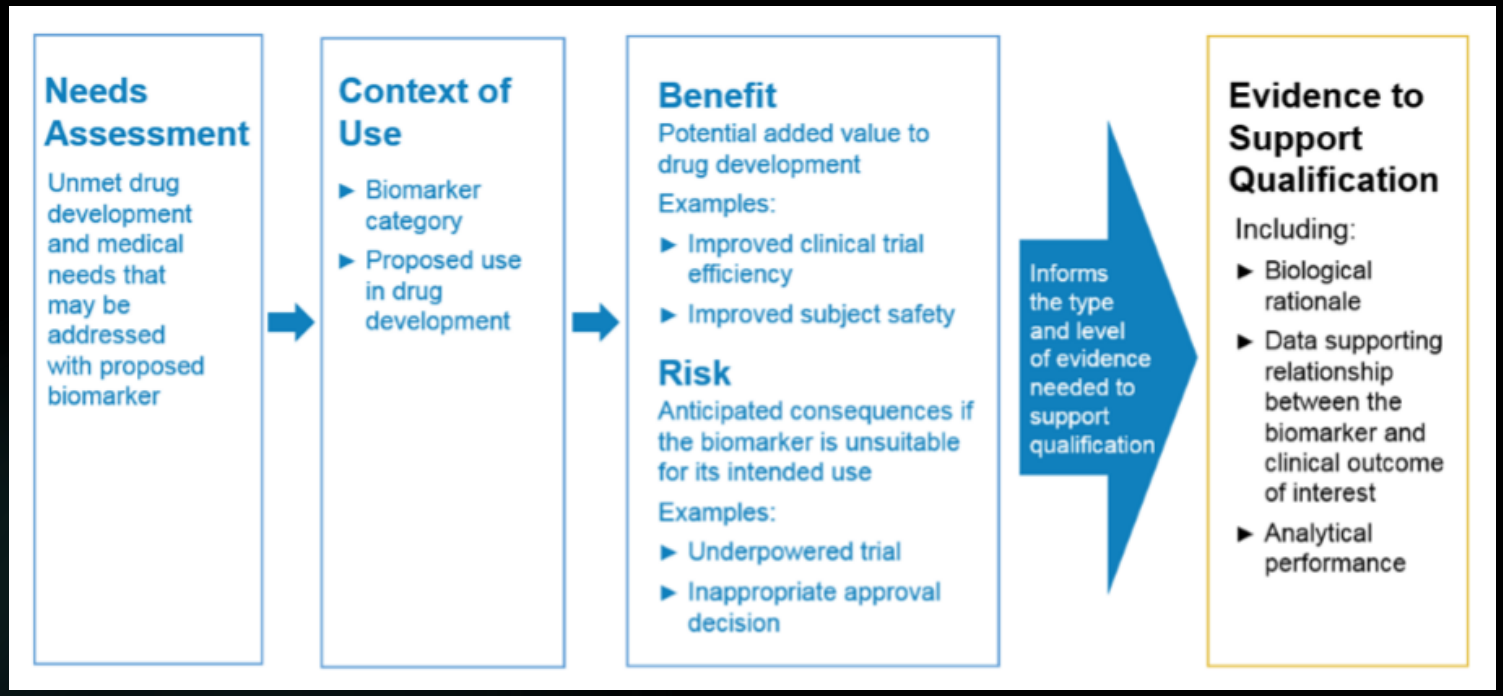
- Substitute measurement for clinical events or pathophysiological parameters
- Three types based on level of clinical validation
  - Validated
    - Strong evidence supporting prediction
    - Can be used for market approval for a given COU
  - Reasonable likely
    - Correlate with clinical endpoint
    - Mechanistic or epidemiological rationale
  - Candidate
    - Potentially biomarker can predict clinical endpoint
    - Not adequate data to establish definitive relationship

Accelerated Approval using Biomarker

- Safety and Innovation Act of 2012, section 901
- Approval can be based on the surrogate endpoint (Biomarker)

- Meaningful therapeutic benefit over available therapies
- Disease-specific empirical evidence
  - Intermediate clinical endpoint
  - Measured earlier than irreversible morbidity or death

FDA: Biomarker Qualification Program

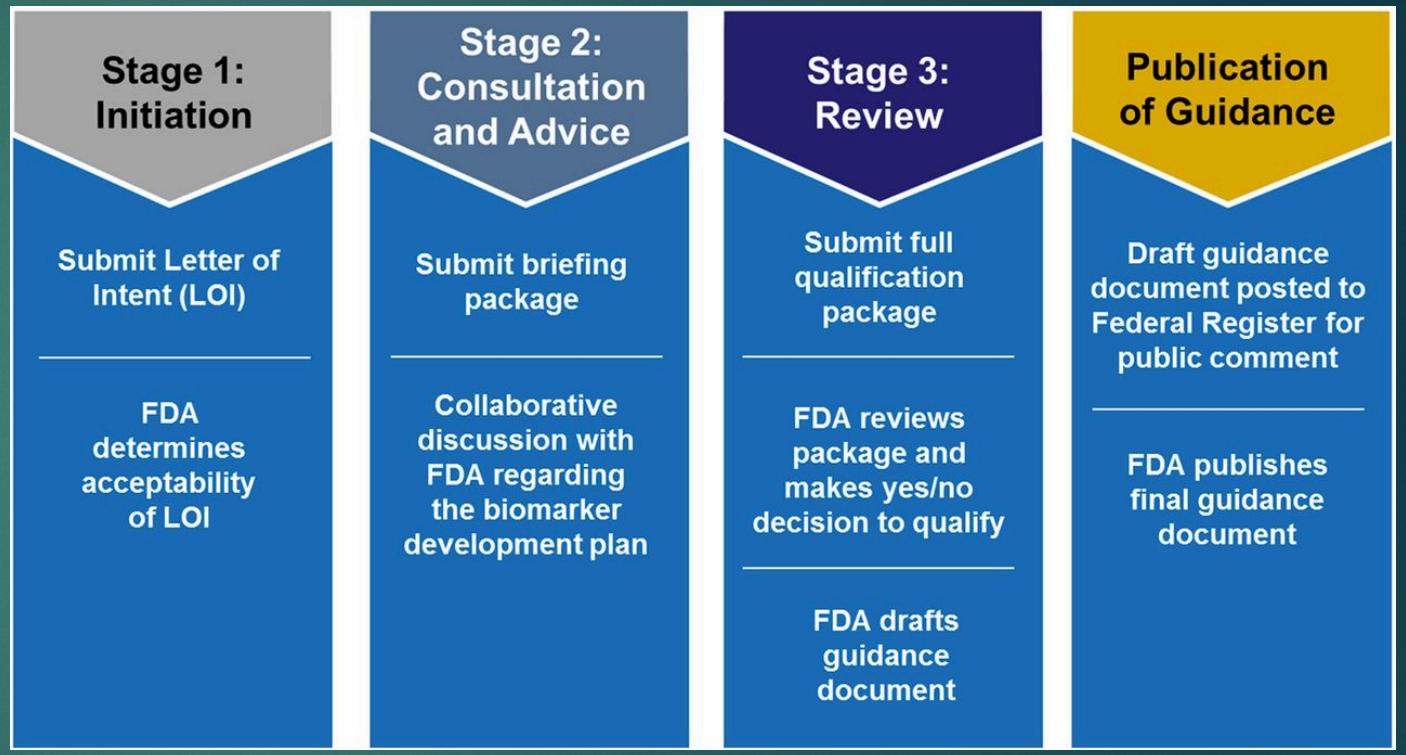


Evidentiary Framework (Source: FDA.gov)

- In response to 21st Century Cure Act, FDA published a guidance for biomarker development
- Three-stage process
  - Letter of Intent
  - Biomarker Qualification Plan
  - Biomarker Full Qualification Package
- Once Validated, a biomarker does not need requalification for approved COU

Biomarker Qualification Program

- Qualification Program
  - Determination that the biomarker can be relied on to have a specific interpretation
  - Within the stated Context of Use
  - Application in drug development and regulatory review.
- Three Stage Process



BEST (Biomarkers, EndpointS, and Tools)

- FDA-NIH Joint Leadership Council (2015)
- BEST resource is created with goals of
  - Harmonization of terms
  - Improved communication
  - Better scientific understanding
- First Phase
  - Glossary of terms
  - Consistency across multiple areas of usage
  - Used for communications by NIH and FDA
- Periodic Update
  - “living” resource

Biomarkers in Basic Research

- Molecular Biomarkers – a foundation of basic research
- Cellular pathways disruptions causing a disease
  - Known biomarkers for disease – to assess affect of experiments
  - Novel biomarkers – from new findings
- Drug Discovery
  - Target Identification/Selection
  - Mechanism of Action of drug
  - Isolation of lead compound
- Assessment of Toxicity of novel chemical entity

Bioinformatics/Genomics Technologies

- Rapid advances in sequencing platforms (NGS) in recent years
  - High-throughput Sequencing
  - Decreased cost
- Better understanding of gene structures and functions
- More sensitive measurement of peripheral gene products
- Integration and consolidation of genetic data analysis in R by Bioconductor
  - Open source collection of validated R packages
  - Over 1500 packages to perform various genomic/genetic analyses

Advances in Sequencing Platforms

- First Generation
  - Sanger Dideoxy Sequencing
  - 100K bases per run (~100 capillaries * length: 1000 bases)
- Second Generation
  - Sequencing by synthesis
  - Massively parallel format
  - Yield = 600 billion bases
- Third Generation
  - DNA or RNA templates
  - Larger sequence lengths per reaction (~1500)

R and “bioconductor.org”

- R has good connectivity with major Genomic platforms
- Extensive volume of R packages accumulated since the Genome project
- Effort to develop a centralized collaboration site with purpose of
  - Sharing and distribution of R packages
  - Deployment of validated R packages

- **Bioconductor (bioconductor.org)**
  - Open source, widely used, easily accessible distribution channel
  - Resource for genomic data analysis and reporting
  - More than 1800 R packages
  - Latest version: 3.10

Gene Expression Data Analysis

- Gene Expression Data Platforms
  - Microarrays – probe based
  - RNASeq – sequence based
- R Data objects
  - Transcripts: ExpressionSet
- Analysis Methods
  - Gene level
    - Differential Gene expression – *limma*, *edgeR*, *DESeq2*
    - Correlation to phenotypic parameters - corr
  - Gene Set or Pathways
    - Enrichment analysis – *GSEABase*, *GSVA*
    - Functional annotation – biomaRt, *DOSE*

Clinical Development

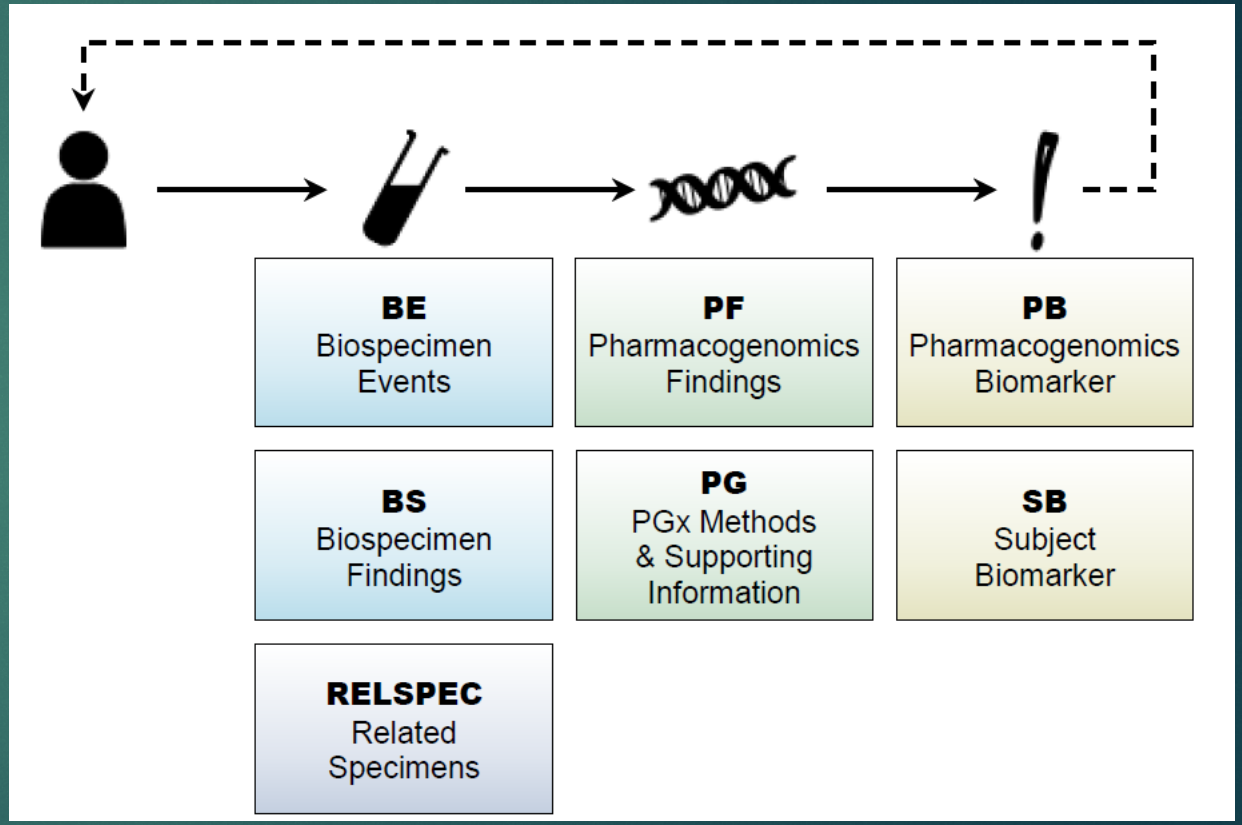
- Biomarkers are used at each stage of clinical development
- Phase-1:
  - Patient selection
  - Dose selection
- Phase 2-3:
  - Experimental Design
    - Stratification
    - Enrichment
  - Study period
    - Patient Selection
    - Safety assessment
    - Efficacy assessment

Post-approval Patient Care

- Post-approval Marker Surveillance
  - Safety biomarkers
- Clinical Decision-making
  - How aggressively intervene (Prognostic biomarker)
  - Most effective module of treatment (predictive biomarker)

CDISC SDTMIG - PGx Domains

- CDISC offers SDTM implementation guide for PGx data
- Recommends three broad categories of data
  - Biospecimen
  - Genetic observation
  - Defines a biomarker or assigns it to a subject



CDISC Guidelines - PGx Domains

- Biospecimen domains
  - BE – Biomarker events:
    - action taken (e.g. transportation, freezing, thawing)
    - accountable for the specimen (e.g., site, laboratory)
  - BS – Biomarker specimens: DNA or RNA samples
    - E.g. specimen volume, quantity of extracted sample, specimen condition
- Genetic Observation domains
  - PF – Pharmacogenomics/Genetics Findings
    - Results from gene expression or genetic variation experiments
  - PG – Pharmacogenomics/Genetics Methods and Supporting information
- Biomarker Details domains
  - PB – Pharmacogenomic/Genetics Biomarker
    - Association between observed data and medical conclusion
  - SB – Subject Biomarker
    - Genetic biomarker attributed to the subject

References:

1. FDA biomarker qualification program: https://www.fda.gov/drugs/drug-development-tool-qualification-programs/cder-biomarker-qualification-program
2. Bioconductor archive: https://www.bioconductor.org
3. CDISC SDTM Implementation Guide for Pharmacogenomics/Genetics. Retrieved from http://www.cdisc.org
4. BEST: Biomarkers, Endpoints, and other Tools. Retrieved from http://www.ncbi.nlm.nih.gov/books/NBK326791