Biomarker Qualification:
Collaboration, Strategy, and Implementation

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Executive Director, Predictive Safety Testing Consortium

February 24th, 2017
Presentation Outline

An introduction to the Critical Path Institute

Overview of Drug Development Tools with an Emphasis on Biomarkers

The Biomarker Qualification Process
   - An example of a qualification project

Collaboration Across Biomarker Stakeholders

Biomarker Qualification Evidentiary Considerations: “Framework for Defining Evidentiary Criteria for Biomarker Qualification”

Insight into Developing a Strategy for the Regulatory Acceptance of Surrogate Endpoint Biomarkers

Summary and Conclusions
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Summary and Conclusions
Independent 501(c)3 founded in 2005 ... “to foster development of new evaluation tools to inform medical product development”

Memorandum of Understanding created between the FDA and C-Path in 2005
C-Path: A Public Private Partnership

- Act as a trusted, neutral third party

- Convene scientific consortia of industry, academia, and government for sharing of data/expertise
  - The best science
  - The broadest experience
  - Active consensus building
  - Shared risk and costs

- Enable iterative EMA/FDA/PMDA participation in developing new methods to assess the safety and efficacy of medical products

- Official regulatory endorsement of novel methodologies and drug development tools
C-Path Consortia

Twelve global consortia collaborating with 1,450+ scientists and 84 organizations

- **Coalition Against Major Diseases**
  - Focusing on diseases of the brain

- **Coalition For Accelerating Standards and Therapies**
  - Data standards

- **Critical Path for Parkinson’s Consortium**
  - Enabling clinical trials in Parkinson’s Disease

- **Critical Path to TB Drug Regimens**
  - Accelerating the development of TB drug regimens and diagnostics

- **Duchenne Regulatory Science Consortium**
  - Duchenne Muscular Dystrophy

- **International Neonatal Consortium**
  - Neonatal clinical trials

- **Multiple Sclerosis Outcome Assessments Consortium**
  - Drug Effectiveness in MS

- **Polycystic Kidney Disease Outcomes Consortium**
  - New imaging biomarker for PKD

- **Patient-Reported Outcome Consortium**
  - Assessing treatment benefit

- **Electronic Patient-Reported Outcome Consortium**
  - Electronic capture of treatment benefit

- **Predictive Safety Testing Consortium**
  - Drug safety

- **Pediatric Trials Consortium**
  - Developing effective therapies for children

- **Biomarkers**
- **Clinical trial simulation tools**
- **Clinical outcome assessment instruments**
- **Data standards**
- **In vitro tools**
C-Path Collaborators

**Industry**
- AbbVie
- Acorda Therapeutics
- Actelion Pharmaceuticals
- Allergan
- Almac
- Amgen
- AstraZeneca
- Biogen Idec
- Boehringer Ingelheim
- Bracket
- Bristol-Myers Squibb
- Celgene
- Cepheid
- CRF Health
- Daiichi Sanyko
- Edetek
- Eisai
- Eli Lilly and Company
- EMD Serono
- Ephibian
- ERT
- Exco InTouch
- Forest Laboratories, Inc.
- GE Healthcare
- Genentech
- Genzyme
- GlaxoSmithKline
- Hoffmann-La Roche, Inc.
- Horizon Pharma
- ICON
- Ironwood Pharmaceuticals
- Johnson & Johnson Pharmaceutical Research & Development, LLC
- Medidata Solutions
- Merck and Co., Inc.
- Meso Scale Discovery
- Millennium: The Takeda Oncology Company
- Mitsubishi Tanabe Pharma Corporation
- Novartis
- Novo Nordisk
- Oracle
- Otsuka Pharmaceutical
- Pfizer
- Pharsight/Certara
- PTC Therapeutics
- PHT
- Sanofi
- Santhera Pharmaceuticals
- Sarepta Therapeutics
- Shire
- Sunovion Pharmaceuticals
- TAG
- Takeda
- Teva Pharmaceuticals
- UCB
- Vertex

**Nonprofit Research Organizations**
- Alzheimer’s Association
- Alzheimer’s Drug Discovery Foundation
- Alzheimer’s Research UK
- Bill & Melinda Gates Foundation
- CDISC
- Cincinnati Children’s Hospital
- Engelberg Center for Health Care Reform
- EDCTP
- Flinn Foundation
- Foundation for National Institutes of Health
- National MS Society
- Parent Project Muscular Dystrophy
- Parkinson’s UK
- PKD Foundation
- Reagan-Udall Foundation
- Science Foundation Arizona
- SRI International
- Stop TB Partnership
- TB Alliance
- US Against Alzheimer’s

**Government and Regulatory Agencies**
- Centers for Disease Control and Prevention
- European Medicines Agency
- Innovative Medicines Initiative
- International Genomics Consortium
- National Institute of Allergy and Infectious Diseases
- National Institute of Diabetes and Digestive and Kidney Diseases
- National Institutes of Health
- National Institute of Neurological Disorders and Stroke
- Pharmaceuticals and Medical Device Agency
- U.S. Food and Drug Administration
- World Health Organization

**Academic Institutions**
- The University of Arizona
- Arizona State University
- Baylor University
- University of California San Francisco
- University of Colorado-Denver
- Emory University
- University of Florida
- Johns Hopkins
- Mayo Clinic
- University of Texas Southwestern Medical Center
- Tufts University
C-Path Core Competencies

• Regulatory qualification of preclinical and clinical biomarkers for safety, efficacy, and trial enrichment

• Outcome assessment instrument development

• Comprehensive modeling & simulation programs

• Novel in vitro tools to expedite proof-of-concept

• Clinical data standards development

• Secure data management, standardization, curation, database development

• Forming and managing large international consortia
C-Path Accomplishments

☑ First preclinical safety biomarkers (7) qualified by the FDA, EMA, and PMDA

☑ First imaging biomarker for trial enrichment qualified by the EMA (for Alzheimer’s disease)

☑ First imaging biomarker for trial enrichment qualified by the FDA and EMA (for Polycystic Kidney Disease)

☑ First Clinical Data Interchange Standards Consortium (CDISC) therapeutic area data standard (Alzheimer’s disease), and additional standards for TB, PD, PKD, MS, and Influenza

☑ First drug-disease-trial model for AD endorsed by the FDA & EMA

☑ First Drug Development Tool for TB Qualified by EMA and included in FDA Guidance for TB Drug Development

☑ First Letter of Support from EMA and FDA for two kidney safety biomarkers
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Summary and Conclusions
The Critical Path Initiative is FDA’s effort to stimulate and facilitate a national effort to modernize the scientific process through which a potential human drug, biological product, or medical device is transformed from a discovery or “proof of concept” into a medical product.

FDA launched the Critical Path Initiative in 2004

- Recognized that drug development was not benefitting from many advances in biomedical sciences and had become challenging and resource intensive
- Called for modernization of scientific and technical tools for drug development to improve the evaluation and prediction of the safety, effectiveness, and manufacturability of medical products
Drug Development Tools (DDT)

DDTs are methods, materials, or measures that aid drug development.

Qualification is a conclusion that within the stated context of use, the DDT can be relied upon to have a specific interpretation and application in drug development and regulatory review.
**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 characteristics are types of biomarkers.

**Examples:**
- Blood glucose (molecular)
- Biopsy-proven acute rejection (histologic)
- Tumor size (radiographic)
- Blood pressure (physiologic)

*Updated definition from BEST (Biomarkers, EndpointS, and other Tools Glossary): http://www.ncbi.nlm.nih.gov/books/NBK326791/*
BEST: Biomarkers, EndpointS, and other Tool resource

BEST:

• A glossary of terminology and uses of biomarkers and endpoints in basic biomedical research, medical product development, and clinical care

• BEST harmonizes terms and definitions and addresses nuances of usage

• Created by the NIH-FDA Biomarker Working Group


• Email biomarkers@ncbi.nlm.nih.gov.
Biomarker Categories

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

Biomarker Categories
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Summary and Conclusions
Biomarker Qualification

Qualification is a formal regulatory review and acceptance process of biomarkers for their use in drug development

“Qualification is a conclusion that within the stated context of use, the biomarker can be relied upon to have a specific interpretation and application in drug development and regulatory review.”
Biomarker Qualification

Qualification:
Qualification results in **scientific acceptance** and **regulatory certainty** of the biomarker

Once qualified the information pertaining to the acceptable use of the biomarker in drug development will be publicly available

Biomarker qualification not just **biomarker discovery** or **clinical validation**, it the formal acceptance of the biomarker by health authorities for use in drug development

Qualification does not denote that a biomarker is acceptable for use in clinical practice as an **in vitro** diagnostic or otherwise
Objectives of Qualification

• To qualify and make DDTs publicly available to be used for a specific context of use in drug development

• To streamline drug development and review of regulatory applications

• To facilitate integration of qualified DDTs in regulatory review

• To provide a framework for scientific collaboration to facilitate DDT development
FDA and EMA Qualification: A Formal Process of Review and Acceptance

Guidance for Industry and FDA Staff
Qualification Process for Drug Development Tools

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2014
Procedural

Letter of Intent to Propose Biomarker Qualification

Letter of Intent (LOI) Harmonization

Biomarker Qualification (at FDA)

• **Submitter/requester** can be a person, a group, organization (including the federal government), or consortium that takes responsibility for and initiates a BQ proposal using the procedures described in the DDT guidance.

• **No fees** for submissions to the BQ program.

• Biomarker qualification is **voluntary**.

• Once qualified for a specific **context of use**, a biomarker can be used by drug developers for other applications for the qualified context, without re-review.

• **Incremental expansion** of the qualified context of use over time may be undertaken.

• Biomarkers considered for qualification are conceptually **independent of the specific test or device** performing the measurement.

• Biomarker qualification is a tool for drug development and **not for approval/clearance of diagnostics or for companion diagnostics for use in clinical practice**.
Biomarker Qualification Concept

Start at the end approach: Up-front conversations around the context of use (COU) since the COU drives the level of evidence needed
Considerations for Biomarker Qualification

Context of Use

The COU statement is a concise description of how a biomarker is intended to be used in drug development. It is comprised of two main elements:

• What category of biomarker is proposed and what information content would it provide?

• What question is the biomarker intended to address? (“What is the biomarker’s specific fit-for-purpose use?”)

Commutability of biomarkers across multiple COU’s (biomarker category and intended use)
Context of Use (COU)

Context of Use

• **Use Statement:**
  Name and identity and purpose of use of the biomarker in drug development

• **Conditions for qualified use:**
  Comprehensive description of conditions and boundaries for the biomarker to be used in the qualified setting
  - Analytically validated assay, threshold/cut-off value/range, interpretation of higher than and lower than threshold levels, action to be taken
  - Interpretation of data
  - Applications to drug development
Context of Use for drug-induced kidney injury biomarkers:

**Claim**
Qualified kidney safety biomarkers are proposed to be used together with monitoring of conventional kidney biomarkers (e.g., serum creatinine and blood urea nitrogen), in early clinical drug development research to support conclusions as to whether a drug is likely or unlikely to have caused a mild injury response in the kidney at the tested dose and duration.

**Study Population**
For use in healthy volunteers and patients with normal kidney function.
Current biomarkers used to monitor kidney safety have significant limitations

- These “gold standard” biomarkers (serum creatinine) change only when 50 to 60% of kidney function is lost

Proposed urinary biomarker panel for drug-induced kidney injury:

1. Clusterin
2. Osteopontin
3. Microalbumin
4. Total Protein
5. N-acetyl-β-(D)-Glucosaminidase (NAG)
6. Kidney Injury Molecule-1 (KIM-1)
7. Cystatin-C
8. Neutrophil gelatinase-associated lipocalin (NGAL)
Biomarkers in Relation to Site of Injury in Nephron

**Glomerular Filtration and Proximal Tubule Function**
- Serum Creatinine
- Urine Cystatin C
- Urine N-acetyl-β-glucosaminidase (NAG)

**Proximal Tubule Injury (Stress)**
- Urine clusterin
- Urine kidney injury molecule-1 (KIM-1)
- Urine N-acetyl-β-glucosaminidase (NAG)

**Loop of Henle Injury (Stress)**
- Osteopontin

**Distal Tubule Injury (Stress)**
- Osteopontin
- Neutrophil gelatinase-associated lipocalin (NGAL)
Learn and confirm qualification strategy

Nonclinical Phase

- Cisplatin, aminoglycosides, and dozens of other renal toxicants were used to demonstrate the superiority of novel biomarkers over sCr for monitoring renal tubular injury (using microscopic histopathology as gold standard)

*Qualification of Seven Biomarkers of Drug-Induced Nephrotoxicity in Rats (2008-2010)*

Clinical Learning Phase

- Prospective healthy volunteer study
- Archived samples from cisplatin study

Clinical Confirmatory Phase

- Aminoglycoside study in cystic fibrosis patients
- Cisplatin study in cancer patients

Submission of data supporting qualification
Clinical Learning Phase Data Summary:
Eight (8) Selected Urinary Biomarkers Show Improved Sensitivity Over sCr to Identify Patients Exposed to Cisplatin

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Mesothelioma Patients: Number/N (%) &gt;T_{SS}^*</th>
<th>Normal Healthy Volunteers: % &gt;T_{SS}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients With Medically Relevant Increases in sCr</td>
<td>Patients Without Medically Relevant Increases in sCr</td>
</tr>
<tr>
<td>Clusterin</td>
<td>19/20 (95.0%)</td>
<td>22/30 (73.3%)</td>
</tr>
<tr>
<td>Osteopontin</td>
<td>20/20 (100.0%)</td>
<td>30/30 (96.8%)</td>
</tr>
<tr>
<td>Microalbumin</td>
<td>20/20 (100.0%)</td>
<td>30/30 (100.0%)</td>
</tr>
<tr>
<td>Total Protein</td>
<td>20/20 (100.0%)</td>
<td>30/30 (100.0%)</td>
</tr>
<tr>
<td>N-acetyl-β-(D)-glucosaminidase</td>
<td>20/20 (100.0%)</td>
<td>27/30 (90.0%)</td>
</tr>
<tr>
<td>Kidney Injury Molecule-1</td>
<td>20/20 (100.0%)</td>
<td>30/30 (100.0%)</td>
</tr>
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<td>Cystatin-C</td>
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<tr>
<td>Neutrophil gelatinase-associated lipocalcin</td>
<td>19/20 (95%)</td>
<td>24/30 (80.0%)</td>
</tr>
</tbody>
</table>

*T_{SS} = statistically significant threshold.
Prospective clinical studies

Two prospective studies in patients currently using medications that have the potential to cause kidney injury.

• Aminoglycoside study in cystic fibrosis patients
  - Patients (n=100): Adult CF patients, acute pulmonary infection treated with IV tobramycin
  - Controls (n=25): Adult CF patients acute pulmonary infection treated with IV fluoroquinolone; Adult CF patients (n=25), no pulmonary infection, no treatment

• Cisplatin study in cancer patients
  - Patients (n=100): Patients with head and neck squamous cell carcinoma, and other cancers treated with cisplatin as single agent or part of chemo treatment cocktail
  - Controls (n=50): Cancer patients receiving non-cisplatin chemo treatment, or radiation treatment

✓ Greater diagnostic predictivity compared to serum creatinine as defined by:
  1. A formal adjudication procedure
  2. A predefined statistical evaluation
In the end....

The drug development community will have a number of qualified urinary biomarkers to be used in conjunction with standard kidney safety biomarkers (serum creatinine) that can be used in subjects/patient with normal kidney function:

1. Clusterin
2. Osteopontin
3. Microalbumin
4. Total Protein
5. N-acetyl-β-(D)-Glucosaminidase (NAG)
6. Kidney Injury Molecule-1 (KIM-1)
7. Cystatin-C
8. Neutrophil gelatinase-associated lipocalin (NGAL)
Initial Observations from Project:

• In both the nonclinical and clinical studies to this point the novel biomarkers appear to be more sensitive than serum creatinine

• Nonclinical data clearly shows that toxicants cause different biomarker responses (based upon mechanism of action and dose)
  - The translation of this effect is currently being tested in the prospective clinical

• It is likely that a panel of biomarkers will be more informative and more generalizable across nephrotoxicant than a single biomarker in humans
Establishment of Traditional Biomarkers

**Alanine aminotransferase (ALT)**

In 1955, Fernando De Ritis, Mario Coltorti and Giuseppe Giusti at the University of Naples discovered that elevated transaminases enzymes can be an indicator of liver damage.

“Elevation in serum ALT >3 ULN and/or preclinical histopathologic evidence of hepatocellular necrosis and/or biliary changes (including repair) are generally accepted...”
Establishment of Traditional Biomarkers

Alanine aminotransferase (ALT)
Alanine aminotransferase (ALT) is the principal reference standard biomarker to diagnose DILI, yet its current application in preclinical to clinical translation for decision-making purposes has imperfections.

1978

- Generally acceptance as a predictable DILI biomarker

- Assay Optimization & Standardization

2009

- U.S. FDA DILI Guidance (Hy’s Law)

“Hepatocellular injury is indicated by rises in AT activities in serum reflecting release of alanine or aspartate aminotransferase (ALT or AST) from injured liver cells. The ability to cause some hepatocellular injury, however, is not a reliable predictor of a drug’s potential for severe DILI.”
Establishment of Traditional Biomarkers

Alanine Aminotransferase (ALT) Acceptance

1955 2009

> 50 years

Novel Biomarker Qualification

1955 2009

< 50 years
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Summary and Conclusions
Multiple Stakeholders in Qualification

**Academic Scientists** – Provide the foundational understanding of the biomarkers biology and potential (biomarker discovery), as well as provide data on the clinical utility/validation of biomarker

**Industry Scientist** – Introduce exploratory biomarkers into clinical trials and work towards regulatory acceptance of biomarkers (qualification)

**Health authorities** – Provide an avenue for the regulatory acceptance of novel biomarkers

**Consortia** – Provide the platform for stakeholder collaboration
The “typical” interaction with FDA

Guidance for Industry
Formal Meetings Between the FDA and Sponsors or Applicants

- **Type A Meeting**: needed to help an otherwise stalled product development program proceed.
- **Type B Meeting**: Pre-IND; certain end-of-phase 1 meetings; end-of-phase 2 and pre-phase 3 meetings; pre-NDA/BLA meetings
- **Type C Meeting**: anything else regarding development and review of a product
Additional ways of working together

• Drug Development Tool Qualification
• Voluntary Exploratory Data Meeting (VXDS)
• Critical Path Innovation Meeting (CPIM)
• Letter of Support
• White paper to inform formal Guidance
• Co-publish (e.g. co-author; companion commentary)
• Co-sponsor workshops and scientific conferences
• Working directly with the regulatory review division
**INFORMAL** interaction with regulators is very valuable

<table>
<thead>
<tr>
<th>Example</th>
<th>Result</th>
</tr>
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<tbody>
<tr>
<td>For ongoing qualification projects, teleconferences without formal minutes (ex. Kidney biomarkers)</td>
<td>Rapid sharing of data and information</td>
</tr>
<tr>
<td>Mechanism to share novel biomarker strategies not ready for qualification (ex. FDA CPIM)</td>
<td>Ability to mutually learn about safety challenges in drug development</td>
</tr>
<tr>
<td>Scientific interaction with regulatory scientists and clinicians (ex. TCs, conferences)</td>
<td>Builds collegial relationship and trust</td>
</tr>
<tr>
<td>Regular interaction of consortia leadership and regulators</td>
<td>Improves coordination, demonstrates mutual commitment to working together</td>
</tr>
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Considerations for Biomarker Qualification

Framework for Defining Evidentiary Criteria for Biomarker Qualification

*Final Version*

Evidentiary Criteria Writing Group

Revised 10/20/16

Considerations for Biomarker Qualification

Largest source of consortia anxiety:
How to determine the level of evidence needed for biomarker qualification?
How to Determine the Level of Evidence Expected for a COU?

Limited and Expanded COU Qualifications:

Qualification Path
- Qualification (1)
- Qualification (2)
- Qualification (3)

Robustness of Context of Use

Expectations:
Data, Evidentiary, and Regulatory
How to Determine the Level of Evidence Expected for a COU?

Benefit of using the biomarker

Risk
Considerations for Biomarker Qualification

General Evidentiary Criteria Framework Components

1. **Need Statement**
   - Knowledge gap?
   - Drug development need?

2. **COU**
   - Class of Biomarker?
   - What is the question the biomarker is addressing?

3. **Benefit**
   - Improved sensitivity
   - Improved selectivity
   - Mechanistic context

4. **Risk**
   - Consequence of false positive
   - Consequence of false negative

5. **Evidentiary Criteria**
   - Characterization of Relationship Between the Biomarker and Clinical Outcome
   - Biological Rationale for Use of Biomarker (if known)
   - Type of Data and Study Design (i.e., Prospective, Retrospective, etc.)
   - Independent Data Sets for Qualification
   - Comparison to current standard
   - Assay performance
   - Statistical Methods to Use
Considerations for Biomarker Qualification

General Evidentiary Criteria Framework Components

Defining the Biomarker Program
1) Describe the drug development need

2) Define the COU (i.e., how the biomarker will be used in a drug development context)

3) Consider potential benefits should the biomarker project be successful (i.e., improved sensitivity or selectivity)

4) Consider risks associated with the intended use of the biomarker in a drug development program (i.e., frequency and consequence of false negatives or false positives)

5) Determine the evidence needed to support the COU based on the Benefit and Risk
Considerations for Biomarker Qualification

- **Assay performance** (analytically validated method and understanding of potential sources of variability in the measurement).

- Characterizations of the various relationships among the biomarker, the clinical outcomes, and the treatment (where applicable) required for the proposed COU.

- **Biological rationale** for use of the biomarker (if available)

- **Type of data and study design needed** to assess the strength of association of the biomarker with its proposed clinical outcome: retrospective or prospective, registry data, and/or randomized controlled trial (RCT) data.

- **Reproducibility of data** (need for test dataset and confirmatory dataset).

- Comparison to current standards

- Use of appropriate, **pre-specified statistical methods** to demonstrate the hypothesized relationships for the COU.

- **Strength of evidence**: the level of evidence needed depends on the type of biomarker and its COU.
How to Determine the Level of Evidence Expected for a COU?

Kidney Safety Biomarker Project:

Use of novel biomarkers in individuals with normal renal function

*VS.*

Use of novel biomarkers in individuals with normal renal function and in individuals with altered function due to disease
How to Determine the Level of Evidence Expected for a COU?

Kidney Safety Biomarker Project:

Use of novel biomarkers with conventional biomarkers

VS.

Replacement of conventional biomarkers with novel biomarkers
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Summary and Conclusions
Strategy for the Regulatory Acceptance of Surrogate Endpoint Biomarkers

**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. A surrogate endpoint does not measure the clinical benefit of primary interest in and of itself, but rather is expected to predict that clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.

If we want to develop therapies for chronic disease we will need **surrogate endpoint biomarkers** to demonstrate the effectiveness of our interventions.

Or, we need to figure out how to run 10 yearlong clinical trials in an accelerated and cost effective manner.
Strategy for the Regulatory Acceptance of Surrogate Endpoint Biomarkers

However, it is not readily apparent what the appropriate path is to developing a surrogate endpoint biomarker.

Furthermore, it appears that it will take a long time to derive such biomarkers to accelerate drug development.

In order to obtain such acceptance by regulators and the scientific community, significant evidence is required across multiple therapeutics interventions demonstrating the biomarkers relationship to the ultimate desired outcome.

So where do we start?
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. A surrogate endpoint does not measure the clinical benefit of primary interest in and of itself, but rather is expected to predict that clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.
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**Pharmacodynamic Biomarker:** Indicate that a biological response has occurred in a patient who has received a therapeutic intervention. May become clinical trial endpoints and for a small subset, 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. A surrogate endpoint does not measure the clinical benefit of primary interest in and of itself, but rather is expected to predict that clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.

1. Understanding of disease progression relative to accepted disease endpoints (Natural History of Disease).

2. Longitudinal assessment of the biomarkers behavior over the course of the disease.
Development of Quantitative Tools to Support Biomarker Qualification

Fundamental component of biomarker-disease models
- Biomarker-disease models are drug-independent
- Can be used to optimize entry criteria

Prognostic Biomarkers for trial enrichment
- Total Kidney Volume for PKD
- Soluble Amyloid for Alzheimer Disease
Development of Quantitative Tools to Support Biomarker Qualification

- This effort involved simultaneously modeling:
  - Biomarker trajectory (longitudinal time-varying covariates)
  - Disease Endpoint, hazard function (time-to-event)

- Joint modeling is considered as the gold standard method for assessing the effect of longitudinal time-varying covariates in a time-to-event analysis of clinical endpoint (Sweeting et al., 2011; Tsiatis, & Davidian, 2004)
Development of Quantitative Tools to Support Biomarker Qualification

Fundamental component of biomarker-disease models

- Biomarker-disease models are drug-independent
- Can be customized by introducing a drug-biomarker
Development of Quantitative Tools to Support Biomarker Qualification

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Clinical Trial Endpoint
Development of Quantitative Tools to Support Biomarker Qualification

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Surrogate Endpoint
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An introduction to the Critical Path Institute

Overview of Drug Development Tools with an Emphasis on Biomarkers

The Biomarker Qualification Process
  - An example of a qualification project

Collaboration Across Biomarker Stakeholders

Biomarker Qualification Evidentiary Considerations: “Framework for Defining Evidentiary Criteria for Biomarker Qualification”

Insight into Developing a Strategy for the Regulatory Acceptance of Surrogate Endpoint Biomarkers

Summary and Conclusions
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Novel biomarkers can provide better insight into new chemical entities progressing through drug development

However, in order to routinely and consistently use novel biomarkers across multiple drug development programs regulatory acceptance is needed (Biomarker Qualification)

It is difficult for a single organization or stakeholder group to qualify a biomarker in a reasonable amount of time; thus, collaboration is required

Furthermore, we must all work together to define the optimal scientific and regulatory path for biomarker qualification (Evidentiary Considerations for Biomarker Qualification)
Summary and Conclusions

Data sharing by key stakeholders (academic investigators and pharmaceutical companies) is required for many of our qualification goals.

Likewise, novel biomarkers will need to be included in late phase clinical development programs by pharmaceutical companies.

Finally, a collaborative relationship with health authorities must be established and maintained.
Thank You

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