Biomarkers: Physiological & Laboratory Markers of Drug Effect

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Why Are Biomarkers Important?

- Diagnosis is the foundation of therapy
- Biomarkers are quantitative measures that allow us to diagnose and assess the disease process and monitor response to treatment
- Biomarkers are also crucial to efficient medical product development
- As a consequence of scientific, economic and regulatory factors, biomarker development has lagged significantly behind therapeutic development

Biomarker Definition

- "A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention"

BIOMARKERS DEFINITIONS WORKING GROUP: BIOMARKERS AND SURROGATE ENDPOINTS: PREFERRED DEFINITIONS AND CONCEPTUAL FRAMEWORK. CLIN PHARMACOL THER 2001;69:89-95.

Biomarkers Have Many Uses in Medicine

- Biomarkers important in clinical medicine include diagnostic, prognostic or physiologic status information, for example, vital signs, serum electrolytes, "x-rays" and other imaging modalities. Much of medical practice involves interpreting and monitoring biomarkers
- Markers of drug effect or response--the subject of this lecture--are a subset of the general class of biomarkers

Using Biomarkers of Drug Effect in Clinical Practice

- Disease and disease subtype diagnosis
- Prognostic determination
- Selection of appropriate therapy
  - Maximize efficacy
  - Minimize toxicity
- Selection of correct dose
- Monitoring outcomes (good and bad)

BIOMARKERS IN DRUG DEVELOPMENT

Use of Biomarkers in Early Drug Development and Decision Making

- Evaluate activity in animal models
- Bridge animal and human pharmacology via proof-of-mechanism or other observations
- Evaluate safety in animal models, e.g., toxicogenomics
- Evaluate human safety early in development

Examples of Biomarkers Commonly used in Drug Development

- Safety biomarkers: serum creatinine and blood chemistries; CBC, CXR, ECG
- Drug phamacokinetics (usually serum levels)
- Pharmacodynamic (efficacy) biomarkers:
  - Blood glucose
  - Urine, sputum, etc cultures
  - Pulmonary function tests

Use of Biomarkers in Later Drug Development and Decision Making

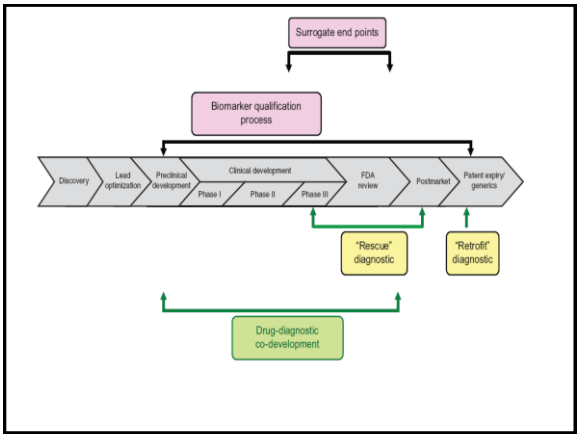
- Evaluate dose-response and optimal regimen for desired pharmacologic effect
- Use safety markers to determine dose-response for toxicity
- Select or deselect patients for inclusion in trials
- Determine role (if any) of differences in metabolism on above

Biomarkers and Personalized Medicine

- It is assumed that new biomarkers will enable personalized medicine
- Many of these markers will utilize new technology: genomics, proteomics, etc
- Individual markers for:
  - Drug metabolism
  - Interactions
  - Drug safety risks
  - Probability of response or non-response

Biomarkers and Personalized Medicine

- In some cases a biomarker will be co-developed with a therapeutic (e.g., for patient selection): this is termed co-development
- In some cases a biomarker will be sought to improve the benefit-to-risk for an already-developed therapy: this is a "rescue"
- In some cases a biomarker will be discovered to improve a long-used therapy: a "retrofit"



BIOMARKER USE IN CLINICAL TRIALS OF DRUG EFFECTIVENESS

Clinical Endpoint Definition

- "A characteristic or variable that reflects how a patient feels, functions or survives"
- Usually related to a desired effect, ie efficacy
- Clinical endpoints are preferred for use in efficacy trials and are usually acceptable as evidence of efficacy for regulatory purposes

Surrogate Endpoint Definition

- A biomarker intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm, or lack of benefit) based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence

SURROGATE MARKER

Use of this term is discouraged because it suggests that the substitution is for a marker rather than for a clinical endpoint

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Use of Surrogate Endpoints in Clinical Drug Development

- Use to assess whether drug has clinically significant efficacy: this is often faster than using clinical endpoint
- Surrogate endpoints may be used to support "accelerated approval" of a drug if the surrogate is deemed "reasonably likely" to predict a clinical endpoint of interest
  - Drugs approved under accelerated approval must undergo subsequent trials to demonstrate clinical efficacy
  - Only used in serious and life-threatening illnesses that lack acceptable therapy
- A few surrogate endpoints are acceptable for full approval (e.g., are "validated")

Biomarkers used as Surrogate Endpoints

- "Validated Surrogate Endpoints"
  - Blood pressure
  - Bone mineral density for estrogenic compounds
  - Hemoglobin A1C for glycemic control
  - Use can lead to "full" approval
- "Non-Validated Surrogates" used for accelerated approval
  - Short terms studies of effect on HIV copy number
  - Tumor shrinkage
  - Use can lead to "accelerated" approval

The Most Widely Used Surrogate Endpoint*

BLOOD LEVELS AS A SURROGATE FOR CLINICAL EFFICACY AND TOXICITY IN THE EVALUATION OF GENERIC DRUGS

*** Comment by Carl Peck: CDDS WORKSHOP, McLean, VA, May 13, 1998**

DEVELOPMENT AND QUALIFICATION OF BIOMARKERS

Fate of Most Candidate Biomarkers

- Discovered in academic laboratory
- Clinical series results published
- Further small academic series published
- Some uptake in academic centers in clinical care
- Assay may be commercialized as laboratory service

Fate of Most Candidate Biomarkers

- Small number may be developed into commercially available laboratory tests
- Fewer may become integrated into clinical care
- Evidence base for use often remains slim/controversial
- Not adopted for regulatory use because of absence of needed evidence (e.g., PSA)

Future of Drug Development and Biomarker Development Tightly Linked

- Biomarkers represent bridge between mechanistic understanding of preclinical development and empirical clinical evaluation
- Regulatory system has been focused on empirical testing: skewing overall clinical evaluation towards "all empirical"
- Mechanistic clinical evaluation lacking

Developing Biomarkers for Use in Drug Trials: a New Model

- FDA draft guidance: "Qualification of drug development tools" 10/20/10
  - Groups develop the evidence needed for a specific use: demonstrate "fitness for use"; process for FDA consultation
  - Includes new biomarkers
  - Submit evidence to FDA per guidance
  - Agency reviews and, if indicated, publishes findings of acceptance

Stimulating the Use of Biomarkers in Drug Development

- FDA's Critical Path Initiative: proposal to use consortia to qualify biomarkers through resource sharing
- Currently such consortia are ongoing in areas such as animal safety testing and overall biomarker development
- Clinical safety biomarkers of great interest

Why Use Consortia for Biomarker Qualification?

- No group's "job" is to qualify biomarkers
- Requires significant resources and multiple experiments
- Often qualification can be "piggybacked" onto animal and clinical studies done for other purposes
- Multiple parties benefit from results

Biomarker Development Consortia

- Predictive Safety Consortium
  - C-Path Institute, Tucson AZ
  - Animal safety biomarkers generated as a part of animal toxicology testing
  - Thousands of animal tox studies done each year in US for drug development purposes
  - Firms had developed in-house biomarkers but not shared them

Predictive Safety Testing Consortium

- Fourteen pharmaceutical companies joined consortium
- Agreed to cross-validate markers for organ-specific drug injury
- Have submitted first qualification package to FDA for renal injury markers: precursor of new qualification process
- FDA and EMEA have accepted for use in animal studies

Other Biomarker Consortia

- SAE consortium
  - Industry consortium
  - Genetic basis of serious rare adverse events
- "The Biomarker Consortium"
  - NIH/FDA/PhRMA/BIO/patient groups/ many others
    - Discovery and qualification of biomarkers
- Cardiovascular Markers
  - Duke University/FDA/others
  - Research on digital ECG warehouse
  - Cardiac biomarker projects

Promising Safety Biomarkers

- Drug Metabolizing enzyme status
  - 6-Mercaptopurine: enzyme TPMT
  - "Strattera": enzyme CYP 2D6
  - Irinotecan: enzyme UGT1A1
  - Warfarin: enzyme CYP 2C9; pharmacodynamic biomarker VK0RC1-- safety and efficacy
- Genetic Basis of Rare, Serious Adverse Event
  - Abacavir: HLA-B*5701 and hypersensitivity
  - Carbamazepine: HLA-B*1502 and Stevens-Johnson Syndrome
  - More to come, e.g., hepatic injury with lumiracoxib or exanta

Potential Imaging Biomarkers

- FDA Central and Peripheral Nervous System Drug Advisory Committee meeting: Oct 26, 2008
- Three sponsors presented development plans for 3 different imaging agents for detection of amyloid in diagnosis of Alzheimer's disease
- Difficult challenge because of lack of a gold standard other than histologic verification
- Jan 20, 2011 the Advisory Committee discussed an NDA for florbetapir, a PET imaging drug for diagnosis of Alzheimer's

Potential Genomic Efficacy Biomarkers

- Metabolism of prodrugs: necessary for conversion to active drug in vivo
  - Clopidogrel
  - Tamoxifen
- Pathway markers in cancer: targeted therapy
  - Recent Oncology Drug Advisory Committee meeting on -RAS and 2 EGFR targeted drugs (Erbitux, Vectibix) to treat colon cancer (Dec 16, 2008); label change to restrict treatment to individuals without mutated k-RAS

REGULATORY ACCEPTANCE OF SURROGATE ENDPOINTS

How are New Surrogate Endpoints "Validated" for Regulatory Use?

- There is no standardized process
- In some cases, acceptance based on long time clinical use plus adequate data from trials
- In other cases (e.g., HIV) acceptance driven by crisis

HIERARCHY OF BIOMARKERS* (Classic view)

TYPE 0: NATURAL HISTORY MARKER (Prognosis)

TYPE I: BIOLOGICAL ACTIVITY MARKER (Responds to therapy)

TYPE II: SINGLE OR MULTIPLE MARKER(S) OF THERAPEUTIC EFFICACY (Surrogate endpoint, accounts fully for clinical efficacy)

*** Mildvan D, et al.: Clin Infect Dis 1997;24:764-74.**

"Validation" of Biomarkers (e.g., for use as Surrogate

BIOLOGICAL PLAUSIBILITY

- **EPIDMIOLOGIC EVIDENCE THAT MARKER IS A RISK FACTOR**
- **MARKER MUST BE CONSISTENT WITH PATHOPHYSIOLOGY**
- **MARKER MUST BE ON CAUSAL PATHWAY**
- **CHANGES IN MARKER REFLECT CHANGES IN PROGNOSIS**

STATISTICAL CRITERIA

- **CHANGES IN MARKER MUST BE CORRELATED WITH CLINICAL OUTCOME** (but correlation does not equal causation)

(Not confounded by adverse drug effects)

ADDITIONAL SUPPORT FOR BIOMARKER as SURROGATE*

SUCCESS IN CLINICAL TRIALS

- EFFECT ON SURROGATE HAS PREDICTED OUTCOME WITH OTHER DRUGS OF SAME PHARMACOLOGIC CLASS
- EFFECT ON SURROGATE HAS PREDICTED OUTCOME FOR DRUGS IN SEVERAL PHARMACOLOGIC CLASSES

OTHER BENEFIT/RISK CONSIDERATIONS

- SERIOUS OR LIFE-THREATENING ILLNESS WITH NO ALTERNATIVE THERAPY
- LARGE SAFETY DATA BASE
- SHORT-TERM USE
- DIFFICULTY IN STUDYING CLINICAL ENDPOINT

* Temple R: JAMA 1999;282:790-5.

History of Surrogate Endpoint Use

- Blood pressure measurements and cholesterol levels accepted in 1970s-80s based on epidemiologic data
- Problems with use of surrogate endpoints identified in late 1980s

  CAST outcome:
  - Use: antiarrhymics for prevention of sudden death
  - Surrogate: suppression of VBP's
  - Mortality increased in treatment arms

Temple. "A regulatory authority's opinion about surrogate endpoints". Clinical Measurement in Drug Evaluation. Wiley and Sons. 1995

Result: Use of Surrogates Discouraged

- Surrogate EP supposed to "completely correlate with the clinical endpoint"
- This is not possible and has led to serious (but I would argue, misplaced) disillusionment with the use of biomarkers
- Flemming TR, DeMets DL: Surrogate endpoints in clinical trials: are we being misled? Ann Intern Med 1996;125:605-13

Surrogate Endpoint Development: 1990s

- HIV epidemic spurred the use of new surrogate endpoints for antiretroviral therapy: highly controversial at first given CAST experience
- Rigorous statistical criteria for assessing correlation of candidate surrogate with clinical outcome were published*
- No surrogate EP has ever met these criteria

*Prentice. Stat in Med 8: 431, 1989

Surrogate Endpoint Development: HIV

- HIV RNA copy number is now used as early drug development tool, surrogate endpoint in trials (under accelerated approval), and for clinical monitoring of antiviral therapy
- Lack of complete correlation with clinical outcomes has not compromised utility
- Successful development of antiretrovirals and control of HIV infection

Surrogate Endpoint Use: 2000s

- Controversy over use of glycemic control as efficacy endpoint: rosiglitazone
  - Dispute is misguided
  - Real argument is over how much premarket cardiovascular safety data to accumulate
- Controversy over use of LDL cholesterol (as assessed by another biomarker, carotid artery intimal thickness on ultrasound): Vytorin

Fundamental Problems with the Current Conceptual Framework for Surrogate Endpoints

- There is no "gold standard" clinical outcome measurement – concept of "ultimate" clinical outcome is flawed
- Survival: data show that desirability of longer survival dependent on quality of life, in many individuals' estimation.
- Generalizability of any single outcome measure (e.g., mortality) can be limited by trial parameters (e.g., who was entered)
- Confusion between desirability of prolonged observation (for safety and long term outcomes) and use of surrogate
- Can put "too many eggs" in the surrogate basket!

Additional Problems with Surrogate Endpoint Framework

- Per-patient view of outcomes very different from population mean view of outcomes.
- For example, "ultimate" benefit in survival of 8% over placebo not meaningful to you if you are not in the 8% who actually respond
- Newer (and older, e.g., metabolizing enzymes) biomarkers provide information at the individual level

How Likely are New Surrogates?

- Clearly, need robust pipeline of new biomarkers being used in drug development
- Use in many drug development programs and in multiple trials adds generalizability
- New candidates will likely emerge
- Regulatory agencies need to better articulate how longer term safety evaluation would be performed

Biomarkers for Drug Effect in Clinical Practice

- Biomarker use
  - In drug development=qualification
  - As a surrogate endpoint= regulatory acceptance
  - In clinical practice as diagnostic=clinical utility, i.e., does use of the diagnostic add clinical value greater than its harm?
  - Often clinical utility of co-developed diagnostics will be demonstrated in the development program

Table 1 Questions related to biomarker development and validation

Activity	Question being addressed	Setting
Biomarker discovery and development	Is there an informative marker that correlates with a clinical state?	Laboratory
Analytical validation	Does the test measure the biomarker reliably?	Laboratory
Clinical validation	Does the test predict the clinical state?	Clinical research
Biomarker qualification	Does the test provide reliable information?	Drug development
Clinical utility evaluation	Is the test worth doing?	Health care
Surrogate end-point evaluation	Does the test predict the desired clinical response?	Drug development
Cost-effectiveness evaluation	Is the test worth paying for?	Reimbursement
Comparative effectiveness evaluation	Is the test worth doing in the real world, as compared with other options?	Health care

Summary

- Important public health need for development of additional biomarkers to target and monitor therapy
- This requires use in clinical trials during drug development
- Business model/regulatory path for such markers is not clear to industry
- Clarification and stimulus required

Summary

- Definitions for biomarkers, clinical outcomes and surrogate endpoints have been developed
- Further development of the model needed in order to increase use and utility of markers in drug development
- FDA has recently established a process to assist in evaluation and development of biomarkers used in drug development