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.”


- Note that a good biomarker is quantitative
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

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

Current Examples

- Early detection/stratifying risk of disease
  - BRCA1 testing
  - Blood pressure, LDL cholesterol, HgBA1c
  - Sensitive tests of short term memory; CSF measurements; imaging technologies in Alzheimer’s (in development)

- Disease subtype
  - Tests for toxin production in bacteria
  - Hormone sensitivity in breast cancer
Current Examples

- Prognostic determination
  - Hormone receptor and genetic profiling of breast cancer; cancer histologic type in general
  - Cardiac ejection fraction in heart failure
  - LDL cholesterol, blood pressure, BMI etc to stratify risk of cardiovascular disease

Current Examples

- Selection of appropriate therapy: maximize efficacy
  - Genetic CFTR mutation status in cystic fibrosis
  - Drug resistance testing for selection of appropriate antimicrobial therapy
  - Targeted cancer drugs: Herceptin (breast cancer), Velbora (melanoma), Xalkori (lung cancer) etc.

Current Examples

- Selection of appropriate therapy: minimize toxicity
  - HLA B*5701 testing prior to Abacavir therapy to identify those at higher risk for hypersensitivity reactions
  - HLA B*1502 testing prior to carbamazepine therapy to identify those at higher risk for Stevens-Johnson syndrome or TENS
Current Examples

- Selection of appropriate dose
  - Tetrabenazine for treatment of Huntington’s chorea: patients requiring over 50mg/day should be genotyped for CYP2d6 status.
  - Generally, use of drug metabolizing enzyme status to adjust doses
  - Use of measure of renal and hepatic function to modify dosing

- Monitoring therapy
  - HIV: emergence of resistant virus; virus copy number
  - Monitoring peripheral blood counts to assess toxicity of chemotherapy
  - Under development: more sensitive tests to monitor for drug-induced renal injury

Use of Biomarkers Improves the Precision of Therapy

- Currently many therapeutic interventions still trial and error (e.g., antidepressants, initial antibiotic therapy, anti-rheumatic therapy, etc)

- By identifying likely responders, eliminating those at high risk, selecting personalized dose, and monitoring therapy, outcomes of treatment can be substantially improved, and drug development become more successful
Biomarkers in drug development

Use of Biomarkers in Early Drug Development and Decision Making

- It's all about prediction: current drug development prone to late-stage failures. Can biomarkers improve success rate?
- 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

Use of Biomarkers in Later Drug Development and Decision Making

- Evaluate dose-response and optimal regimen for desired pharmacologic effect: diseases that lack pharmacodynamic or other rapidly responsive marker (e.g., Alzheimers) pose difficult development problems
- 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
Examples of Biomarkers Commonly used in Drug Development

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

Biomarkers and Personalized Medicine

- New biomarkers are beginning to enable personalized medicine
- Many of these markers utilize new technology: genomics (currently), proteomics, etc (future)
- Individual markers for:
  - Drug metabolism
  - Interactions
  - Drug safety risks
  - Probability of response or non-response

Rise of Targeted Therapies: Predicting Drug Response

- Dozens of cancer therapies approved by FDA for tumors carrying specific mutations: more by the month!
- Hepatitis C drugs by HCV genotype
- Rare disease genetic subsets
- These therapies often have improved treatment effect and thus more positive benefit/risk assessment
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)
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

Developing Biomarkers for Use in Drug Trials: a New Model

- FDA Guidance: “Qualification of drug development tools” 1/14
  - 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
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
- Submitted first qualification package to FDA for renal injury markers
- FDA and EMEA have accepted for use in animal studies; undergoing human testing

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
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”).

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**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 term studies of effect on HIV copy number
  - Tumor shrinkage (radiographic) or “progression free survival”, i.e., time to (usually) radiographic progression
  - 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

Regulatory Acceptance of Surrogate Endpoints

Current Use of Surrogates

- About 45% of all new drug approvals use surrogate EP’s (depending on definition)
- Most are not accelerated approvals
- Novel surrogates most frequently used in rare disease settings
- Some of the accelerated approval surrogates may “graduate” over time to “validated” surrogates
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., accelerated approval for HIV) acceptance driven by crisis
- Accelerated approval standard (“reasonably likely) needs to be articulated
- Current Congressional interest in this topic

“Validation” of Biomarkers (e.g., for use as “full” Surrogate)

**BIOLOGICAL PLAUSIBILITY**

- EPIDEMIOLOGIC 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 “full” 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

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: antiarrhythmics for prevention of sudden death
    - Surrogate: suppression of VBP’s
    - Mortality increased in treatment arms


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

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

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
- Similar scenario currently ongoing for chronic HCV

Surrogate Endpoint Use: 2000s

- Controversy over use of glycemic control (Hgb A1c) 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. Recently completed outcome trial reported improvement in CV outcomes.
- FDA continues to accept surrogates in rare diseases and in cancer, as well as LDL cholesterol and HgbA1c

How Likely are New Surrogates?

- Clearly, need robust pipeline of new biomarkers 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 acceptance criteria and how longer term safety evaluation would be performed
Questions about biomarker evidence depends on the setting

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

- Important public health need for development of biomarkers to target and monitor therapy to improve the outcomes of drug treatment (precision medicine)
- This requires development of evidence about the performance of the test, as well as use in clinical trials during drug development
- Use of response biomarkers for targeted therapy is rising rapidly and fueling success in some diseases (e.g., many cancers)

Summary

- Definitions for biomarkers, clinical outcomes and surrogate endpoints have been developed and published
- FDA has established a process to assist in evaluation and development of biomarkers used in drug development
- A rigorous evidence-development process is essential to the future of "targeted" or "personalized" medicine