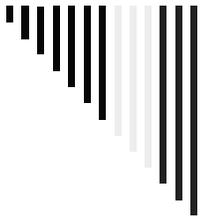




Biomarkers: Physiological & Laboratory Markers of Drug Effect

Janet Woodcock, M.D.
Director, Center for Drug
Evaluation and Research
Food and Drug Administration
February 4, 2010



Why Are Biomarkers Important?

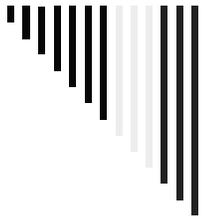
- Diagnosis is the foundation of therapy
 - Biomarkers are quantitative measures that allow us to diagnose and assess the disease process and monitor response to treatment
 - Biomarkers are also crucial to efficient medical product development
 - As a consequence of scientific, economic and regulatory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

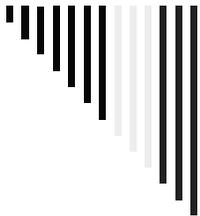


Biomarkers Have Many Uses in Medicine

- Markers of drug effect or response (laboratory, physiological, or other) are a subset of the general class of biomarkers
- Other biomarkers may include diagnostic, prognostic or physiologic status information not linked to drug response

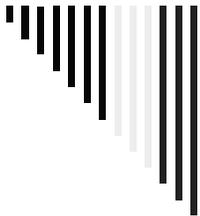


BIOMARKERS AND CLINICAL ENDPOINTS IN DRUG TRIALS: DEFINITIONS



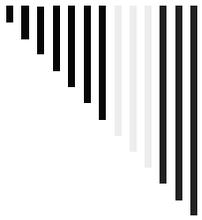
Clinical Endpoint Definition

- “A characteristic or variable that reflects how a patient feels, functions or survives”
 - Clinical endpoints 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
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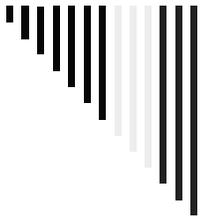
SURROGATE MARKER

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

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



BIOMARKERS IN DRUG DEVELOPMENT



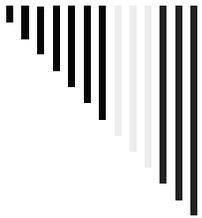
Use of Biomarkers in Early Drug Development and Decision Making

- 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 pharmacokinetics
 - Pharmacodynamic (efficacy) biomarkers:
 - Blood glucose
 - Urine, sputum, etc cultures
 - Pulmonary function tests
-



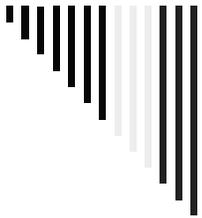
Use of Biomarkers in Later Drug Development and Decision Making

- 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
-



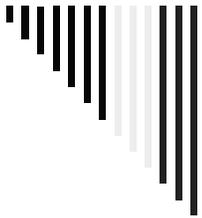
Biomarkers and Personalized Medicine

- 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
-



Use of Surrogate Endpoints in Late 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
 - 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
 - “Non-Validated Surrogates” used for accelerated approval
 - HIV copy number
 - Tumor shrinkage
-



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**

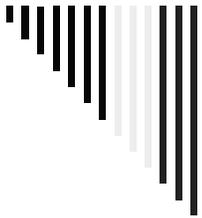


Use of Biomarkers in Clinical Practice

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

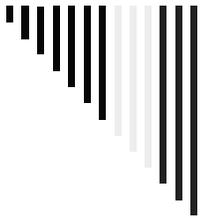


DEVELOPMENT AND QUALIFICATION OF BIOMARKERS



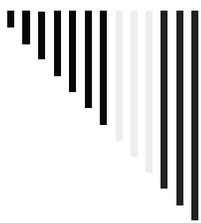
Fate of Most Candidate Biomarkers

- 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)
-



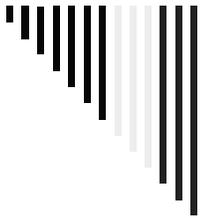
Future of Drug Development and Biomarker Development Tightly Linked

- 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
-



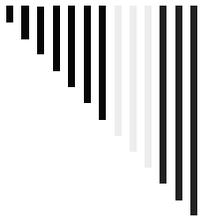
Stimulating the Use of Biomarkers in Drug Development

- 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
-



Developing Biomarkers for Use in Drug Trials: a New Model

- Idea of “qualification”:
 - Develop the evidence needed for a specific use: demonstrate “fitness for use”
 - Make evidence public
 - Process to submit evidence to regulatory agencies
 - Agencies review and, if indicated, publish findings of acceptance
-



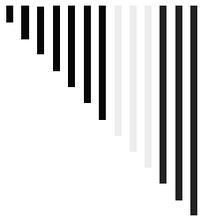
Stimulating the Robust Use of Biomarkers in Drug Development

- Implement new biomarker use throughout preclinical and clinical development
 - “Qualify” biomarker for intended use: less focus on surrogate endpoints
 - Goal is understanding mechanistic bases for individual response to therapy to increase *informativeness* of development process
 - Achieve more predictable drug development and therapeutic outcomes
-



Barriers to Progress

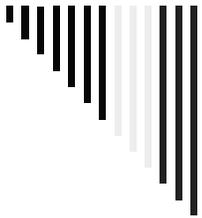
- Evidence development expensive: business model for diagnostic companies not compatible
 - Frequently need multiple assays using many compounds/preclinical or clinical settings
 - Science not considered as “innovative” as basic discovery
-



Promising Safety Biomarkers

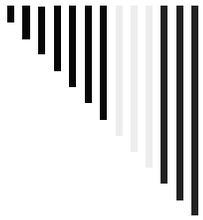
- Drug Metabolizing enzyme status
 - 6-Mercaptopurine: enzyme TPMT
 - “Strattera”: enzyme CYP 2D6
 - Irinotecan: enzyme UGT1A1
 - Warfarin: enzyme CYP 2C9; pharmacodynamic biomarker VKORC1-- safety and efficacy

 - 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
-



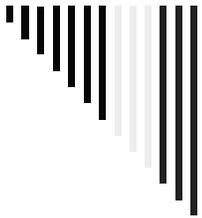
Potential Imaging Biomarkers

- 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
-



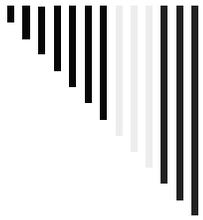
Potential Genomic Efficacy Biomarkers

- 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 (Erbix, Vectibix) to treat colon cancer (Dec 16, 2008); label change to restrict treatment to individuals without mutated k-RAS
-



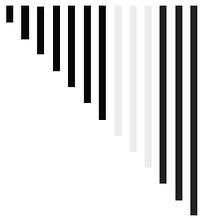
Biomarker Development Consortia

- 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
-



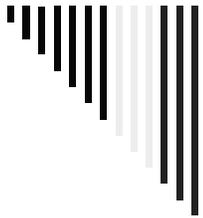
Predictive Safety Testing Consortium

- 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
 - FDA and EMEA have accepted for use in animal studies
-



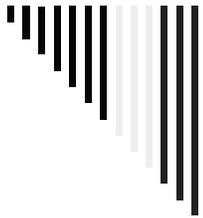
Other Biomarker Consortia

- 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
-



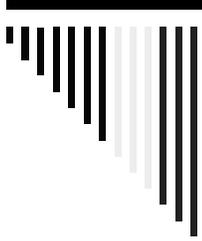
Why Use Consortia for Biomarker Qualification?

- 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
-

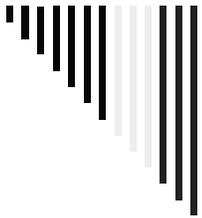


Regulatory Qualification of Biomarkers

- Until recently, regulators basically waited until a new biomarker was widely accepted in clinical practice and had a robust evidence base
 - Unfortunately, this can take decades
 - FDA has established a process whereby qualification packages can be submitted and reviewed for regulatory acceptance
 - Process guidance will be issued soon
-

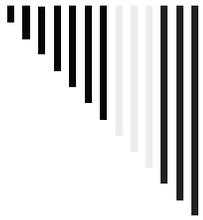


REGULATORY ACCEPTANCE OF SURROGATE ENDPOINTS



How are New Surrogate Endpoints Accepted 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
-



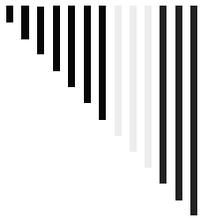
HIERARCHY OF BIOMARKERS *(Classic view)

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

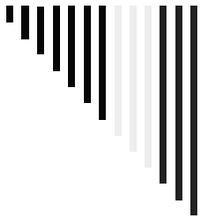
BIOLOGICAL PLAUSIBILITY

- **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 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.



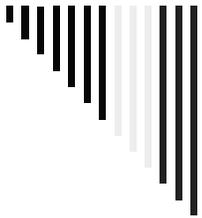
History of Surrogate Endpoint Use

- 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: antiarrhythmics 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
-



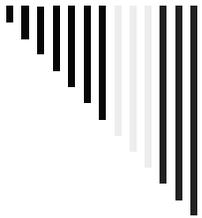
Surrogate Endpoint Development: 1990s

- 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*

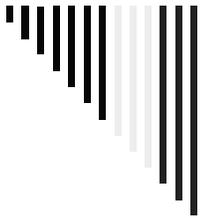
- No surrogate EP has ever met these criteria

*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
-



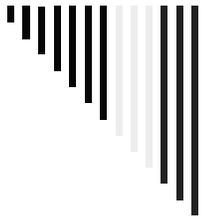
Surrogate Endpoint Use: 2000s

- 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
-



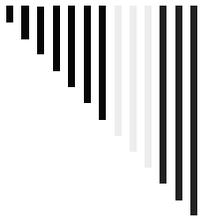
Fundamental Problems with the Current Conceptual Framework for Surrogate Endpoints

- 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!
-



Fundamental Problems with Current Conceptual Framework for Surrogate Endpoint Development

- Patient outcomes are multidimensional—a single outcome measure (whether clinical or surrogate endpoint) can miss domains of interest.
 - Very difficult to capture both benefit and harm within a single measure—very unlikely for a biomarker.
 - The concept of “ultimate clinical outcome” includes parameters such as duration of observation that are important dimensions. However, knowledge about these dimensions could be acquired outside of the biomarker measurement
-



Additional Problems with Surrogate Endpoint Framework

- Per-patient view of outcomes very different from population mean view of outcomes.

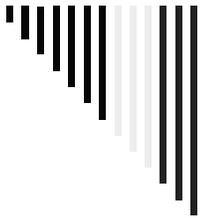
 - For example, “ultimate” benefit in survival of 8% over placebo not meaningful to you if you are not in the 8% who actually respond

 - Newer (and older, e.g., metabolizing enzymes) biomarkers provide information at the individual level
-



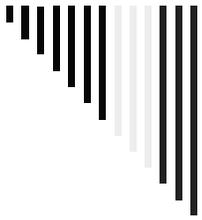
How Likely are New Surrogates?

- 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
-



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
 - Single measurements will rarely capture all dimensions of clinical outcomes
-



Summary

- FDA is developing these concepts as part of its “Critical Path” Initiative.
 - Development will include process for refining general framework as well as individual projects on biomarker and surrogate endpoint development
-