

Biomarker Validation: Why, which, and how?

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Biomarker Validation: Why?

Internal Industry decision making:

- Dose justification
 - Safety
 - Efficacy
- Decision to promote/ kill a compound in development (pipeline)

Regulatory Decision making

- Use of biomarkers for MAA or NDA
 - Improving delivery of new drugs to patients
 - Optimizing drug development

Why?

TITLE 21, PART 314, SUBPART H

Sec. 314.510 approval based on a **surrogate endpoint** or on an effect on a clinical endpoint other than survival or irreversible morbidity

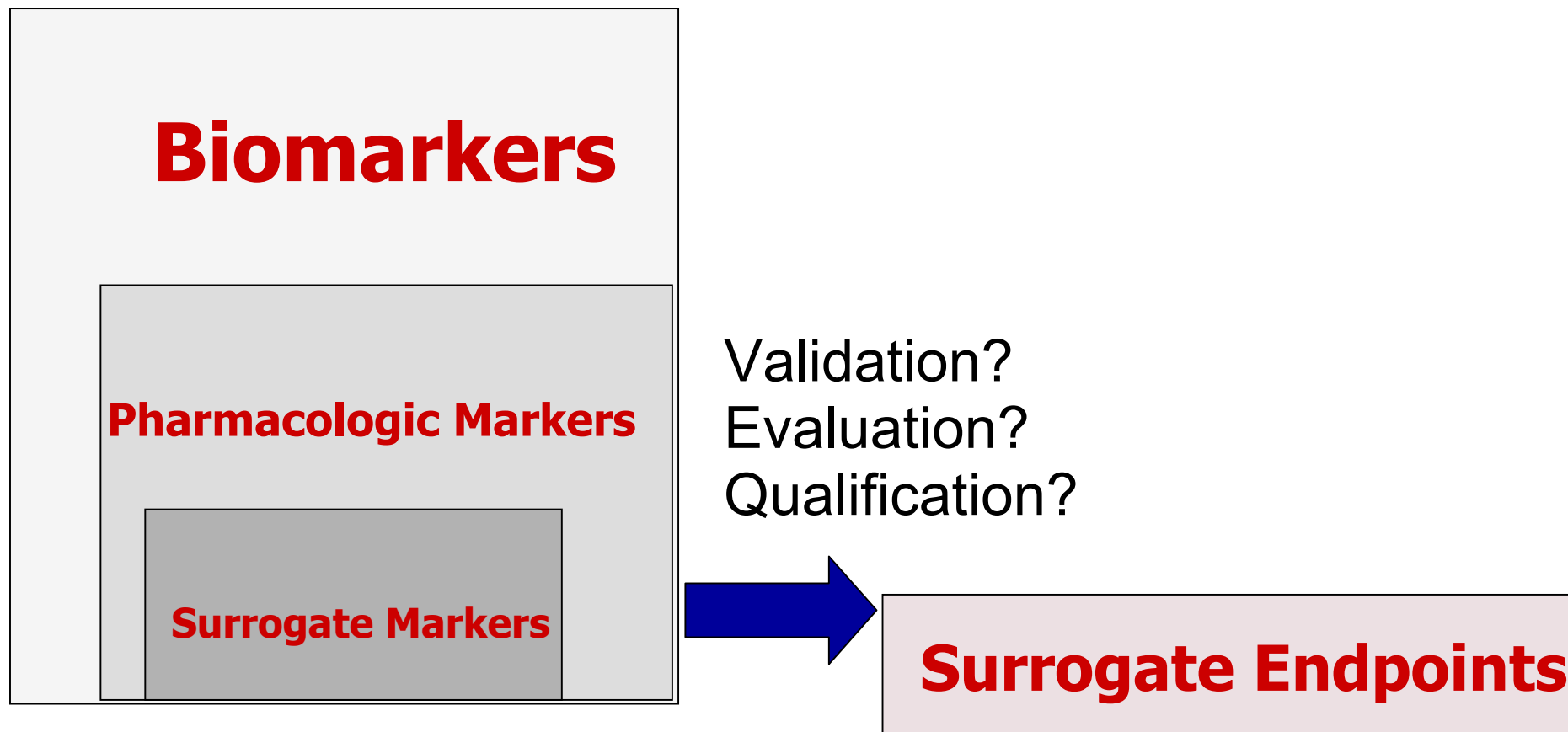
“FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a **surrogate endpoint** that is reasonably likely ... to predict clinical benefit...”

Biomarker Validation

Which?

- Marker must be consistent with pathophysiology /biologic plausability
- Epidemiologic evidence that biomarker is a risk factor
- Should be a prognostic biomarker
- Biomarker must be on intervention pathway
- Changes in marker reflect changes in prognosis
- Effects of treatments on the biomarker should explain/be associated with effects of treatments on the clinical endpoint
- Effect on biomarker has predicted outcome with other drugs of same pharmacologic class
- Effect on biomarker has predicted outcome for drugs in several pharmacologic classes

Terminology?



Surrogate Endpoint

A surrogate endpoint of a clinical trial is a laboratory measurement or a physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions or survives. Changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint.

Robert J. Temple

Director of the Office of Medical
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Uncertainty of performance of individual biomarkers

Is 'Validation' the key?

Validating a Surrogate Endpoint How?

- Effects of treatments on the biomarker should explain/be associated with effects of treatments on the clinical endpoint
- Effect on biomarker has predicted outcome with other drugs of same pharmacologic class
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Test prediction across trials?

Statistics?

Prentice, R.L. 1989 *Stat Med* **8**, 431-40.

Katz, R. 2004 *J American Soc. Exp. NeuroTher* **1**, 189-195.

Boissel, J.P. et al. 1992 *Eur. J Clin Pharm.* **43**, 235 – 244.

Lesko, L. & Atkinson, A. 2001 *Annu. Rev Pharmacol Toxicol* **41**, 347 – 366.

Williams, S.A. et al 2006 *Nat. Rev. Drug Discovery* **5**, 897-902.

Statistical Principles -- Evidence for Surrogacy

ICH Guidance E9 – 1998 Statistical Principles for Clinical Trials

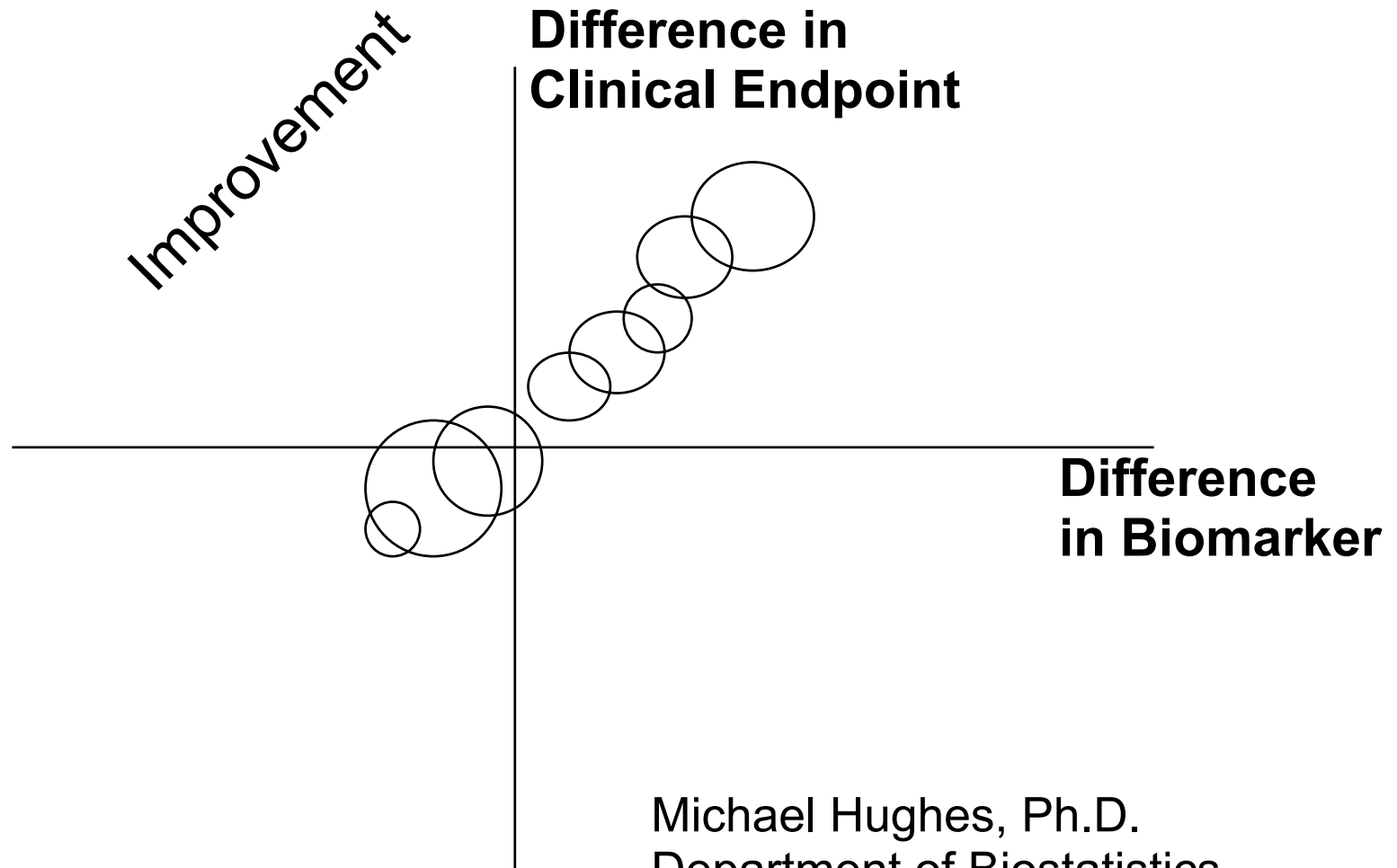
- Discussion of ‘Surrogate Variables’

“First, it may not be a true predictor of the clinical outcome of interest.”

Strength of the Evidence for Surrogacy depends upon

- Biological plausibility of the relationship
- Demonstration in epidemiological studies of the prognostic value of the surrogate for clinical outcome
- Evidence from clinical trials that treatment effects on the surrogate correspond to effects on the clinical outcome

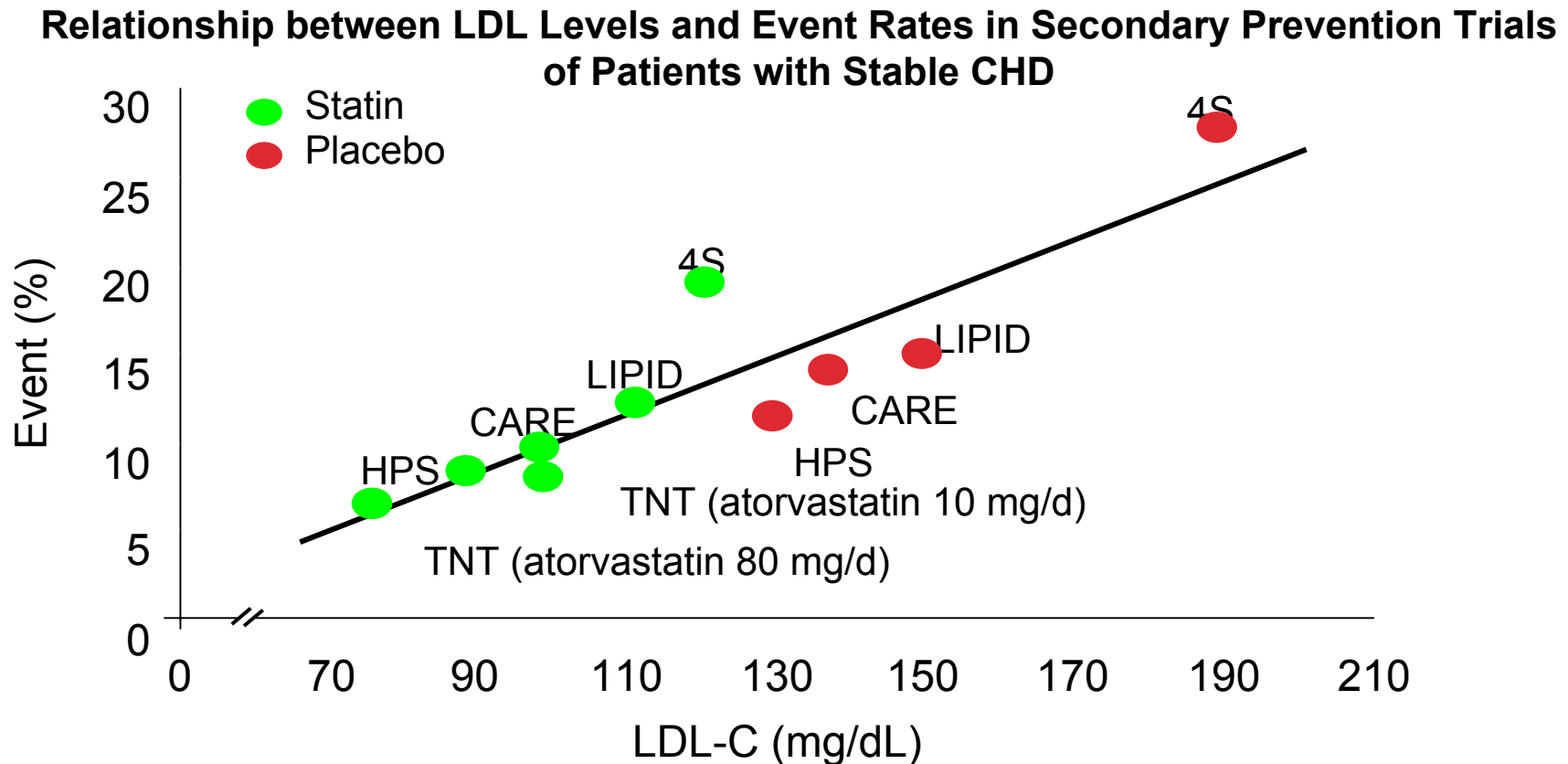
Validating a Surrogate Endpoint



Michael Hughes, Ph.D.
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HMG-CoA Reductase Inhibitor: Secondary Prevention

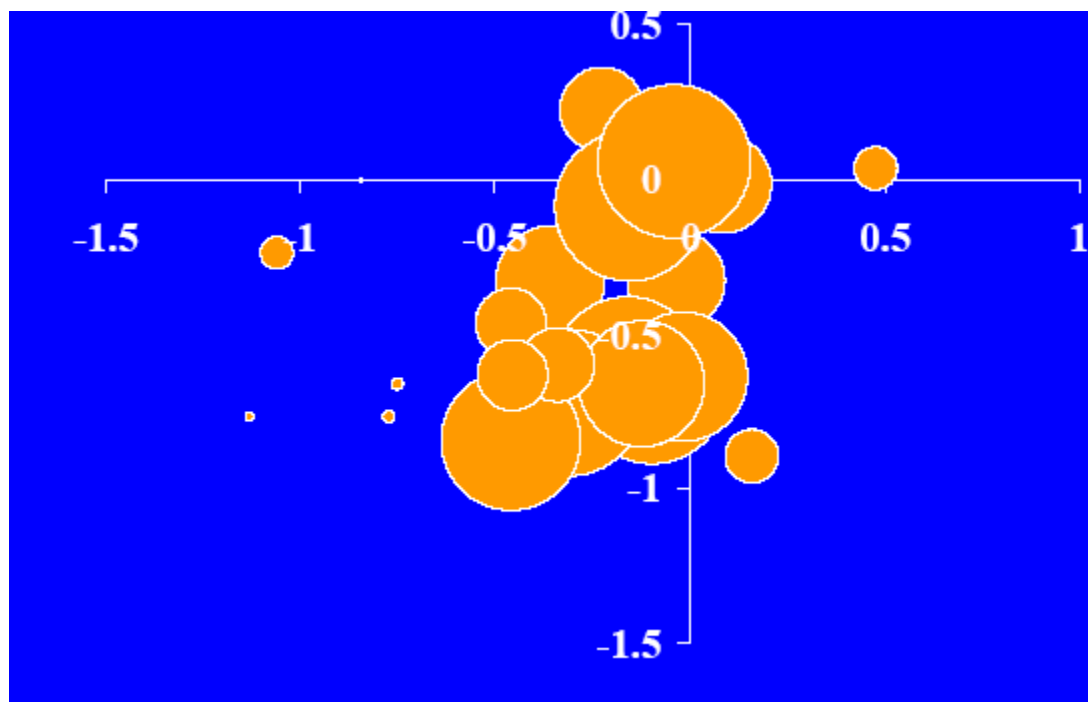
LaRosa JC et al. *NEJM*. 2005;352:1425-1435



LDL-C=Low density lipoprotein cholesterol; TNT=Treating to New Targets; HPS=Heart Protection Study; CARE=Cholesterol and Recurrent Events Trial; LIPID=Long-term Intervention with Pravastatin in Ischaemic Disease; 4S=Scandinavian Simvastatin Survival Study.

Validating a Surrogate Endpoint

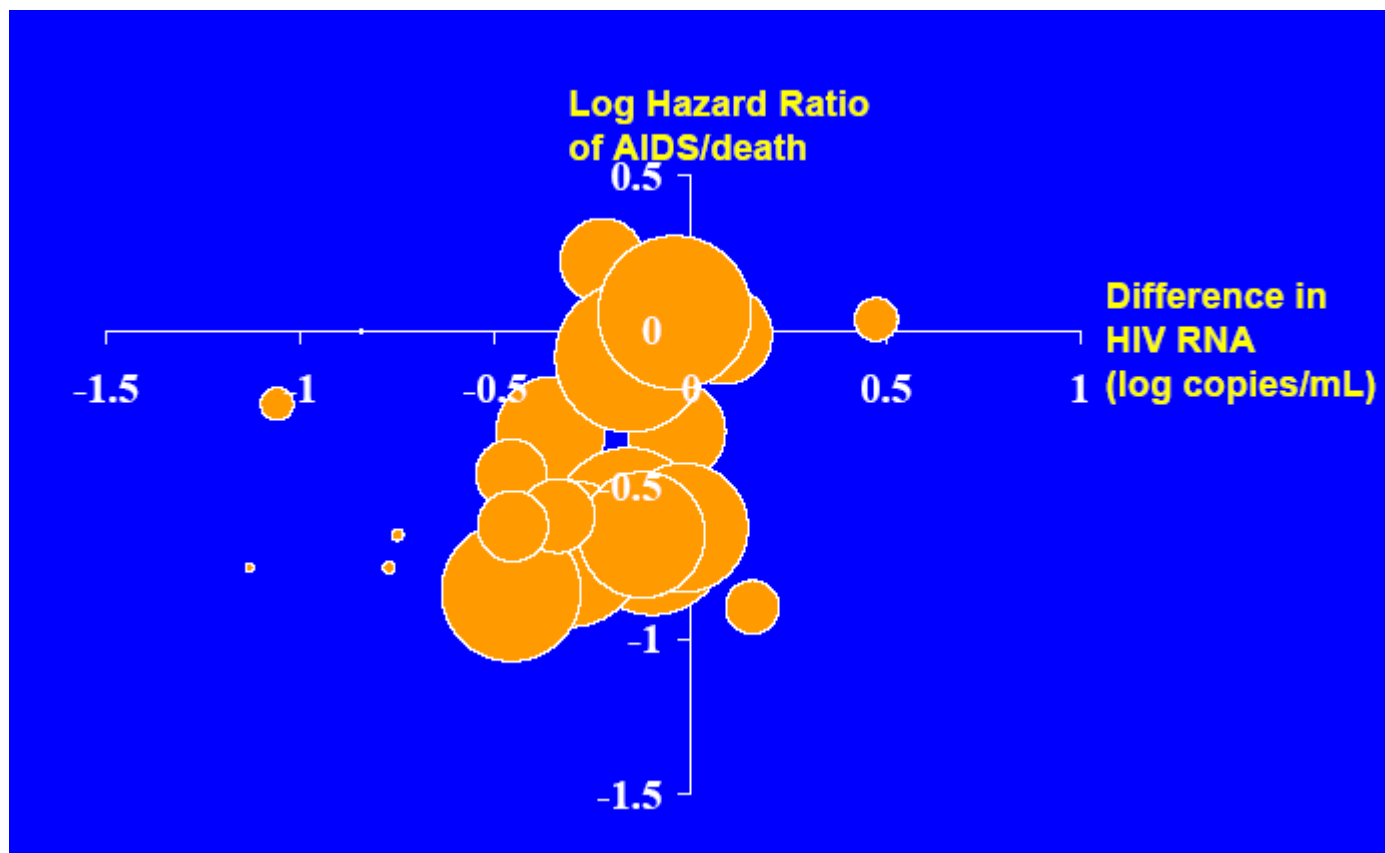
**Difference in
Clinical Endpoint**



**Difference
in Biomarker**

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Validating a Surrogate Endpoint



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Disadvantages of Surrogate Endpoints or Biomarkers: You never really know?

Biomarkers/ Surrogate Endpoints may not be 'true' predictor of clinical outcome

- Biomarker effect may explain only a small part of observed reduction of risk
- Biomarkers must be 'fit to purpose'

Biomarkers/ Surrogate Endpoints relationship may vary between drug classes

- Heterogeneity of treatment effect

Biomarkers/ Surrogate Endpoints may not yield quantitative measure of clinical benefit

“There is no ‘surrogate’ for safety...”

‘Validation’

The term validation is widely applied to biomarker performance characteristics.

There is no clear line of demarcation as to when a biomarker becomes *‘validated.’*

How much of the observed outcome must be explained by the biomarker response ($r^2 = .99, .95$) in order for it to be validated?

In science there is no 100% certainty, there are only data which support (or refute) a hypothesis with probabilities approaching 100% (usually 95%).

The process of validation (acceptance of surrogate endpoint) is currently highly dependent on subjectivity.

‘Validation’

Validation --a progressively increasing degree of certainty.

When is this certainty reached?

Is it ‘I know it when I see it’?

‘Validation’

Validation --a progressively increasing degree of certainty balanced against risk.

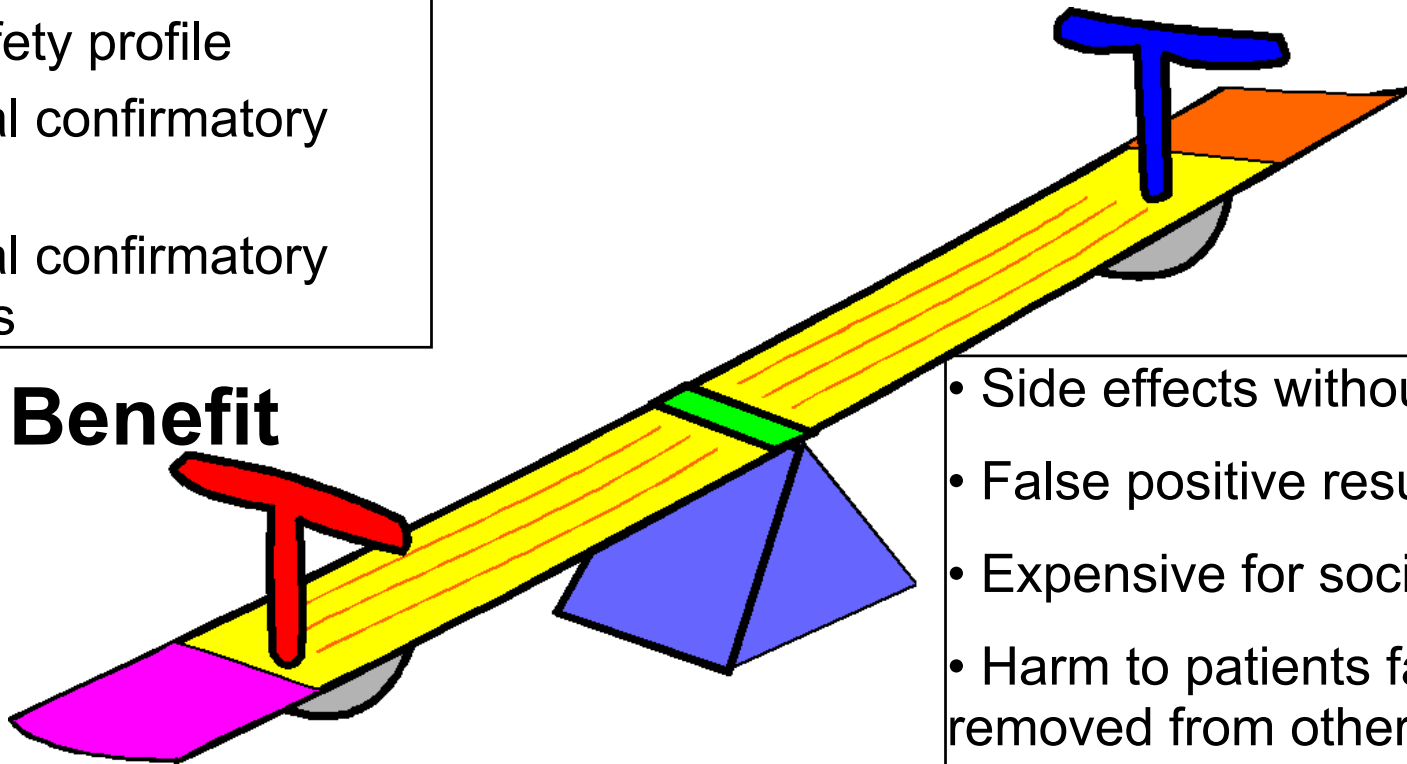
The degree of certainty needed depends on many factors, e.g. the product, the therapeutic context, and risks (or perceived risks) of validation (or failure to accept validation).

Progression to Surrogate Endpoint (Validation) must contain risk:benefit

Risk

- Unmet medical need
- Good safety profile
- Additional confirmatory studies
- Additional confirmatory biomarkers

Benefit



- Side effects without benefit
- False positive result
- Expensive for society
- Harm to patients falsely removed from other effective treatment

Additional Support For Biomarkers*

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.**

Biomarker Validation

- Validation is a continually ongoing, iterative, process by which one improves understanding of biomarker characteristics through experimental study.
- A priori determination of what evidence is necessary to provide a 'high degree of assurance' while balancing risks.
 - Several approaches might be taken to address subjectivity among shareholders:
 - Benefit:Risk assessment modelling
 - Cost-effectiveness approach
 - Must occur through collaborative working between Agencies, Industry and Academia, progressing towards a global approach.

Quantitative Benefit-Risk assessment

Quantitative benefit-risk assessment could be applied to biomarker validation

- Quantitative benefit-risk assessment could employ a standardized, quantitative and transparent process for the evaluation of biomarker performance
- Quantitative benefit-risk assessment is currently being developed as an informed discussion generation tool for drug review and interpretation of safety and efficacy data.
- Biomarker validation would also benefit from quantitative, model based, evaluation.

The greatest value of a mathematical model is the critical examination of data and assumptions.

Cost-effectiveness approach

Qualification of biomarkers in terms of cost-effectiveness

- Monetary cost is assigned to harm (*i.e.* quality-adjusted life years)
- Consequences of each type of false result (false-positives and false-negatives) is converted to financial units.
- Balance of decision is made within the framework of biomarker qualification 'Principles of Good Practice'¹.

¹ Williams, S.A. et al 2006 *Nat. Rev. Drug Discovery* **5**, 897-902.

Conclusions

- Biomarkers validation is only meaningful in context
 - There is no clear line of demarcation as to when a biomarker becomes 'validated.'
- Progression to Surrogate Endpoint (Validation) must contain risk: benefit
 - Standardized, quantitative and transparent process for the qualification of biomarker to a surrogate endpoint through quantitative benefit-risk assessment or a cost-effectiveness approach.
- Biomarker validation to surrogate endpoints is difficult
 - Will only be possible through collaborative working between Agencies, Industry and Academia, progressing towards a global approach.