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# **Biomarkers and Surrogates**

## ***Appraising Persuasiveness***

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*The views expressed are those of the author, and do not necessarily represent an official FDA position*

# Roles for Response Biomarkers

i.e., Pharmacodynamic Biomarkers

- Proof of concept studies
- Dose ranging studies
- Predictive characteristic identification
- Short-term responsive patient identification
- Supportive evidence
- Evidence of effectiveness
  - ❖ Surrogate endpoint

# Surrogate Endpoint

- Stands in place of an effectiveness endpoint
  - Feels
  - Functions
  - Survives
- Usually intended to temporally predict a clinically meaningful outcome
  - Assumptions about future clinical course after initiation of drug treatment

# Feels and Functions as Effectiveness

- Feels
  - A patient's physical sensation or perceived mental state related to health within typical 'daily' life
  - Pain
  - Severely low mood (depression)
- Functions
  - A patient's ability to perform an activity that is a meaningful part of typical 'daily' life
  - Not isolated physiologic processes (eg liver metabolism)
  - Not ability to perform actions not part of usual life

# Surrogate Endpoint

- Fully justified – conventional approval
- Reasonably likely to predict – accelerated approval
- Disadvantage
  - Temporal shortening of studies limits safety data
  - Off-target adverse effects may be difficult to discern

# Issues for Evaluation

- Disease related
  - Do we know the underlying primary cause?
  - How well do we understand the complete pathophysiologic process from primary cause to meaningful clinical outcome?
    - ❖ How detailed is the knowledge?
    - ❖ How strongly do we believe our “knowledge” (interpretation of scientific observations) is complete and correct?

# Issues for Evaluation – Biomarker Focused

- What clinical outcome is it expected to predict?
- When is the clinical outcome expected?
  - Relative to the measurement of the biomarker
- What is the physiologic concept thought to indicate efficacy?
- How should that concept be measured?
  - The biomarker is the measurement
- Is the biomarker in the direct pathophysiologic pathway leading to that clinical outcome?
  - Versus a side branch

# Issues for Evaluation – Biomarker Focus

- Is it in a unitary part of the pathophysiologic pathway leading to the clinical outcome?
  - Versus in one of several parallel pathologic pathways
- Do we know the anatomic location where the biomarker functions in the disease process?
- Is the biomarker being sampled at the site where it functions in the pathophysiology?
  - If not, how do measurements at the site of sampling relate to effects at the site of function?
- What is the shape of the biomarker – clinical outcome relationship?
  - Major question – For further discussion

# Drug-related Issues for Evaluation

- How certain are we of the mechanism of drug action?
- Where in the pathophysiology sequence does the drug act?
  - Relationship to biomarker's location in the pathophysiology
- What is known about the time course relationship of drug administration (or readministration) and effects on the biomarker?
  - When should the biomarker be sampled?
- What are the assumptions about drug effect over time between biomarker sampling and clinical outcome?

# Potential Sources of Information

- Clinical trials of specific drug candidate
  - Biomarker – Clinical relationship
- Clinical trials of other interventions
  - Same or different mechanism
- Understanding of disease pathophysiology and clinical course
- Understanding of normal human physiology
- Information from related diseases
- Animal models of the disease
  - Pathophysiology
  - Biomarker relationship
  - Treatment effects on biomarker and clinical

# Strength of Surrogate

- Answers to some of these questions are not quantitative
  - Quantitative data valuable where possible
  - Statistics on quantitative data informative
  - Statistical robustness of data strengthens conclusions
- Evaluations are reasoned, not calculated
- Judging the knowledge
  - Is the totality of the information persuasive?
  - Judgment is integral

# Illustrative Examples

- Acute MI
  - Arterial blood flow
- Alpha1-antitrypsin Deficiency
  - Enzyme Levels
- Phenylketonuria
  - Phe blood level
- Fabry Disease
  - Renal capillary endothelial histology
- MPS 1
  - Urinary GAG

# Acute MI

- Clinical outcome is mortality
- Intravenous thrombolytic agent is the treatment
- Biomarker is the concept of blood flow (patency)
  - How and when is blood flow evaluated?
- Development of reteplase (R-PA)
- RAPID-2 Study
  - Evaluated biomarker
- GUSTO-III Study
  - Evaluated clinical outcome

# Acute MI

## RAPID 2

	TIMI 3 - %		TIMI 2&3 - %	
	60 min	90min	60min	90min
R-PA	<b>51</b>	<b>60</b>	<b>82</b>	<b>83</b>
T-PA	37	45	66	73

- R-PA superior to T-PA
  - Irrespective of which amount or when the concept of blood flow is assessed

# Acute MI

## RAPID 2

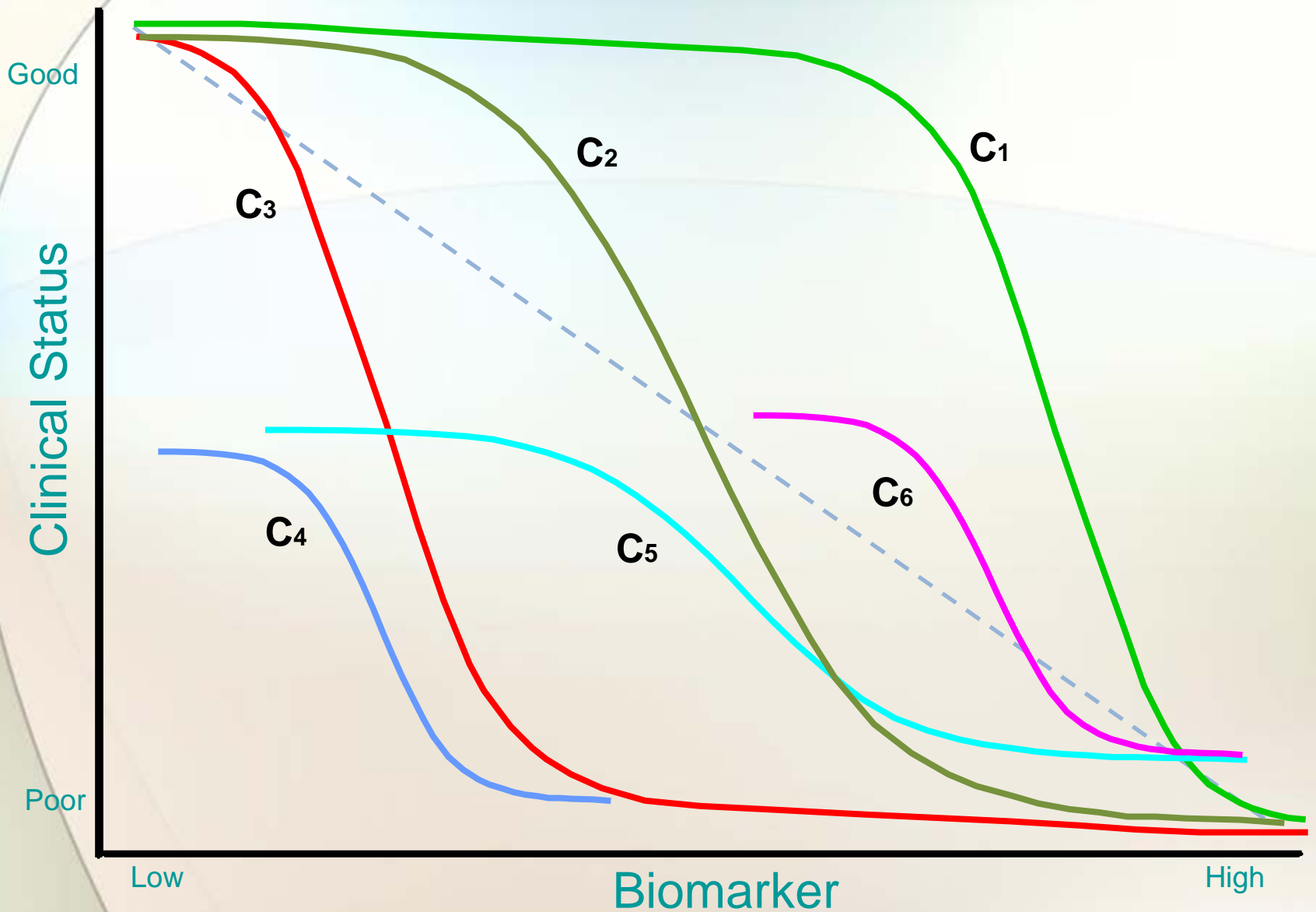
	TIMI 3 - %		TIMI 2&3 - %		30 min	
	60 min	90min	60min	90min	TIMI3	TIMI2&3
R-PA	<b>51</b>	<b>60</b>	<b>82</b>	<b>83</b>	27	<b>67</b>
T-PA	37	45	66	73	<b>39</b>	<b>66</b>

## GUSTO-III

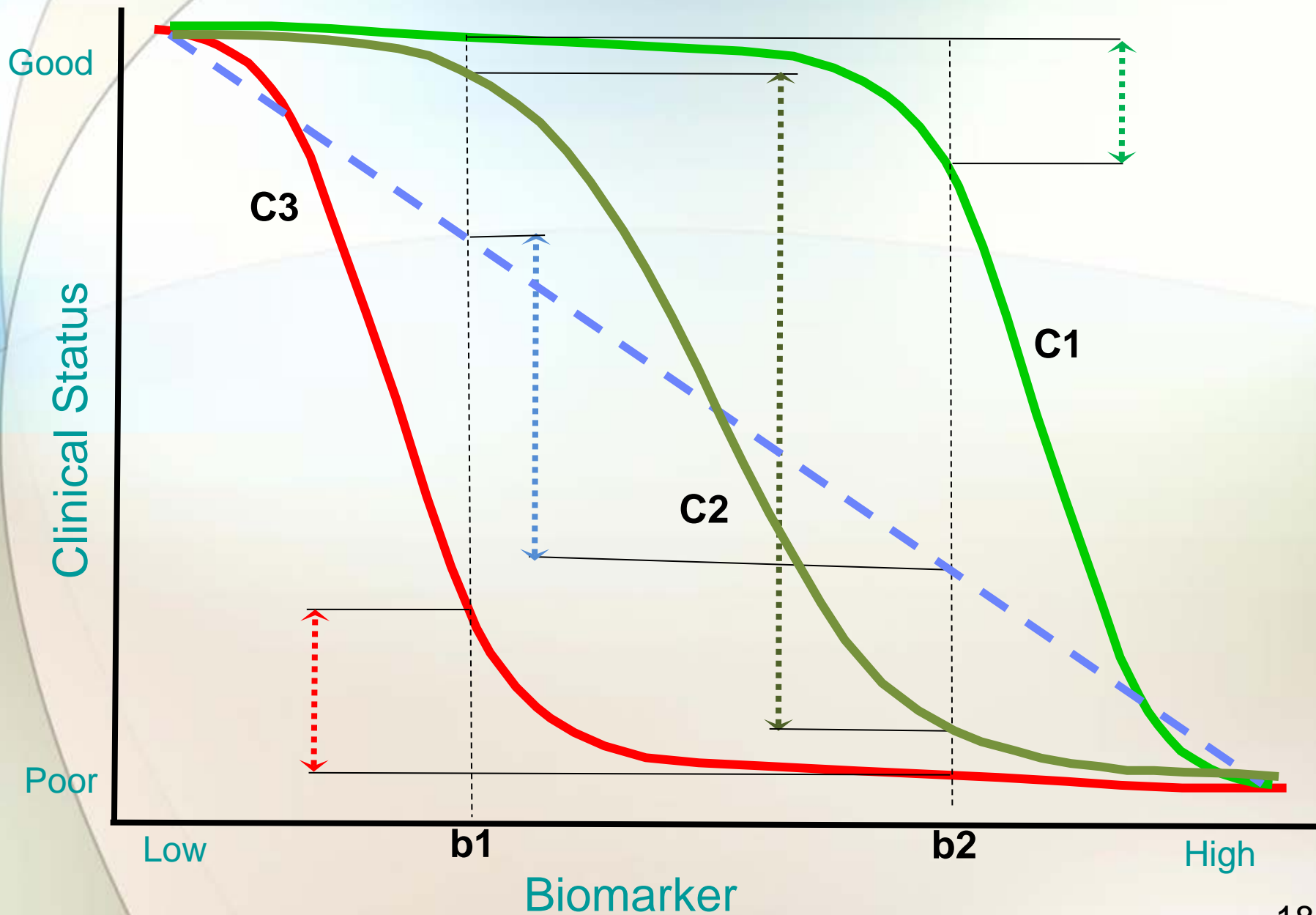
R-PA	7.5	Mortality %
T-PA	<b>7.2</b>	

- Concept indicating efficacy is blood flow
  - How and When should it be measured?
  - What is the shape of the relationship?

# Clinical – Biomarker Relationship



# Clinical Effects of Biomarker Change



# Alpha-1 Antitrypsin Deficiency

- Monogenic, autosomal recessive disorder
  - *SERPINA1* gene; Alpha-1 antitrypsin protein
- Approval based on surrogate of serum concentration during treatment
- Protein predominantly made in liver
- Distributed to body via bloodstream
- Protects the lung tissue from proteolytic damage
  - Protein within the interstitial space, alveolar surface
- Predominant clinical manifestation is emphysema
- Treatment is IV infusion of human Alpha-1 antitrypsin
  - Replacement of missing protein

# Alpha-1 Antitrypsin Deficiency

- Basis of disease known
  - Physiology well understood
- Pathophysiology mostly well understood
  - Some uncertainties in pathophysiology AFTER point of treatment intervention and biomarker measurement
- Treatment mechanism well understood in relation to pathophysiology

# Alpha-1 Antitrypsin Deficiency

- Biomarker directly in pathophysiologic process
- Shape of Biomarker-Clinical relationship poorly understood overall
  - Adequately understood in a subset of patients in a narrow biomarker range
- Important aspects
  - Narrow population
    - ❖ Only those with emphysema
  - Efficacious serum level identified
    - ❖ Only for the identified population
    - ❖ Via comparison to natural history of intermediate deficiency patients

# Phenylketonuria

- Monogenic, autosomal recessive disorder
  - PAH gene, phenylalanine hydroxylase protein
- Approval based on surrogate of decreased blood Phe levels
- Protein predominantly made in liver, stays in liver
  - Liver transforms Phe into tyrosine
- Phe is an essential amino acid
  - Phe enters blood stream from GI system
  - Phe removed from blood stream by liver
  - Phe distributed to body via bloodstream

# Phenylketonuria

- Chief clinical manifestation is CNS toxicity
  - Phe exposure is through bloodstream
- Primary treatment is dietary restriction
  - Difficulty leads to inadequate control in some patients
- Pathophysiology largely well understood
  - Some uncertainties in pathophysiology AFTER point of biomarker measurement

# Phenylketonuria

- New treatment is tetrahydrobiopterin (BH4)
  - BH4 is cofactor for PAH enzyme
  - Expected to increase endogenous PAH activity when small, but not absent, amount of residual enzyme activity
- Important aspects
  - Narrow population
    - ❖ Only those with response to trial of therapy
    - ❖ Only those with inadequate control by diet
  - Phe levels considered efficacious based on historical experience with inadequately controlled patients

# Fabry Disease

- Monogenic, X-linked recessive disorder
  - GLA gene,  $\alpha$ -galactosidase A protein deficiency
- Accelerated Approval based on surrogate of capillary endothelium deposits of GL3
- Intracellular enzyme
  - Made & used in many tissues and cell types
- Lysosomal storage disorder of substrate GL3 in multiple locations
  - Including blood vessel endothelium & walls
- Most serious manifestations due to small arterial blood vessel occlusion
  - Infarcts in kidney, brain, cardiac

# Fabry Disease

- Early steps in pathophysiology well understood
  - Uncertainties in successive portion of pathway
    - ❖ Relative sources of GL3 for different tissues
    - ❖ Final trigger for clinical vascular occlusive events
- Treatment is IV  $\alpha$ -galactosidase A
  - Intended to be taken up by multiple cell types
    - ❖ Into lysosomes
  - Decrease GL3 accumulation

# Fabry Disease

- Notable uncertainties related to biomarker interpretation
- Infarcts are from small blood vessel injury, not capillary events
  - But endothelium of capillaries and small arterioles similar, exposed to same blood contents
  - Renal capillaries measured; likely similar for brain and cardiac capillaries
  - Biomarker in renal tissue; kidney injury is a major manifestation
- Shape of biomarker- clinical outcome relationship ill defined

# Fabry Disease

- Large magnitude and extent of biomarker effect
- Patient designated good outcome if:
  - At least 95% of capillaries with no or trace GL3
  - At least 50% with none
- Untreated state shows nearly all capillaries with substantial GL3 deposits
- Biomarker results
  - Most treated patients had good biomarker outcome
  - No untreated patients had good biomarker

# Mucopolysaccharidosis I

- Monogenic, autosomal recessive lysosomal storage disorder
  - Alpha-L-iduronidase (IDU) deficiency
- Biomarker considered – urine GAG level
- Lysosomal enzyme, glycosaminoglycans (GAGs) are substrate
- Range of severity, partly related to residual IDU activity
- Multiple organs affected
  - Hurler form: cardiopulmonary function severely impaired (multiple causes), connective tissue injury with restricted movement of limbs, skeletal deformities

# Mucopolysaccharidosis I

- Primary cause of disease understood
- Early steps in pathophysiology understood
  - Uncertainties in successive steps with variability of clinical course
- Treatment is IV infusion of IDU enzyme
  - Intended to be taken up from circulation into lysosomes throughout body
  - Decrease GAG storage and cellular injury from GAG overload
- Uncertainties related to biomarker

# Mucopolysaccharidosis I

- Renal impairment not a prominent manifestation
  - Urine biomarker does not relate to renal impairment
- Shape of urine GAG – tissue storage relationship poorly known
  - Unknown if relationship same for all tissues or different tissue by tissue
- Which clinical manifestations mostly closely related to urine GAG unknown
- Reduced urine GAG excretion has disease-specific GAG levels still substantially higher than in normal subjects
- Product approved based on clinical assessments

# Accelerated Approval

- Should be a goal only after careful thought
- Requires plan to verify clinical benefit
  - Difficulty of verification may be increased in rare diseases
- Mistaken belief in efficacy has disadvantages
  - Patient burden from treatment without benefit
    - ❖ Effort, 'side effects' (common AE), cost
  - Safety risk without benefit
  - May be impediment to develop a second treatment, which might be truly efficacious