



## Disclaimer:

Presentation slides from the Rare Disease Workshop Series are posted by the EveryLife Foundation for Rare Diseases for educational purposes only. They are for use by drug development professionals and statisticians, and are not to be used to guide the prescribing or use of any of the drugs mentioned in the slides. To obtain information on a particular drug, refer to the drug labeling. Do not reproduce or distribute the slides (full set or any portion of) without the permission of the author.

# Rare Disease Workshop Series

---

## Replacement (Surrogate) Endpoints in Clinical Development

November 8, 2011

Thomas R. Fleming, Ph.D.

*Professor of Biostatistics  
University of Washington*

*t Fleming@u.washington.com*

\* IOM, 2010. *“Evaluation of Biomarkers & Surrogate Endpoints in Chronic Disease:.”* Washington DC. National Academies Press

# Some Characteristics for Study Endpoints in Clinical Trials

---

- Well defined & reliable
- Sensitive
- Clinically meaningful

A “Clinically Meaningful Endpoint”:

...a direct measure of how a patient

“functions, feels or survives”...

... Robert Temple, FDA

# Clinically Meaningful Endpoints in Phenylketonuria:

---

- *Overall Clinical Efficacy*
  - ~ **Functions:** Ability to conduct normal activities
    - School difficulties: special ed, req'd tutoring, repeated classes
    - Work difficulties: job losses, poor work attendance, inadequate comprehension of instructions, lack of attention
  - ~ **Feels:**
    - Emotional instability: angry outbursts, unstable relationships, forgetfulness, inconsistent behavior, poor \$ management
    - Loneliness, poor social relationships, anxiety, depression
  - ~ **Survives**
    - ...Physician or Observer administered & PROs...

# Potential Clinically Meaningful Endpoints

---

## Patient Reported Outcomes:

*“Any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else”.*

- \* FDA Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. (December , 2009)

# Potential Clinically Meaningful Endpoints

---

- Patient Reported Outcomes:
  - ... Clinically Meaningful Endpoints, but with need to confirm:
    - Reliability, Sensitivity, Validity (Content, Construct, etc)
    - Clinical Relevance, Interpretability
    - Integrity, including need for:
      - blinded assessment, control of missing data,  
and adjustment for multiplicity
- \* FDA Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. (December , 2009)

# Biomarkers & Clinically Meaningful Endpoints in Phenylketonuria:

---

- *Biological Activity: Phenylalanine Concentrations*
- *Overall Clinical Efficacy*
  - ~ **Functions:** Ability to conduct normal activities
    - School difficulties: special ed, req'd tutoring, repeated classes
    - Work difficulties: job losses, poor work attendance, inadequate comprehension of instructions, lack of attention
  - ~ **Feels:**
    - Emotional instability: angry outbursts, unstable relationships, forgetfulness, inconsistent behavior, poor \$ management
    - Loneliness, poor social relationships, anxiety, depression
  - ~ **Survives** ...Physician or Observer administered & PROs...

# Biomarkers as Surrogates for Clinical Efficacy Endpoints

---

*“Biomarkers are measurements of biological processes. Biomarkers include physiological measurements, blood tests and other chemical analyses of tissue or bodily fluids, genetic or metabolic data, and measurements from images. Cholesterol and blood sugar levels are biomarkers, as are blood pressure, enzyme levels, measurements of tumor size from MRI or CT, and the biochemical and genetic variations observed in age-related macular degeneration. Emerging technologies have also enabled the use of simultaneously measured “signatures,” or patterns of co-occurring sets, of genetic sequences, peptides, proteins, or metabolites as biomarkers. These signatures can also be combinations of several of these types of measurements; ideally, each component of a signature is identified.”*

[IOM, 2010. “Evaluation of Biomarkers & Surrogate Endpoints in Chronic Disease”. Washington DC. National Academies Press].

# Categorization of Nomenclature Outcome Assessments

Direct Measures of  
Patient “Functions,  
Feels, Survives”

Indirect Measures #

**Psychomodulated –**  
(Dependence on  
patient motivation or  
clinician judgment  
to perform the test)

**Biomarkers –**

(e.g. H<sub>b</sub>A<sub>1c</sub>, CD-4, PSA,  
CEA, antibody levels,  
TIMI-III flow  
HDL, LDL,  
blood pressure,  
body temperature,  
urine GAG, urine KS  
Phe, cardiac rhythm,  
blood cultures, PCR,  
quantitative measures  
from radiology imaging.)

Patient  
(symptoms)

Clinician  
(PANNS for  
schizophrenia  
syndrome)

Observer  
(seizures,  
infant  
behavior,  
death)

Patient  
(rescue meds  
for pain,  
alcohol  
presentation  
test )

Clinician  
(TM bulging,  
Limb Spasticity,  
6MWT, PFTs,  
9-hole peg test)

Observer  
(rescue meds  
for pain)

# Presumes that relationship to a direct outcome has been demonstrated

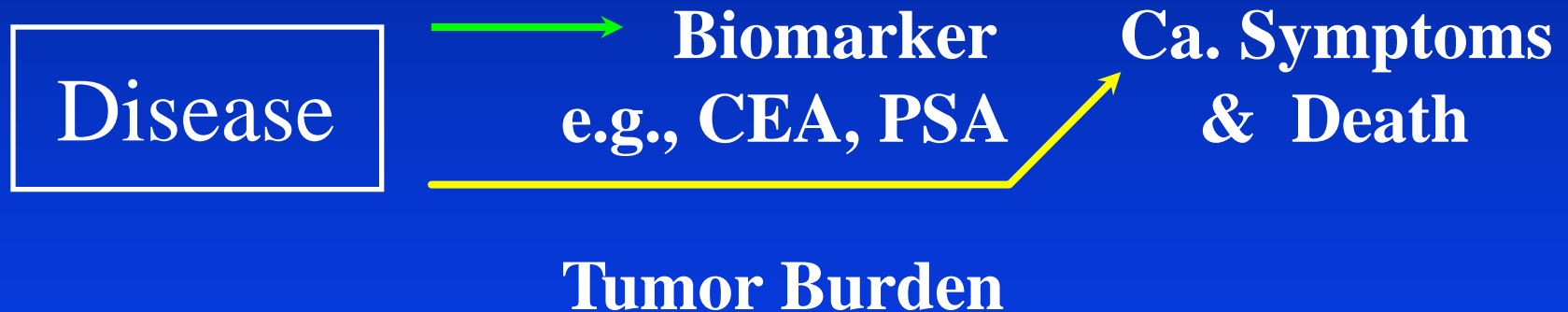
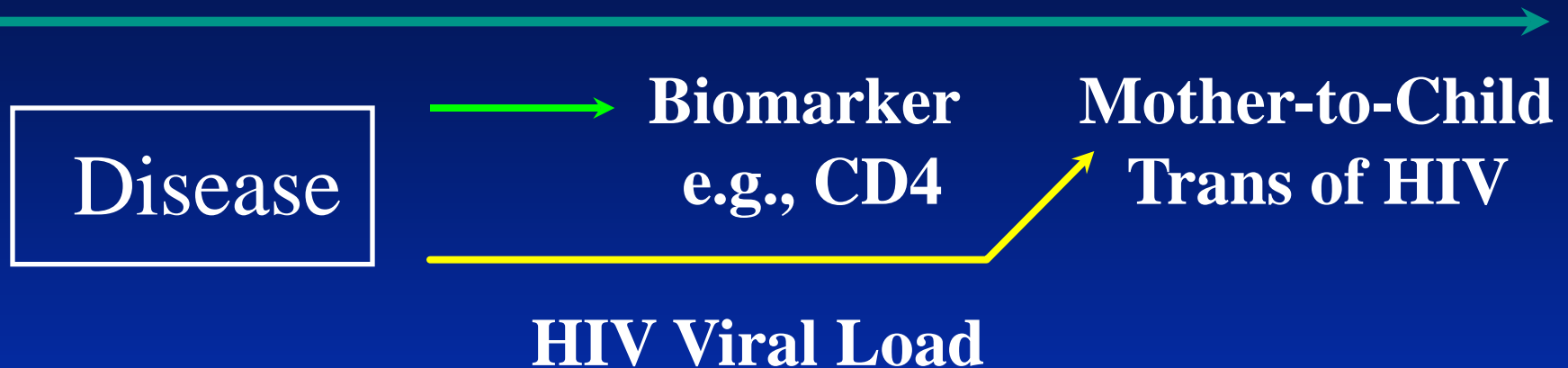
# Biomarkers (as Replacement Endpoints)

---

Treatment effects on Biomarkers:

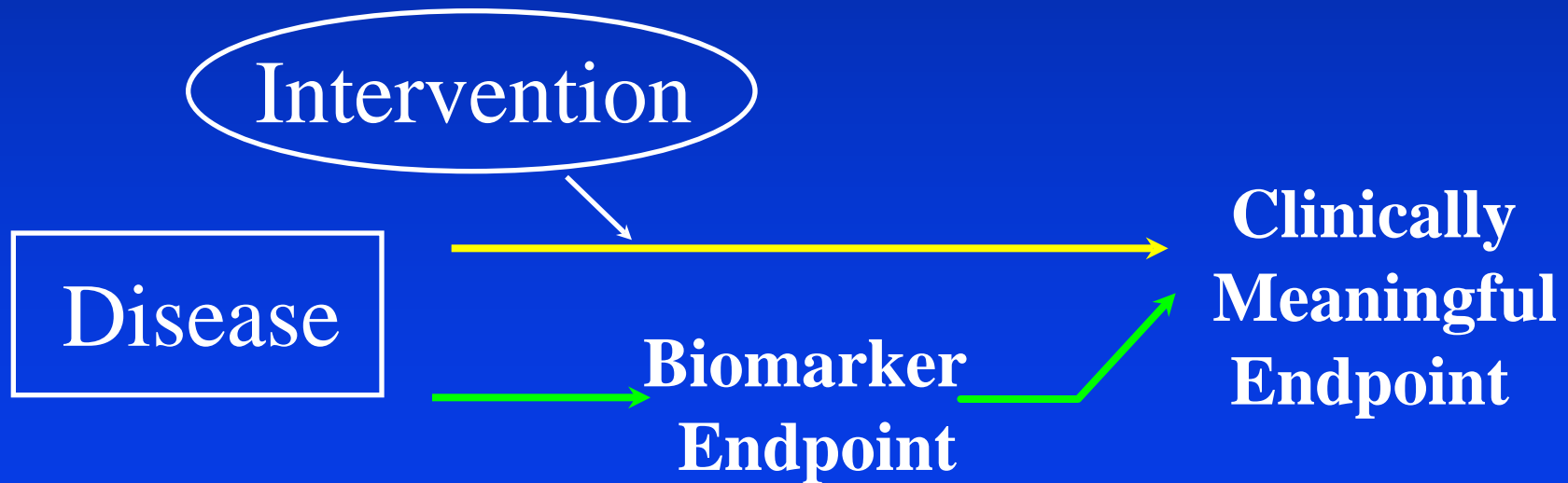
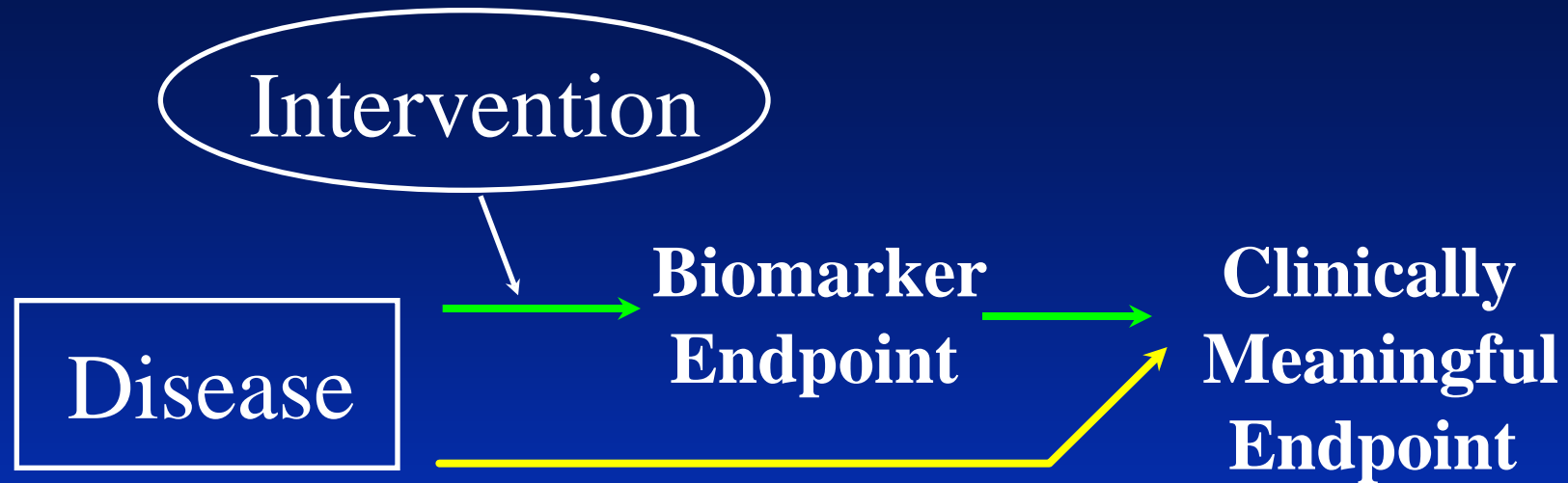
- Establish *Biological Activity*
- But not necessarily *overall Clinical Efficacy*
  - ~ Ability to conduct normal activities
  - ~ How a patient feels
  - ~ Overall Survival

The Biomarker Endpoint is not  
in the Causal Pathway of the Disease Process.



- “Correlates”: Useful for Disease Diagnosis,  
or Assessing Prognosis
- “Valid Surrogates”: Replacement Endpoints

# Multiple Pathways of the Disease Process

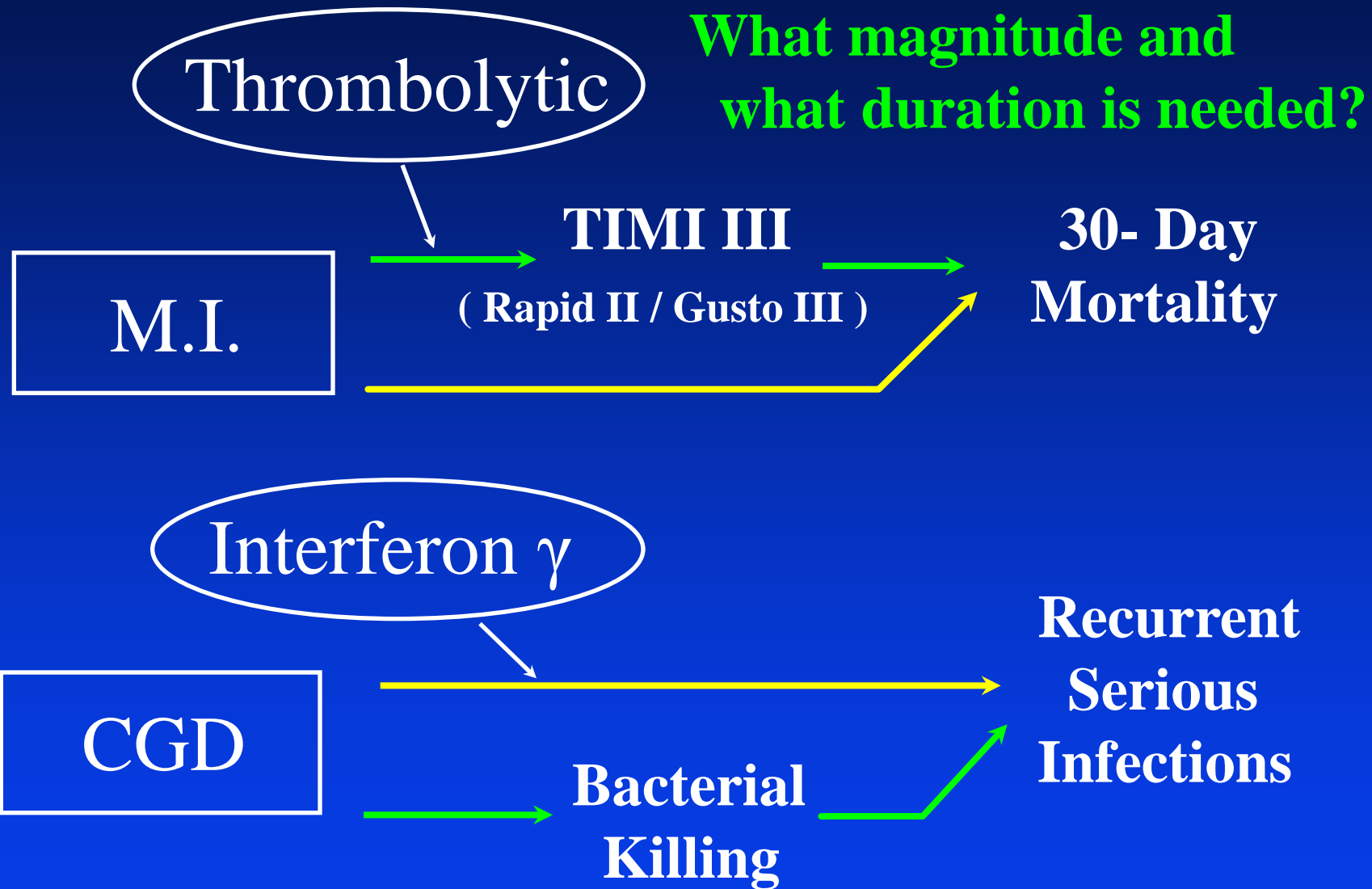


# Biomarker (Surrogate) in Chronic Granulomatous Disease

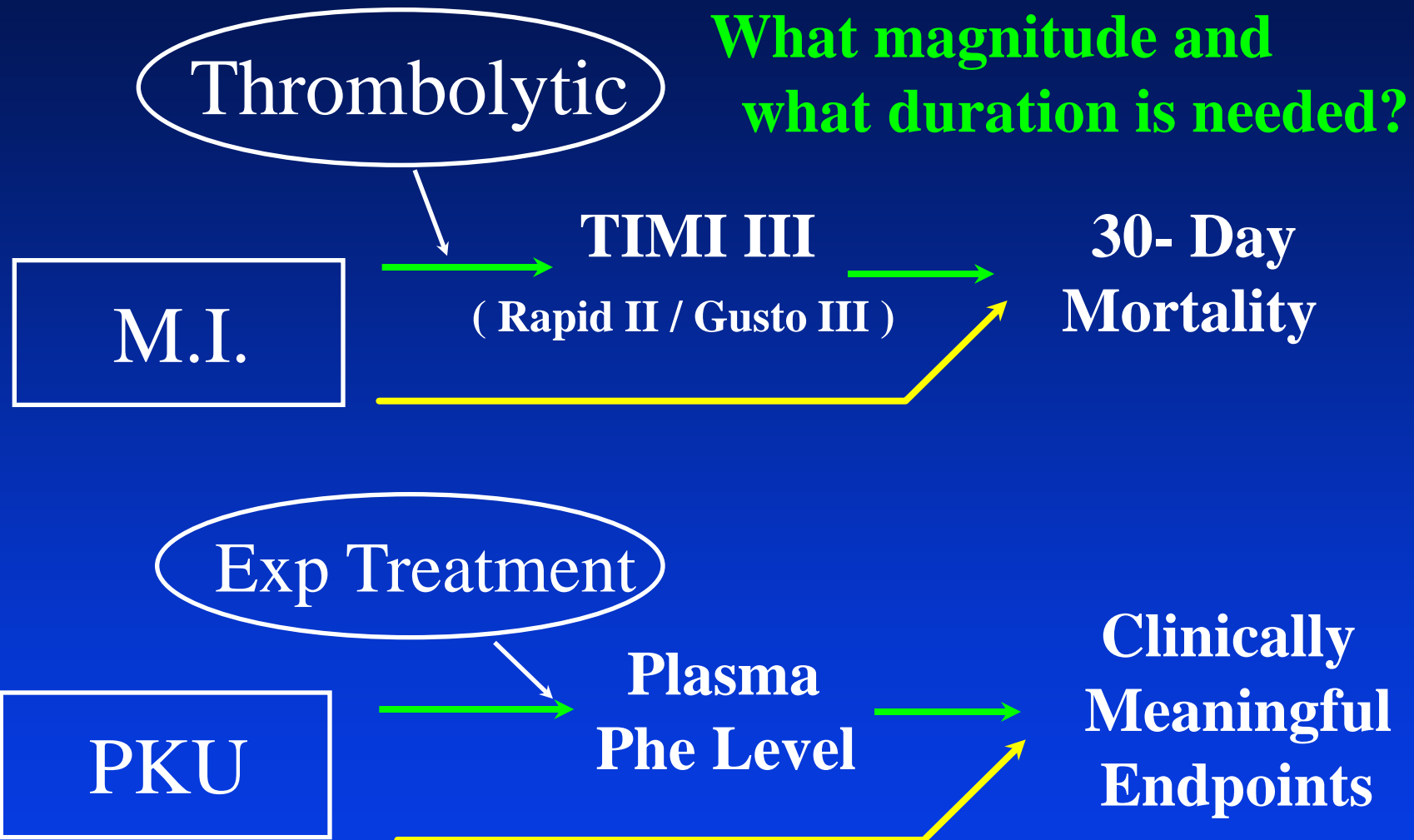
---

- CGD → Recurrent Serious Infections
- Interferon  $\gamma$  ...Increase Bacterial Killing and Superoxide Production?
- International CGD Study Group Trial  
Interferon  $\gamma$ :
  - 70% Reduction in Recurrent Serious Infections
  - Essentially No Effect on Biological Markers

# Multiple Pathways of the Disease Process



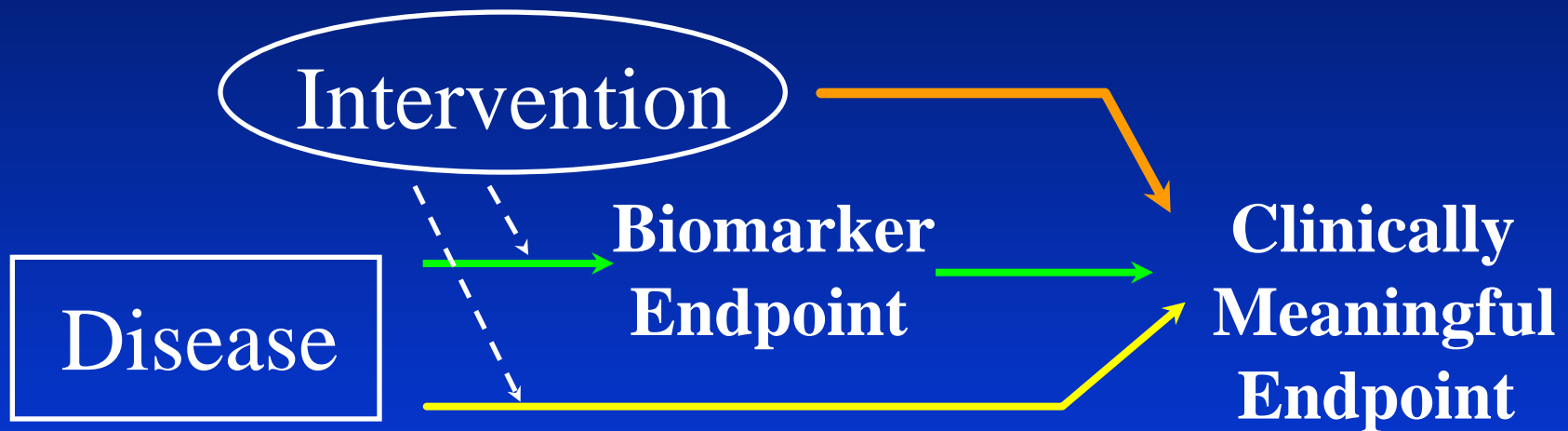
# Multiple Pathways of the Disease Process



# Interventions having Mechanisms of Action Independent of the Disease Process



# Interventions having Mechanisms of Action Independent of the Disease Process



ESAs:  $\uparrow$  **Thrombosis**  $\Rightarrow$   $\uparrow$  Mortality

Cox-2s, Muraglitazar, Rosiglitazone :  $\uparrow$  **CV Risk Factors**  $\Rightarrow$   $\uparrow$  CV Death/ MI /Stroke

Tysabri:  $\uparrow$  **PML**  $\Rightarrow$   $\uparrow$  Morbidity / Mortality

Torcetrapid: **Activates renin angiotensin system**  $\Rightarrow$   $\uparrow$  **BP**  $\Rightarrow$   $\uparrow$  Mortality

Troglitazone:  $\uparrow$  **Serious Hepatic Risks**  $\Rightarrow$   $\uparrow$  Morbidity

Long Acting  $\beta$ -Agonists:  $\uparrow$  Asthma-related deaths

Vytorin: **Blocks pathways linked to CA protection**  $\Rightarrow$   $\uparrow$  Cancer Mortality?

# Validation of Surrogate Endpoints

---

## Property of a Valid Surrogate

- *Net effect of the Intervention  
on the Surrogate Endpoint*  
reliably predicts the  
*Net effect of the Intervention  
on the Clinically Meaningful Endpoint*

# Indirect measures as a replacement for direct assessment of treatment benefit

---

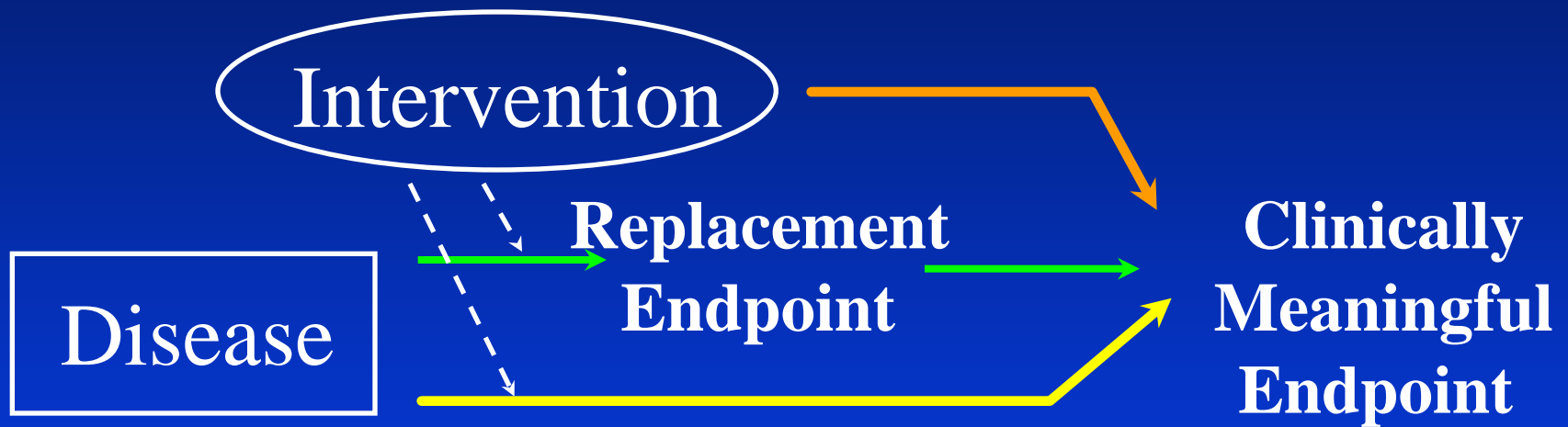
## Clinical

- Comprehensive understanding of the
  - ~ Causal pathways of the disease process
  - ~ Intervention's intended and unintended mechanisms of action

## Statistical

- Meta-analyses of clinical trials data

# Mechanisms of Action of the Intervention & Causal Pathways of the Disease Process



# Indirect measures as a replacement for direct assessment of treatment benefit

---

## Clinical

- Comprehensive understanding of the
  - ~ Causal pathways of the disease process
  - ~ Intervention's intended and unintended mechanisms of action

...allows clinical endpoint trials reduced in size & duration...

## Statistical

- Meta-analyses of clinical trials data

# Illustration of Validating a Surrogate

---

## ➤ Anti-Hypertensives

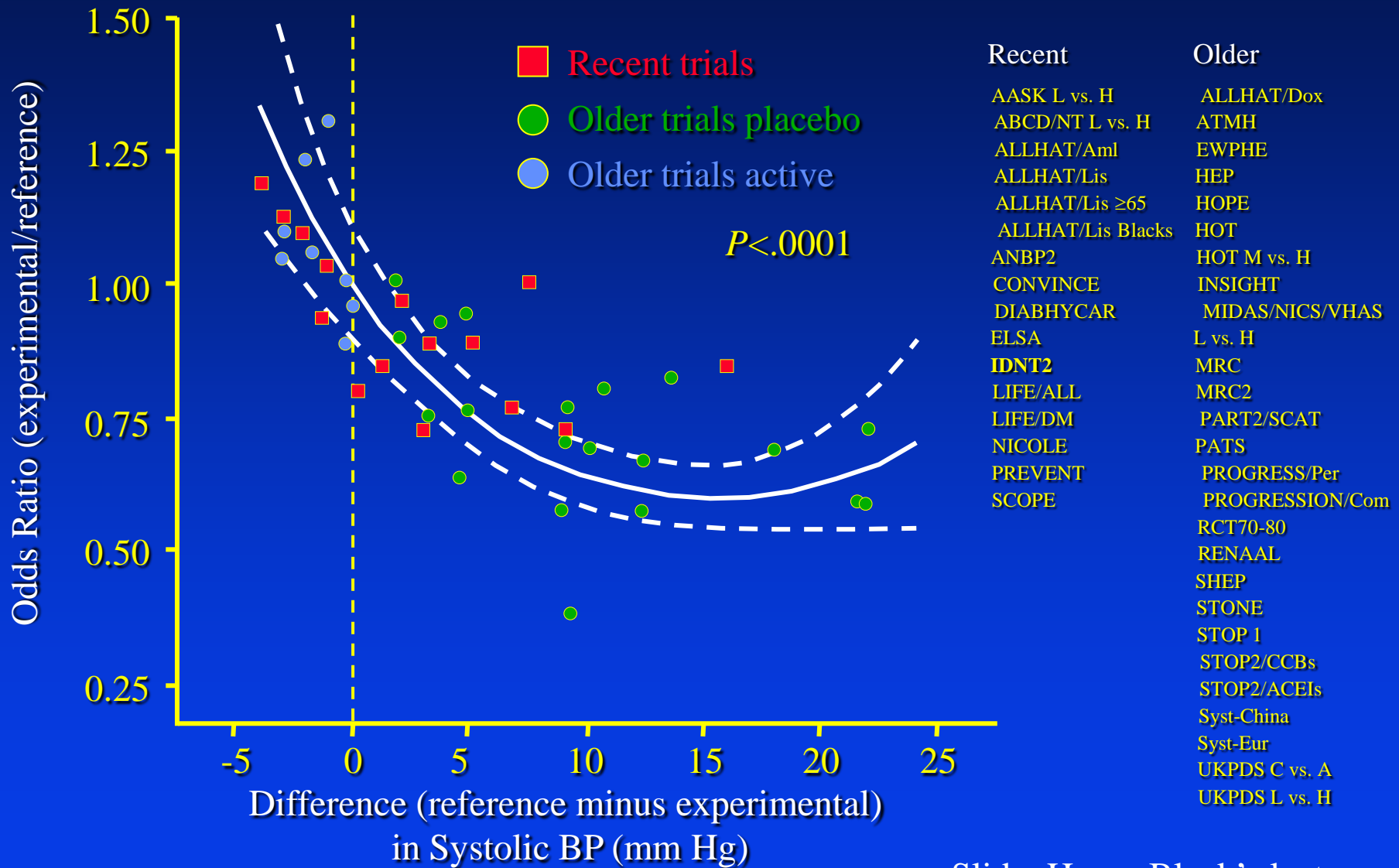
(>500,000 patients from rand trials)

... $\beta$ -blockers, low dose diuretics, ACE-I, CCBs, ARBs...

FDA Cardio-Renal Advisory Committee: 6/15/2005

- Effects on *Blood Pressure* predicting effects on each of the following, considered individually:
  - ✓ *Stroke, MI, CVD, Mortality, Heart Failure*

# Odds Ratio for CV Events and Systolic BP Difference: Recent and Older Trials



Staessen et al. *J Hypertens.* 2003;21:1055-1076.

Slide: Henry Black's lecture

# Illustration of Validating a Surrogate

---

## ➤ Anti-Hypertensives

(>500,000 patients from rand trials)

... $\beta$ -blockers, low dose diuretics, ACE-I, CCBs, ARBs...

FDA Cardio-Renal Advisory Committee: 6/15/2005

- Effects on *Blood Pressure* predicting effects on each of the following, considered individually:
  - ✓ *Stroke, MI, CVD, Mortality, Heart Failure*

# IOM, 2010 “Evaluation of Biomarkers & Surrogate Endpoints in Chronic Disease”

---

- *Analytical Validation*

- ...analysis of analytical performance of an assay...  
e.g., limit of quantitation, across lab reproducibility, etc

- *Qualification*

- ...relationship between biomarker & disease state
  - ...data regarding effects of interventions on both biomarker and clinically meaningful outcomes...

- *Utilization*

- ...determining whether validation & qualification provide sufficient support for the context of use proposed...

# Some Uses of Biomarkers

---

As “Correlates” ...

- Disease Diagnosis
- Assessing Prognosis
- In Patient-specific Therapeutic Strategies
- Primary Endpoints  
in Screening or Proof of Concept Trials
- Measures of Biologic Activity  
in Confirmatory (registrational) trials

# Uses of Biological Markers: High Clinical Utility

---

- As Replacement or “Surrogate” Endpoints...  
*...When one can fully capture effects on the principle causal mechanism of disease process (w treatment lacking key unintended mech)*
- In Identifying Enriched Populations...  
*...When the key mechanism(s) of Rx effect on the causal factor(s) of the disease process are specific to a targeted population (eg, gene) (w treatment possibly having unintended mech)*  
*...EGFR Inhibitors: KRAS Wild Type vs. Mutation*

# Categorization of Nomenclature Outcome Assessments

Direct Measures of  
Patient “Functions,  
Feels, Survives”

Indirect Measures #

**Psychomodulated –**  
(Dependence on  
patient motivation or  
clinician judgment  
to perform the test)

**Biomarkers –**

(e.g. H<sub>b</sub>A<sub>1c</sub>, CD-4, PSA,  
CEA, antibody levels,  
TIMI-III flow  
HDL, LDL,  
blood pressure,  
body temperature,  
urine GAG, urine KS  
Phe, cardiac rhythm,  
blood cultures, PCR,  
quantitative measures  
from radiology imaging.)

Patient  
(symptoms)

Clinician  
(PANNS for  
schizophrenia  
syndrome)

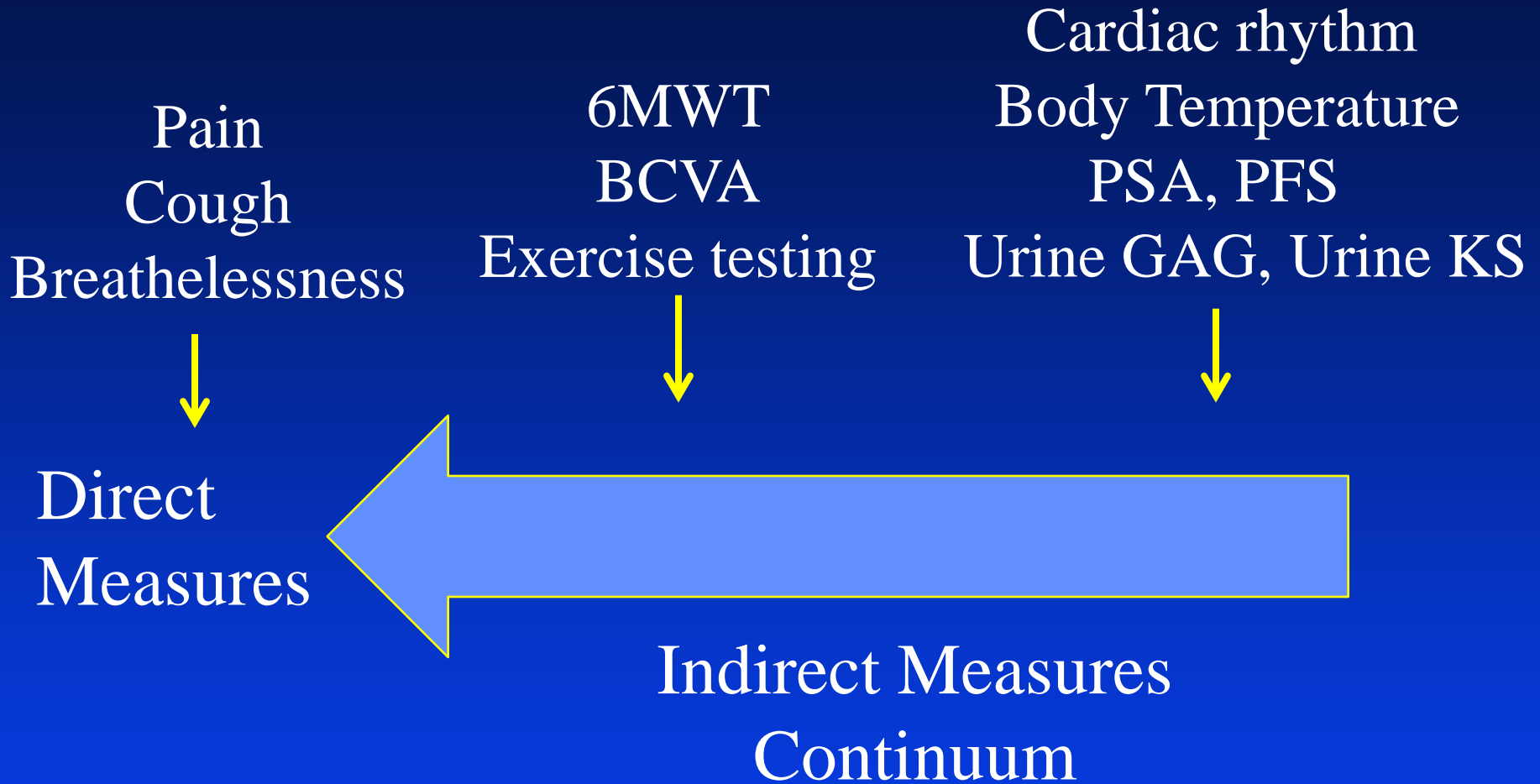
Observer  
(seizures,  
infant  
behavior,  
death)

Patient  
(rescue meds  
for pain,  
alcohol  
presentation  
test )

Clinician  
(TM bulging,  
Limb Spasticity,  
6MWT, PFTs,  
9-hole peg test)

Observer  
(rescue meds  
for pain)

# Presumes that relationship to a direct outcome has been demonstrated



# IOM, 2010 “Evaluation of Biomarkers & Surrogate Endpoints in Chronic Disease”

---

- *Analytical Validation*

- ...analysis of analytical performance of an assay...  
e.g., limit of quantitation, across lab reproducibility, etc

- *Qualification*

- ...relationship between biomarker & disease state
  - ...data regarding effects of interventions on both biomarker and clinically meaningful outcomes...

- *Utilization*

- ...determining whether validation & qualification provide sufficient support for the context of use proposed...

# Replacement Endpoints

---

- A replacement endpoint cannot be deemed to be a generic surrogate endpoint for a particular disease

## Reasons why use needs setting-specific justification:

- Multiple causal pathways of the disease process
- *Magnitude* and *duration* of effect matters
- Intended and *unintended* effects of interventions

- How does evaluating replacement endpoints impact the public?

Response: Need “*reliable*” as well as “*timely*” evaluation  
...not simply “*a choice*”; rather, “*an informed choice*”

# In Rare Diseases, are there risks when “choices” are not “*informed* choices”?

---

- Biologically active but not clinically effective treatments
- Clinically significant risks:
  - Severe hypersensitivity reactions, Anaphylactic reactions
  - Acute respiratory distress, Seizures, Loss of consciousness
  - Cardiac arrhythmias, Pulmonary embolism, Serious Infection
  - Disinhibition...reduced adherence in PKU to dietary restrictions
- Inconvenient schedules, and extremely costly regimens
- Reduced access to other potentially effective regimens