

## **Biomarkers and Surrogate Endpoints in Clinical Trials**

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- \* IOM, 2010. *“Evaluation of Biomarkers & Surrogate Endpoints in Chronic Disease:.”* Washington DC. National Academies Press
- \* Fleming TR, Powers JH: Biomarkers and Surrogate Endpoints in Clinical Trials *Statistics in Medicine* 2012; 31: 2973-2984.

# Lecture Objectives

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- ~ Recognize strong correlation of a biomarker (replacement) endpoint with a direct measure of how a patient feels, functions or survives doesn't justify a conclusion that treatment effect on biomarker status reliably predicts treatment effect on the direct measure of how a patient feels, functions or survives.
- ~ Explain the integral importance, to the rigorous validation of a biomarker as a replacement (or surrogate) endpoint, of:
  - An in depth clinical understanding of
    - ✓ the causal pathways of the disease process; and
    - ✓ intervention's intended & *unintended* mechanisms of action;
  - Meta-analyses of clinical trials showing the relationship between:
    - ✓ the *net* effect of treatment on the biomarker, and
    - ✓ the *net* effect of treatment on direct measures of how a patient feels, functions and survives

# Issues in Replacement (Surrogate) Endpoints

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- ~ **Criteria for Choosing Endpoints**
- ~ *“A Correlate does not a Surrogate Make”*
- ~ **Validation of Replacement (Surrogate) Endpoints**

# Some Characteristics for Study Endpoints in Phase 3 Clinical Trials

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- Consistently & readily measurable
- Sensitive
- Well defined & reliable
- Clinically meaningful

Invasive Procedures:  
E.g., Biopsy, RHC

A “*Clinically Meaningful Endpoint*”:

...a direct measure of how a patient

“*feels, functions or survives*” ...

... Robert Temple, FDA

# Biomarkers & 'Feels, Functions, Survives' Endpoints

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- **Biological Activity:** Hemodynamic Measures in PAH:  
*PVRI, mPAP, CO*
- **Clinical Meaningful Benefit** *SBP, DBP, NT-proBNP*
  - ~ **Functions:** Ability to conduct normal activities
    - *Ability to walk, Ability to engage in recreational activities, Ability for self care, Risk of syncope*
    - *Time in hospital or missing school (overall, or cause specific)*
  - ~ **Feels:**
    - *Chest pain, breathlessness, fatigue, dizziness*
  - ~ **Survives**
    - ...*Physician or Observer administered & PROs...*

# Potential ‘*Feels, Functions, Survives*’ Endpoints

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## Patient Reported Outcomes (PROs):

*“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)

# Patient Reported Outcomes (PROs)

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...Direct Measures of 'Feels', but with need to confirm:

Reliability, Sensitivity, Validity (Content, Construct, etc)  
Clinical Relevance, Interpretability

Integrity, including need for:

blinded assessment & control of missing data...

...Mobilize disease specific interest groups,  
before sponsors plan clinical trials...

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

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# Biomarkers as Replacement Endpoints

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*“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...”*

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

### Biomarkers

Measures depending on patient motivation or clinician judgment to perform the test

e.g.  $H_bA_{1c}$ , CD-4, PSA, PVRI, NT-proBNP, CO HR, Blood Pressure Pulm Arterial Pressure TIMI-III flow HDL, LDL, body temperature, urine GAG, urine KS cardiac rhythm, blood cultures, PCR, quantitative measures from radiology imaging.

Patient (symptoms: <i>chest pain, dyspnea, fatigue, dizziness</i> )	Clinician (PANNS for schizophrenia syndrome, <b>Clinician Global Measures</b> )	Observer ( <i>seizures, infant behavior, stroke, death</i> )
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Patient ( <i>rescue meds for pain, alcohol presentation test</i> )	Clinician ( <i>TM bulging, Limb Spasticity, 6MWD, 3MSC PFTs, 9-hole peg test</i> )	Observer ( <i>rescue meds for pain</i> )
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# John Powers, Dave DeMets, Marc Walton, Laurie Burke, Bob Temple...

# Biomarkers (as Replacement Endpoints)

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... “*Post hoc, ergo, Propter hoc*” ...

Treatment effects on Biomarkers:

- Establish *Biological Activity*
- But not necessarily the net effects on
  - ~ How a patient feels
  - ~ The ability to conduct normal activities
  - ~ Overall Survival

# Issues in Replacement (Surrogate) Endpoints

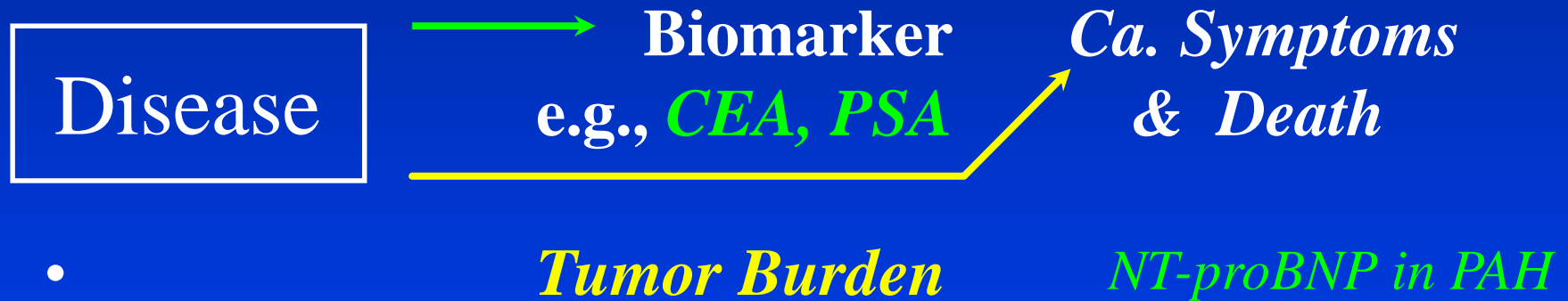
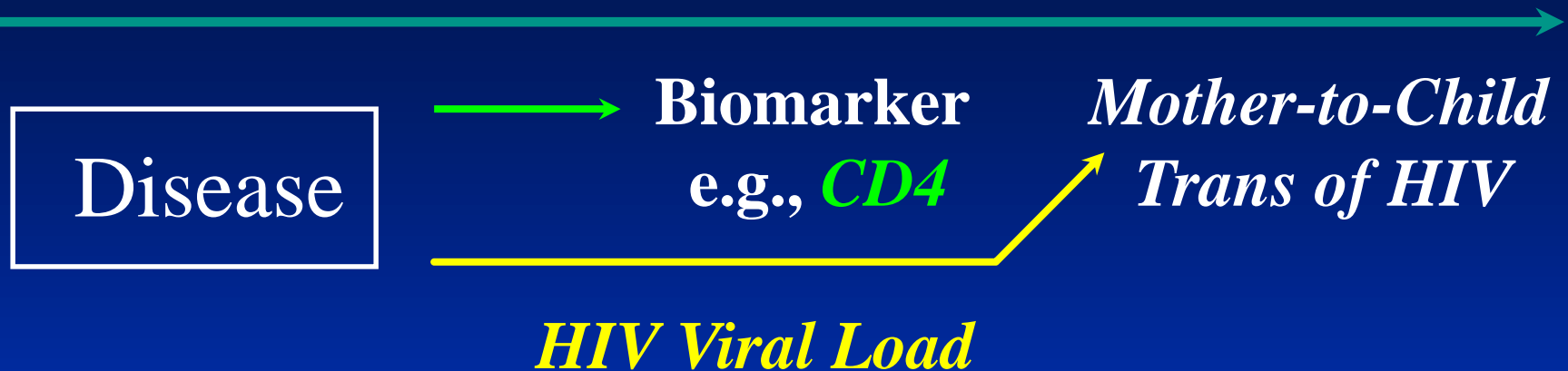
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- ~ Criteria for Choosing Endpoints
- ~ *“A Correlate does not a Surrogate Make”*
- ~ Validation of Replacement (Surrogate) Endpoints

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

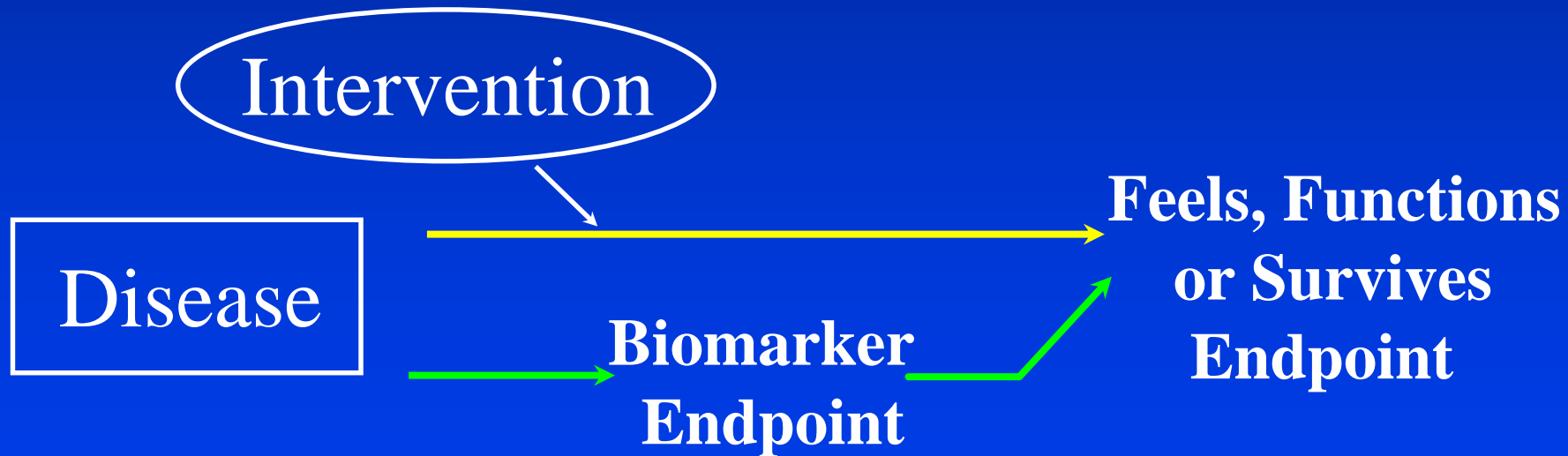
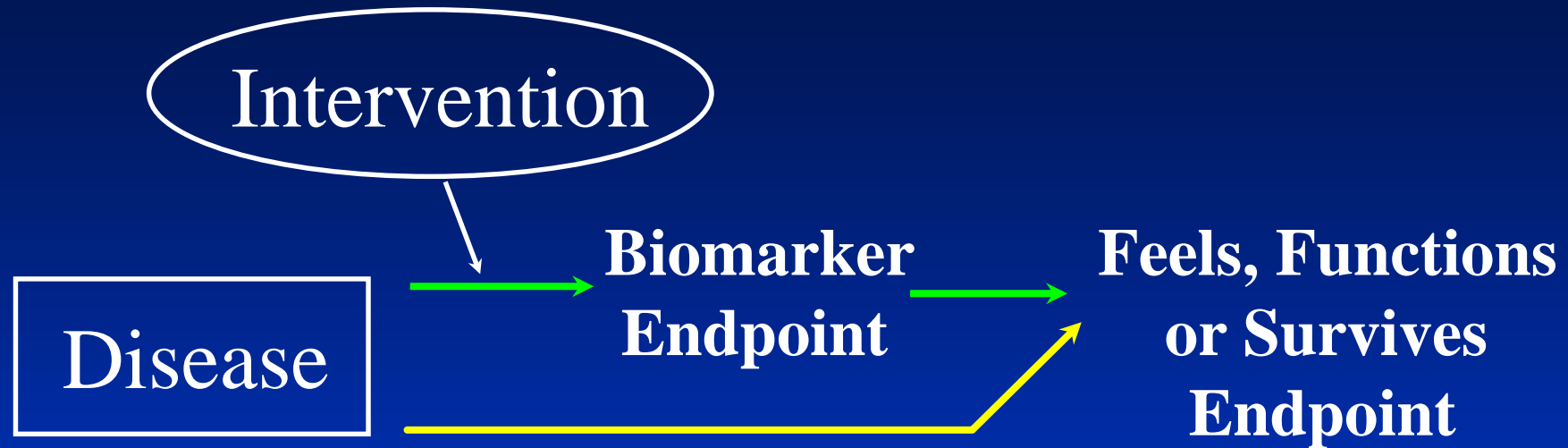


# The Biomarker Endpoint is not in the Causal Pathway of the Disease Process.



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

# Multiple Pathways of the Disease Process



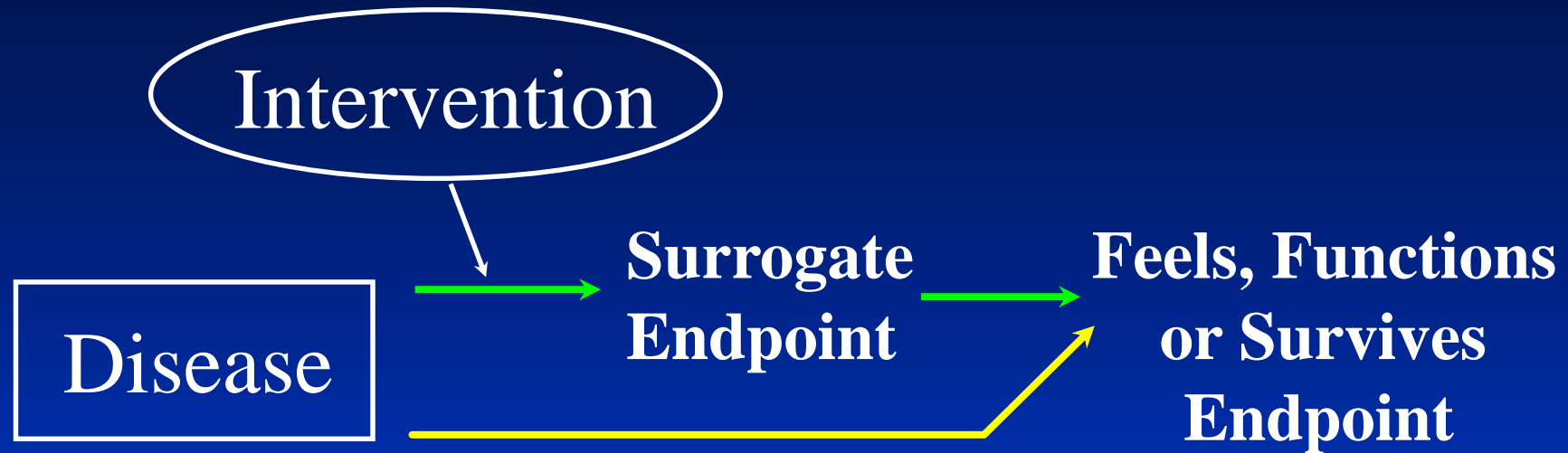
# Biomarker (as a Surrogate) in Chronic Granulomatous Disease

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- 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



# Biomarkers in Acellular Pertussis Vaccines

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(Sweden I Trial with DT control: 10,000 subjects)

- **VE**

	<u>VE</u>	<u>95% CI</u>
SKB	58%	(51%, 66%)
Aventis Pasteur	85%	(81%, 89%)

- **Biomarkers**

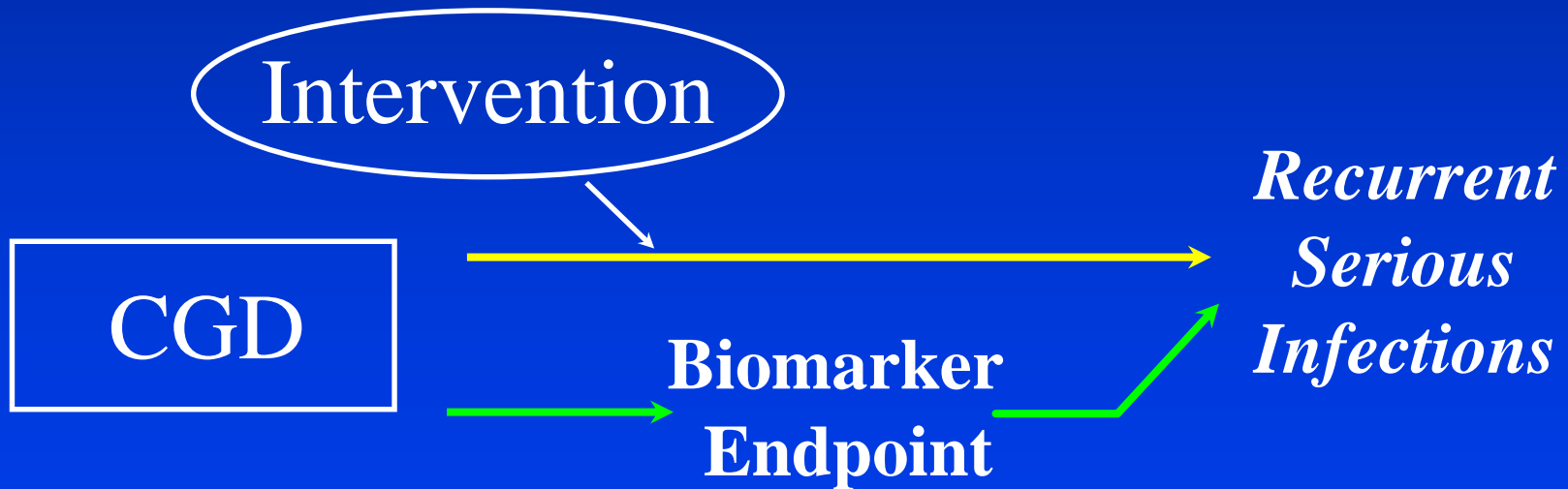
*Filamentous Haemagglutinin (FHA)*  
*and Pertussis Toxoid (PT)* antibody responses  
were superior with the SKB vaccine

# Multiple Pathways of the Disease Process

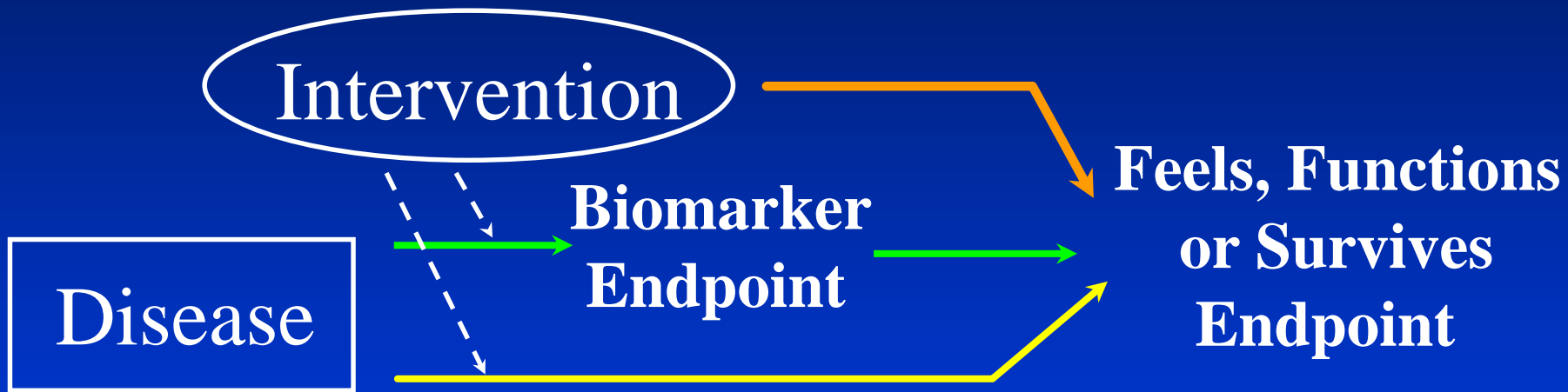


- Other Immune Responses, including those resulting from additional antigens in the vaccines:
  - ~ Pertactin
  - ~ Fimbriae (types 2 and 3)
- Durability of effect

# Multiple Pathways of the Disease Process



# Interventions having Mechanisms of Action Independent of the Disease Process



## Illustration:

### Ventricular Arrhythmia after M.I.

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- Arrhythmia:
  - Risk factor for Sudden Death
- Antiarrhythmic Drugs:
  - Class IC antiarrhythmic agents
    - ...Strong Sodium-Channel Blockade

## Illustration:

### Ventricular Arrhythmia after M.I.

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- Arrhythmia:
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- Antiarrhythmic Drugs:
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    - ...Strong Sodium-Channel Blockade

Cardiac Arrhythmia Suppression Trial:

The drugs, relative to placebo,  
TRIPLE the death rate.

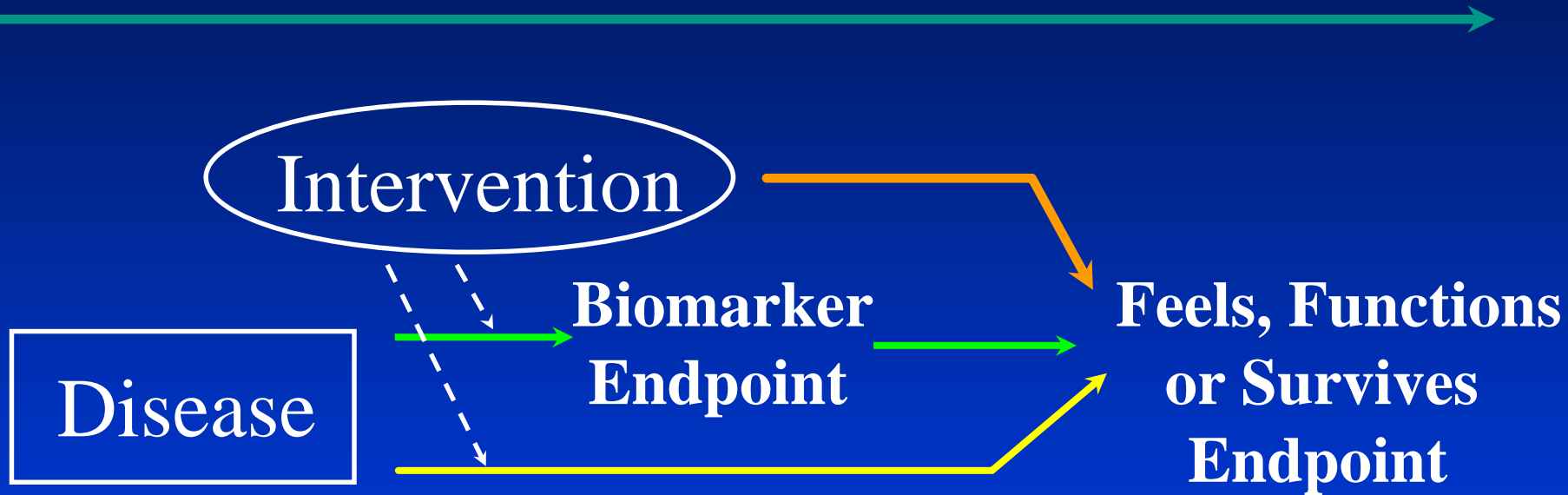
# Interventions having Mechanisms of Action Independent of the Disease Process



"Deadly Medicine" by Thomas Moore



# 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

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

Natalizumab:  $\uparrow$  **Prog. Multifocal Leukoencephalopathy**  $\Rightarrow$   $\uparrow$  Morbidity / Mortality

Ezetimibe/Simvastatin: **Block pathways linked to CA prot.**  $\Rightarrow$   $\uparrow$  Cancer Mortality?

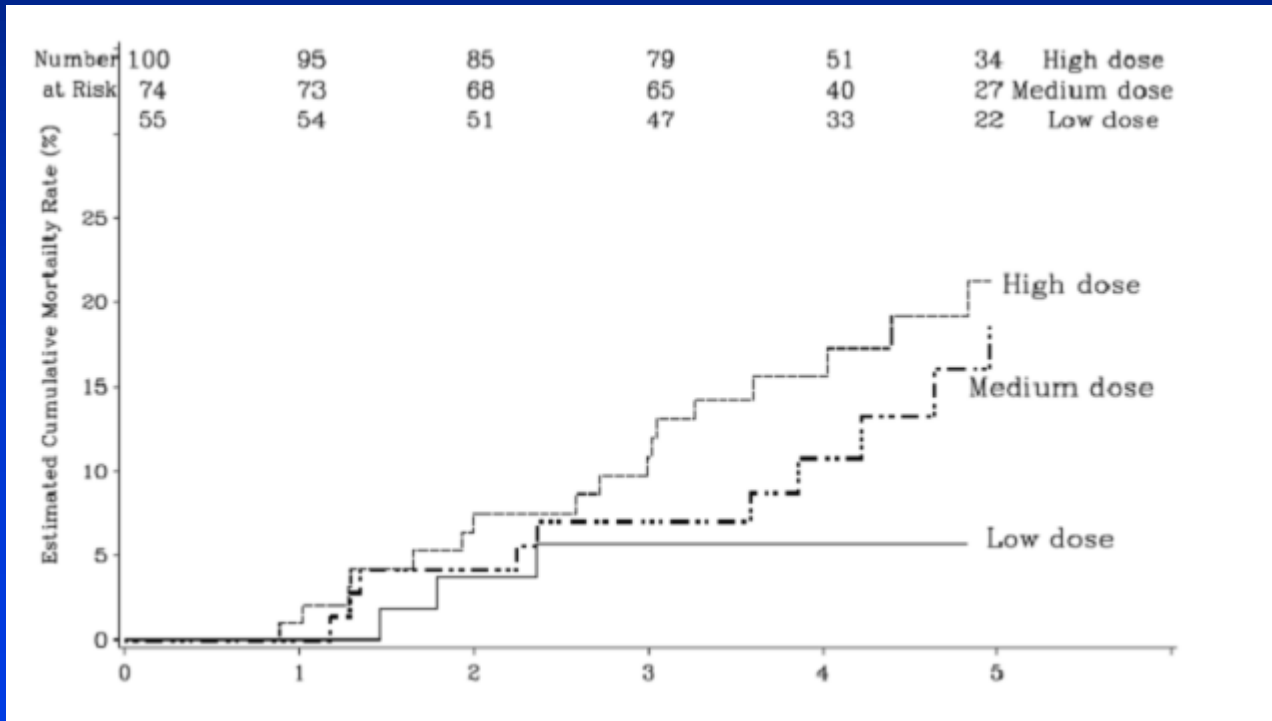
Long Acting  $\beta$ -Agonists:  $\uparrow$  Asthma-related deaths

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

Revatio in Pediatric PAH:  $\uparrow$  doses  $\Rightarrow$  Improved hemodynamics yet  $\Rightarrow$   $\uparrow$  Mortality

# “FDA Drug Safety Communication: FDA recommends against use of Revatio in children with pulmonary hypertension”

“Plot of mortality in the pediatric clinical trial  
as a function of Revatio dose.”



“The hazard ratio for high dose compared to low dose was 3.5 ( $p=0.015$ )”

# Issues in Replacement (Surrogate) Endpoints

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~ Criteria for Choosing Endpoints

~ *“A Correlate does not a Surrogate Make”*

~ **Validation of**

**Replacement (Surrogate) Endpoints**

# End Stage Renal Disease

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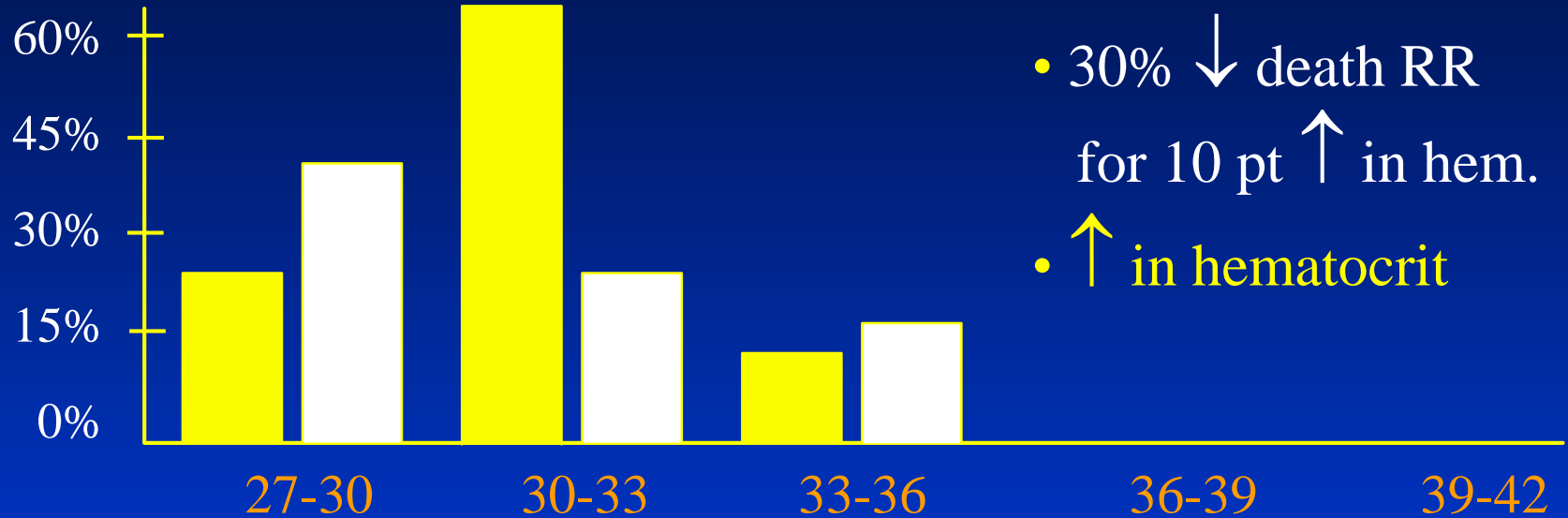


**Goal:** Normalize Hematocrit Values  
 $\Rightarrow$  reduce Death and MI

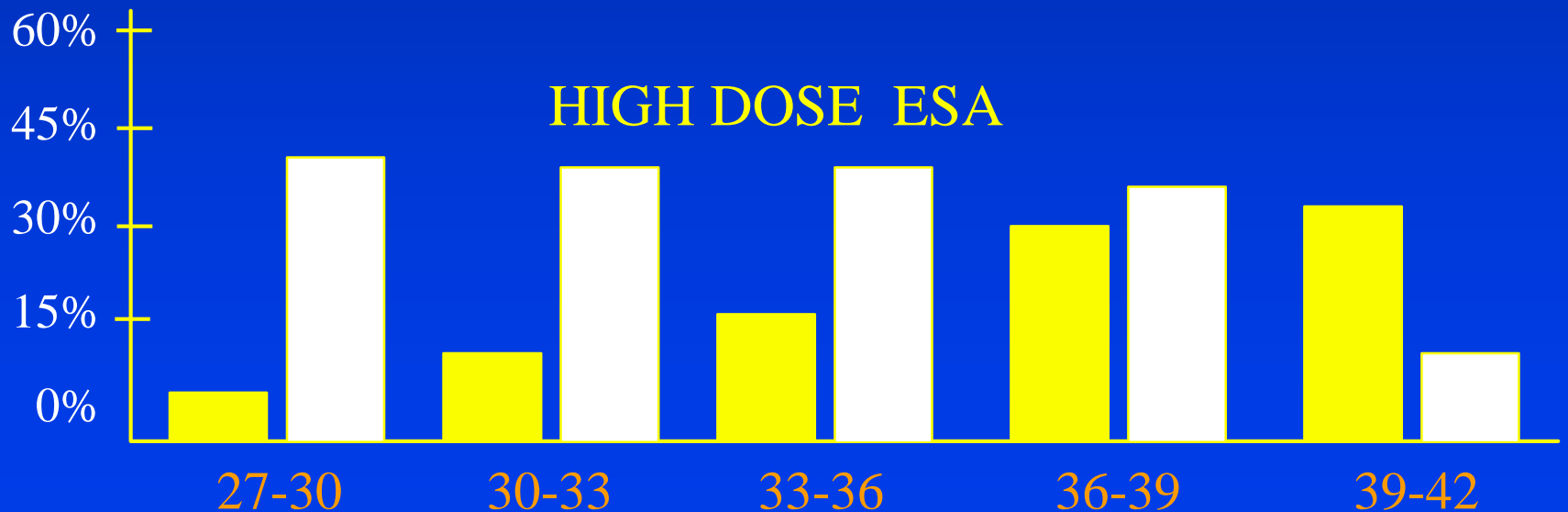
\* Erythropoietin stimulating agent

# Patient Distribution & Percent Deaths by Hematocrit %

## STANDARD DOSE ESA

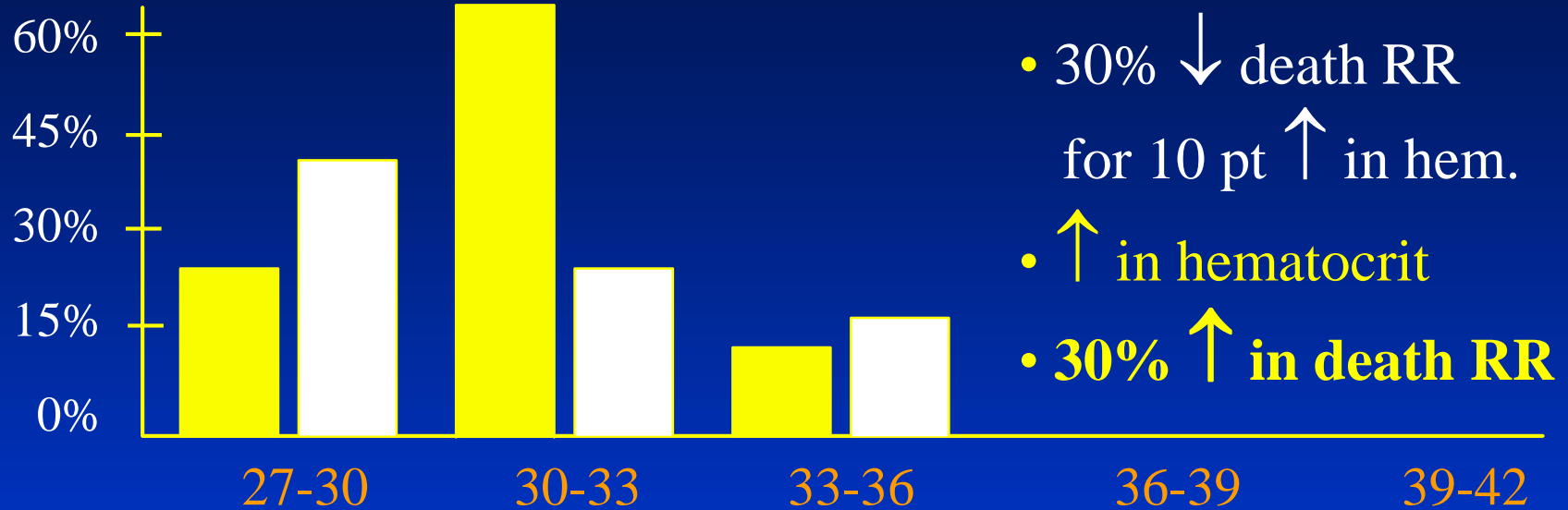


## HIGH DOSE ESA

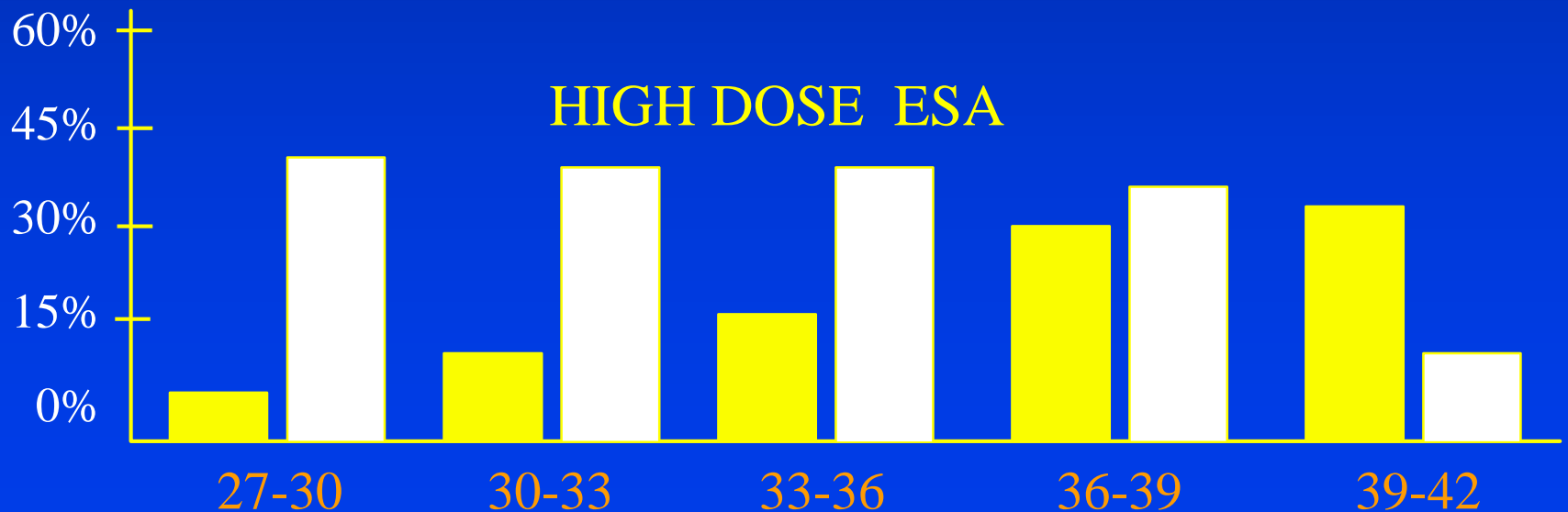


# Patient Distribution & Percent Deaths by Hematocrit %

## STANDARD DOSE ESA



## HIGH DOSE ESA



# End Stage Renal Disease

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## Results (Interim at 1/2 planned endpoints)

	<u>n</u>	<u>Death/MI</u>	<u>Death</u>
Standard Dose	615	<b>164</b>	<b>160</b>
High Dose	618	<b>202</b>	<b>195</b>

Death / MI relative risk: **1.30** (0.94, 1.79)

Besarab et al, NEJM 339:584-590, 1998:

“**↑ in incidence of thrombosis of vascular access sites**”

# Validation of Replacement (Surrogate) Endpoints

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## Property of a Valid

### Replacement (Surrogate) Endpoint:

- *Net effect of the Intervention on the Replacement (Surrogate) Endpoint*

reliably predicts the

*Net effect of the Intervention on the 'Feels, Functions, or Survives' Endpoint*



# Using Replacement (Surrogate) Endpoints for Direct Measures of 'Feels, Functions, Survives'

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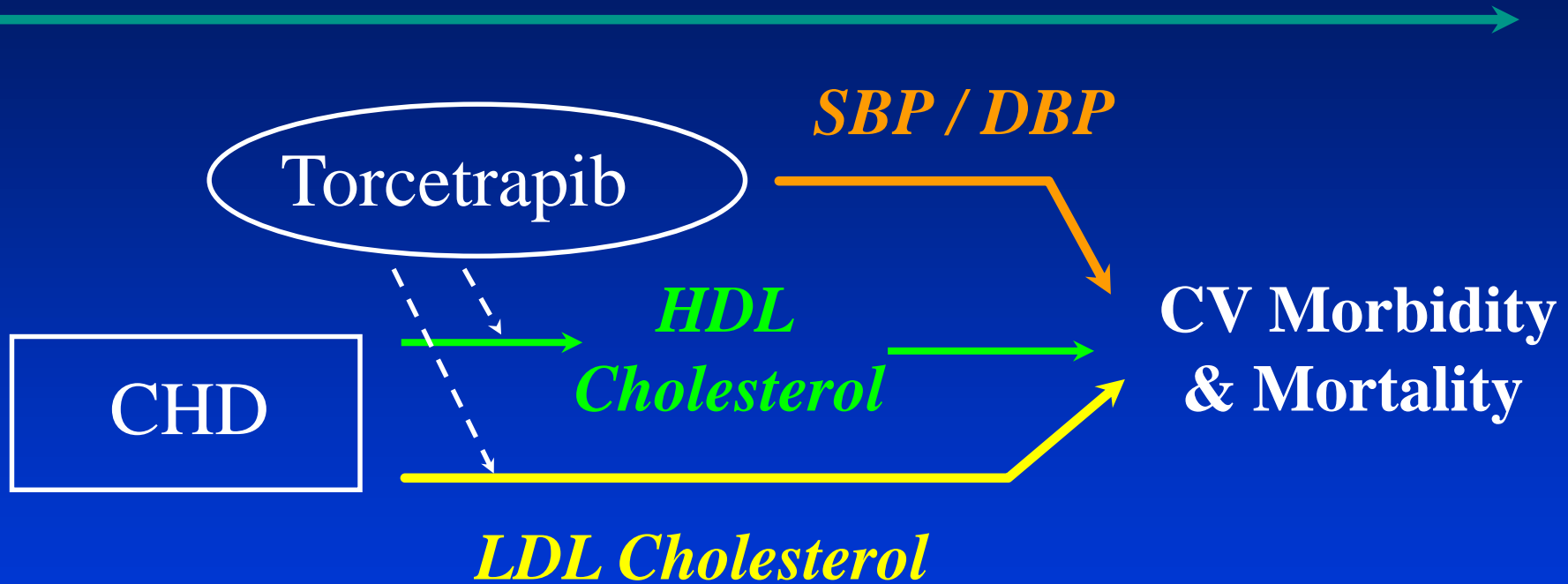
## Clinical

- 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



# Using Replacement (Surrogate) Endpoints for Direct Measures of 'Feels, Functions, Survives'

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## Clinical

- Comprehensive understanding of the
  - ~ Causal pathways of the disease process
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# Illustration of Validating a Surrogate

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## ➤ Anti-Hypertensives

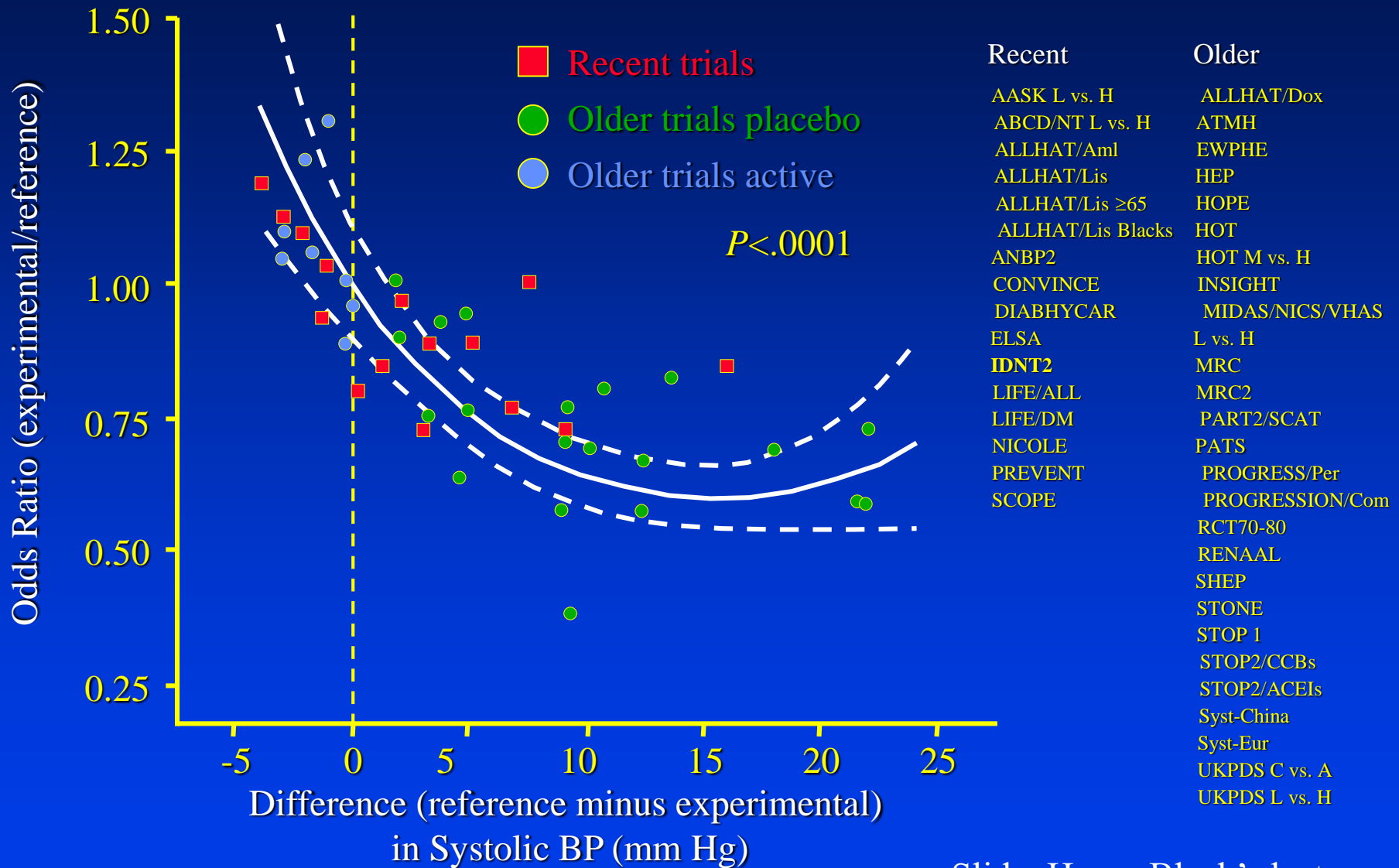
(>500,000 patients from rand trials)

... $\beta$ -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

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## ➤ Anti-Hypertensives

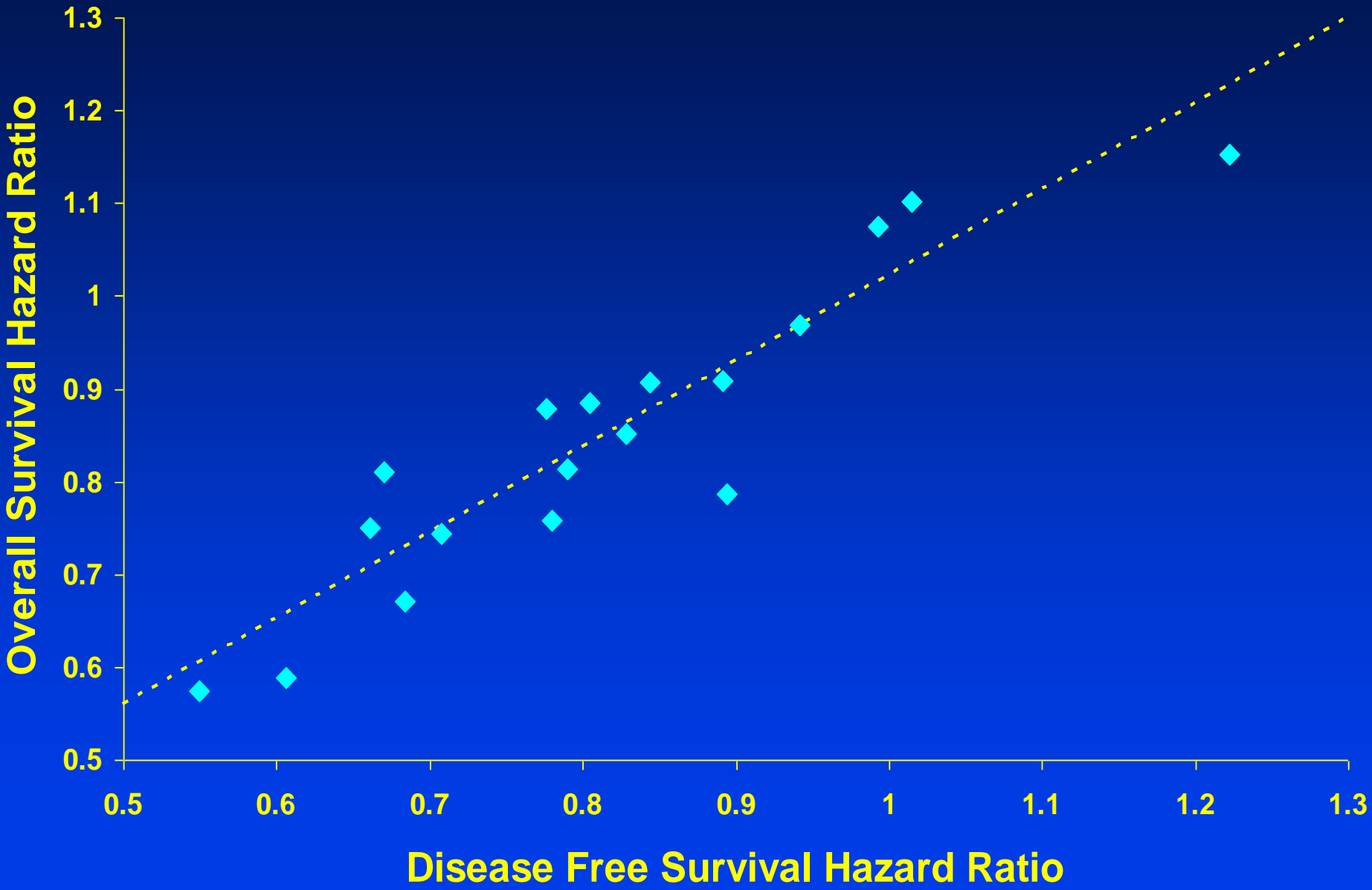
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# Colon Adjuvant: Hazard Ratios for **DFS** vs. **Overall Survival**



# Validation of Surrogate Endpoints

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Illustration:

HPTN 015 Trial (EXPLORE)

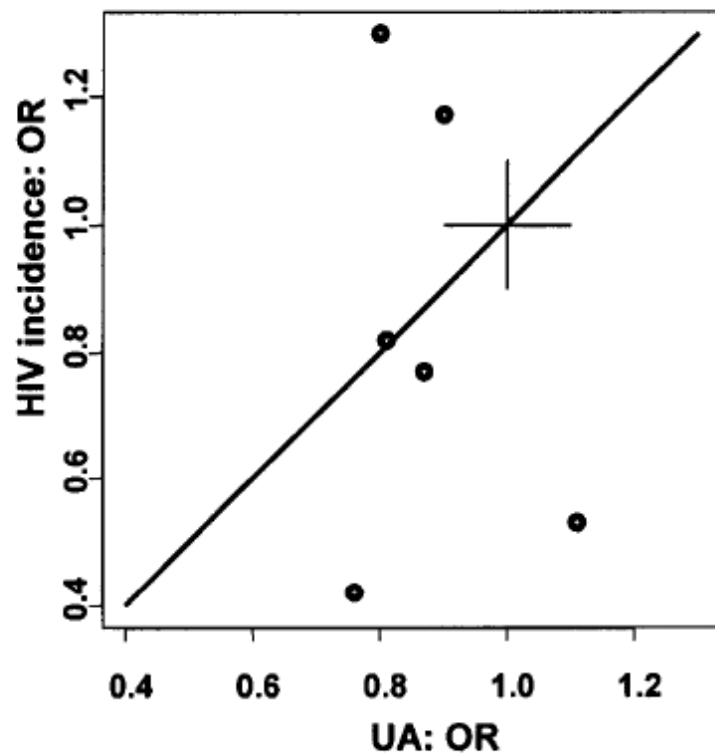
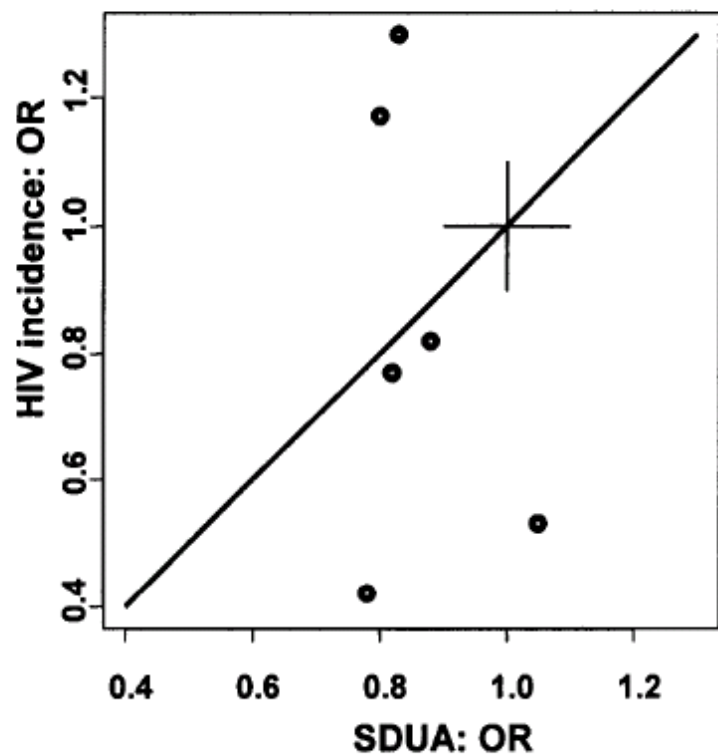
- Clinical Endpoint
  - ~ HIV Infection
- Behavioral Surrogate Endpoints
  - ~ Serodiscordant Unprotected Anal
  - ~ Unprotected Anal



## Enrollment by site

Site	N
Boston	729
Chicago	624
Denver	726
New York	737
San Francisco	736
Seattle	743
TOTAL	4295

# Site-specific Intervention Effects: HIV vs. SDUA/UA



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

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- *Addressing Assay Performance*
  - ...analysis of analytical performance of an assay...  
e.g., limit of quantitation, across lab reproducibility, etc
- *Evidentiary Assessment*
  - ...relationship between biomarker & disease state
  - ...data regarding effects of interventions on both biomarker and clinically meaningful outcomes...
- *Justifying the Proposed Use*
  - ...determining whether available evidence provides sufficient justification for the context of use proposed...

# Some Uses of Biomarkers

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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

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- 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

### Biomarkers

Measures depending on patient motivation or clinician judgment to perform the test

e.g.  $H_bA_{1c}$ , CD-4, PSA, PVRI, NT-proBNP, CO HR, Blood Pressure Pulm Arterial Pressure TIMI-III flow HDL, LDL, body temperature, urine GAG, urine KS cardiac rhythm, blood cultures, PCR, quantitative measures from radiology imaging.

Patient (symptoms: <i>chest pain, dyspnea, fatigue, dizziness</i> )	Clinician (PANNS for schizophrenia syndrome, <b>Clinician Global Measures</b> )	Observer ( <i>seizures, infant behavior, stroke, death</i> )
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# John Powers, Dave DeMets, Marc Walton, Laurie Burke, Bob Temple...

*Chest Pain*  
*Dyspnea*  
*Fatigue*  
*Hospitalization*  
*L.T., Death*

*6-MWD*  
*3-MS*  
*Exercise testing*

*PVRI*  
*NT-proBNP*  
*HR, BP*  
*m-PAP*



**Direct  
Measures**



**Indirect Measures  
Continuum  
in PAH**

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

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- *Addressing Assay Performance*

  - ...analysis of analytical performance of an assay...  
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# Replacement Endpoints

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- 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*”

# Biomarkers & 'Feels, Functions, Survives' Endpoints

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*NT-proBNP*
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    - ...*Physician or Observer administered & PROs...*

# Direct Measures of 'Feels, Functions, Survives' in PAH

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- ~ Overall survival ~ 6MWD @ 48 wks ~ Syncope (freq. & severity)
- ~ NYHA Functional Class (1-2 vs. 3-4) ~ Clinician Global Measures
- ~ Level of successful social interaction with peers (mod. CAMPHOR)
- ~ Days school missed for health-related reasons; Everyday living skills
- ~ Symptoms: SF-36, Borg Dyspnea Score, Pain Measures

Composites of measures of 'Feels, Functions and Survives':

- ~ (E.g. Acute Coronary Syndrome: CV Death, Stroke, MI)
  - ✓ PAH: Death, L.T., PAH Hosp, (NYHA↑ & 6MWT↓)
- ~ (E.g. CABP: Cough, Pleuritic chest pain, Dyspnea, Sputum Prod)
  - ✓ PAH: Chest pain, Dyspnea, Fatigue, Dizziness/Syncope  
....scored as Absent, Mild, Moderate, and Severe....

The endpoint: a) one-point improvement in at least two symptoms  
& b) no worsening of any other symptoms, at day TBD

# Principles & Insights

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- \* Fleming TR, DeMets DL: Surrogate endpoints in clinical trials: Are we being misled? *Annals of Internal Med* 1996; 125:605-613.
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# Principles & Insights

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