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Rare Disease Workshop Series

Introduction to Some Important Issues in Evaluating Efficacy

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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.

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

Topics

- ~ **Criteria for Choosing Endpoints**
- ~ Limitations of Biomarkers
- ~ Patient Reported Outcomes: Challenges
- ~ Minimum Clinically Important Difference

Criteria for Study Endpoints in Clinical Trials

- Measurable/Interpretable
- Sensitive
- Clinically relevant

A “Clinical Endpoint”:

...a direct measure of how a patient

“functions, feels or survives”...

... Robert Temple, FDA

Biomarkers & Clinical 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:** Quality of Life
 - Emotional instability: angry outbursts, unstable relationships, forgetfulness, inconsistent behavior, poor \$ management
 - Loneliness, poor social relationships, anxiety, depression
 - ~ **Survives**

Topics

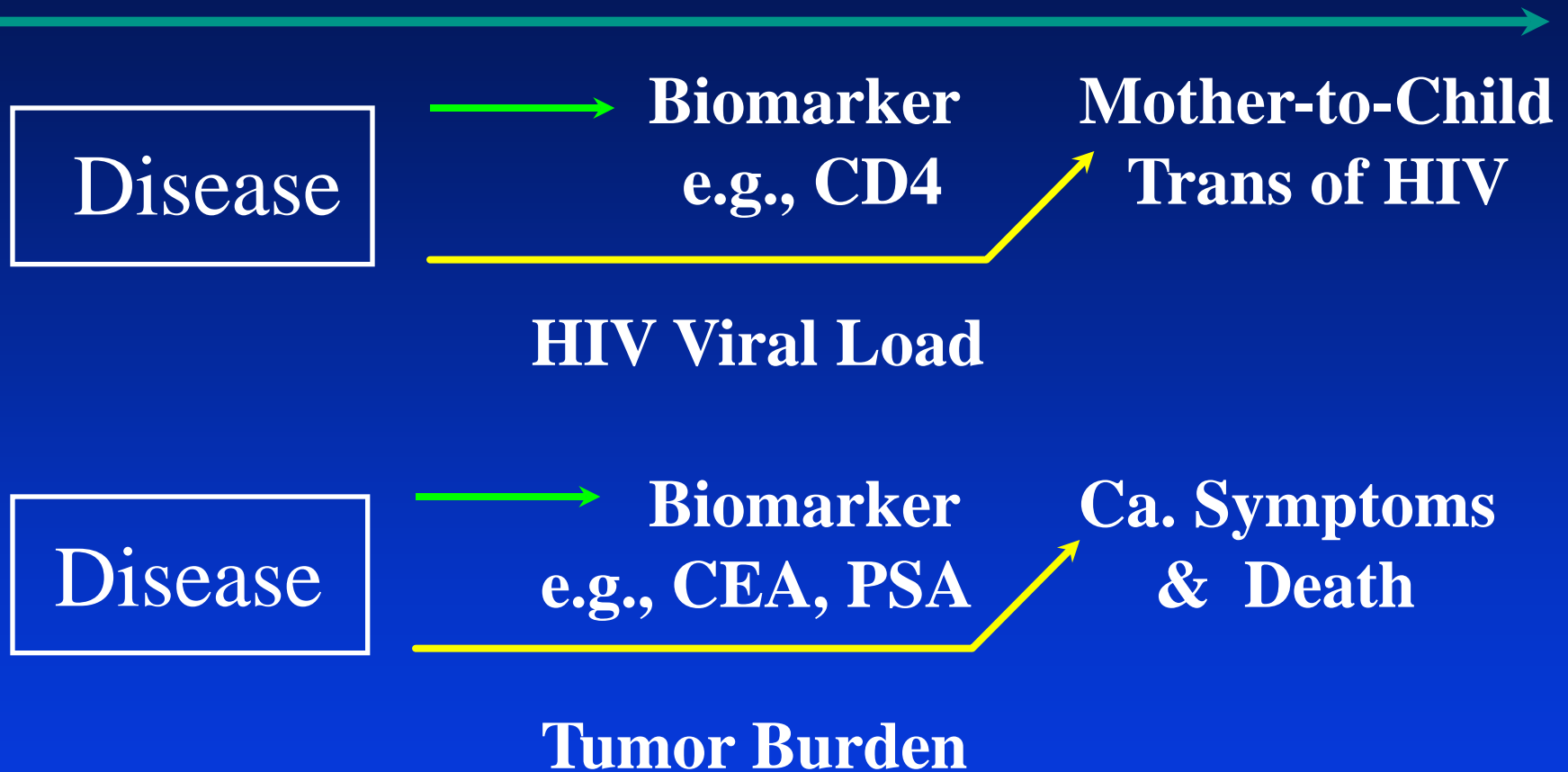
- ~ Criteria for Choosing Endpoints
- ~ **Limitations of Biomarkers**
- ~ Patient Reported Outcomes: Challenges
- ~ Minimum Clinically Important Difference

Biomarkers (Surrogates)

Treatment effects on Biomarkers:

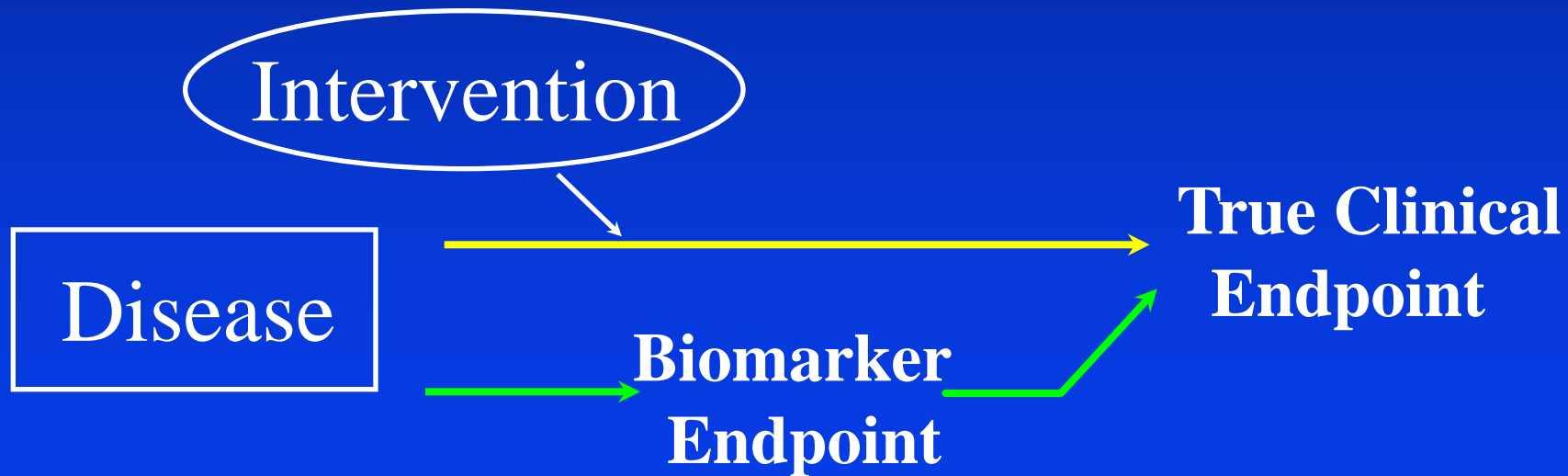
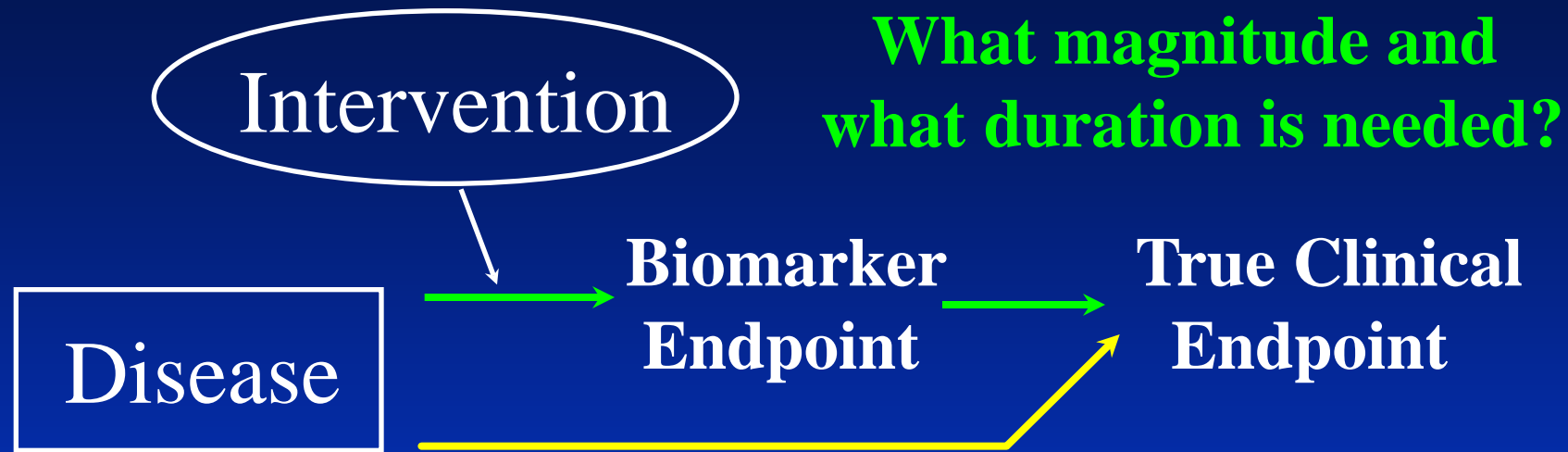
- Establish *Biological Activity*
- But not necessarily *overall Clinical Efficacy*
 - ~ Ability to conduct normal activities
 - ~ Quality of Life
 - ~ Overall Survival

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



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

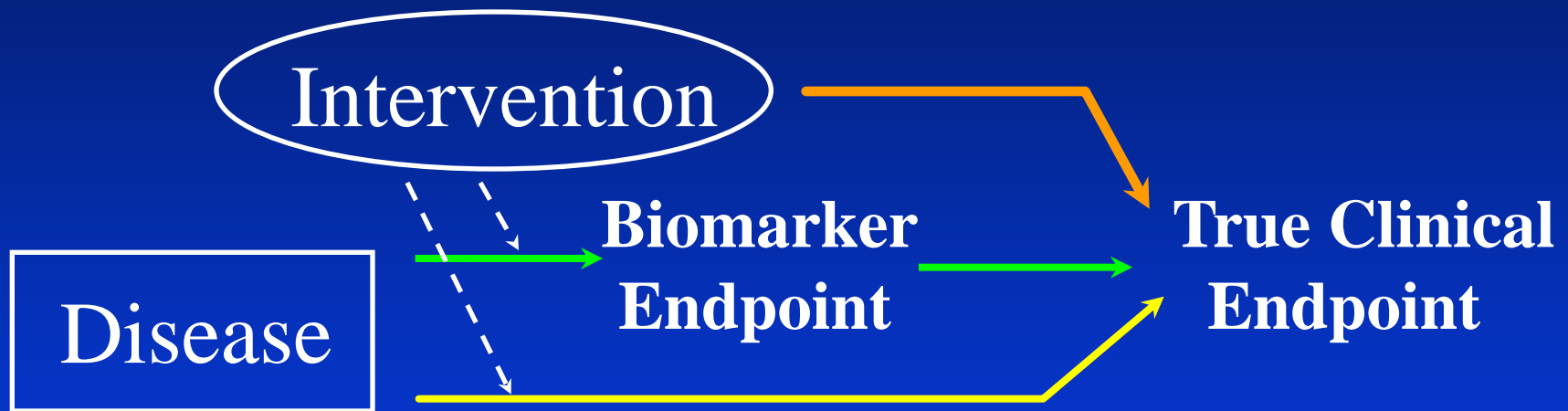
Multiple Pathways of the Disease Process



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 β -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

- *Effect of the Intervention
on the Clinical Endpoint*
is reliably predicted by the
*Effect of the Intervention
on the Surrogate Endpoint*

Prentice's Sufficient Conditions to Validate a Surrogate Endpoint

1. The surrogate endpoint must be correlated with the clinical outcome
2. The surrogate endpoint must fully capture the net effect of treatment on the clinical outcome

Validation of Surrogate Endpoints

Statistical

- Meta-analyses of clinical trials data

Clinical

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

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 clinical outcomes...

- *Utilization*

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

Biomarkers as Surrogate Endpoints

- A biomarker 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 biomarker evaluation impact the public?

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

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 - Loneliness, poor social relationships, anxiety, depression
 - ~ **Survives** . . .Physician administered & PROs...

Potential Clinical Endpoints: Add'l Issues

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 Clinical Endpoints: Add'l Issues

- Patient Reported Outcomes:

... Clinical 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)

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A Wide Array of Potential Clinical Endpoints

Eg.: MPS-I, MPS-II, MPS-IVA, PKU, LEMS, Pompe, Fabry

Functional Status: Functional Outcome Scales

UCSD Performance Based Skills Assessment,
Everyday Living Skills, Vocational Skills, Visual Acuity
6MWD, 3-Minute Stair Climb, Sleep Apnea Score

Clinical Global Measures:

CGI-I, CGI-S, Connors-3, MPS Health Assessment Q

Neuropsychiatric Symptoms:

HAM-D, HAM-A, ADHD Scores

Pain Measures

Primary Goal of Clinical Research

- Not:

“To obtain a statistically significant result”

- Rather:

“To obtain a statistically reliable evaluation regarding whether the experimental intervention is safe and provides clinically meaningful benefit.”

** Fleming, Statistics in Medicine, 2006*

Minimum Clinically Meaningful Difference

Eg.: MPS-I, MPS-II, MPS-IVA, PKU, LEMS, Pompe, Fabry

- Not simply “A *detectable* difference”

Survival: With 3 month median, a one week improvement

Visual Acuity: A one letter difference in BCVA at 12 months

6MWD: A 5 meter improvement at 24 weeks

- Not based on Standard Deviation of the measure
- What about an “*anchor based*” method,
e.g. using patient global rating?
- Are there other appropriate approaches
to identifying the MCID?
- When in the research process should
the MCID be determined?

Topics

- ~ Criteria for Choosing Endpoints
- ~ Limitations of Biomarkers
- ~ Patient Reported Outcomes: Challenges
- ~ Minimum Clinically Important Difference
- ~ **Rare Diseases: Concluding Thoughts**

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