Clinical Trial Readiness

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Speaker's Bureau: none

Equity & Consulting Agreements: none

Clinical Trial Readiness

- Diagnostic criteria -DC
- Metrics of severity - DC
  - natural history
  - response to current therapies
- Biomarkers - DC
- Clinical Trial Endpoints - DC
- Therapeutic interventions

Diagnostic Criteria

Homogenous cohorts

is it dystonia? - DC

dystonia subtypes? - DC

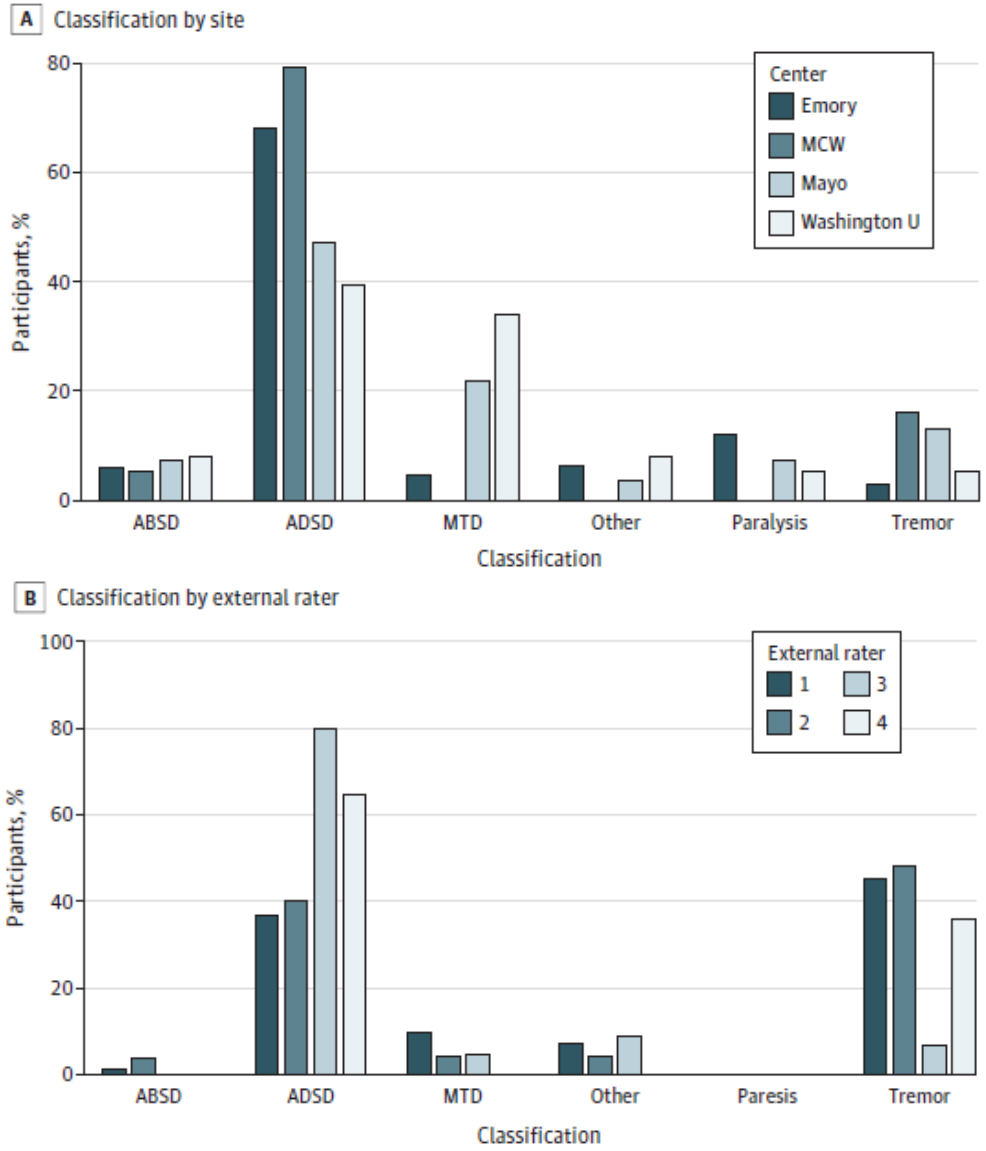
Generalizable results - DC

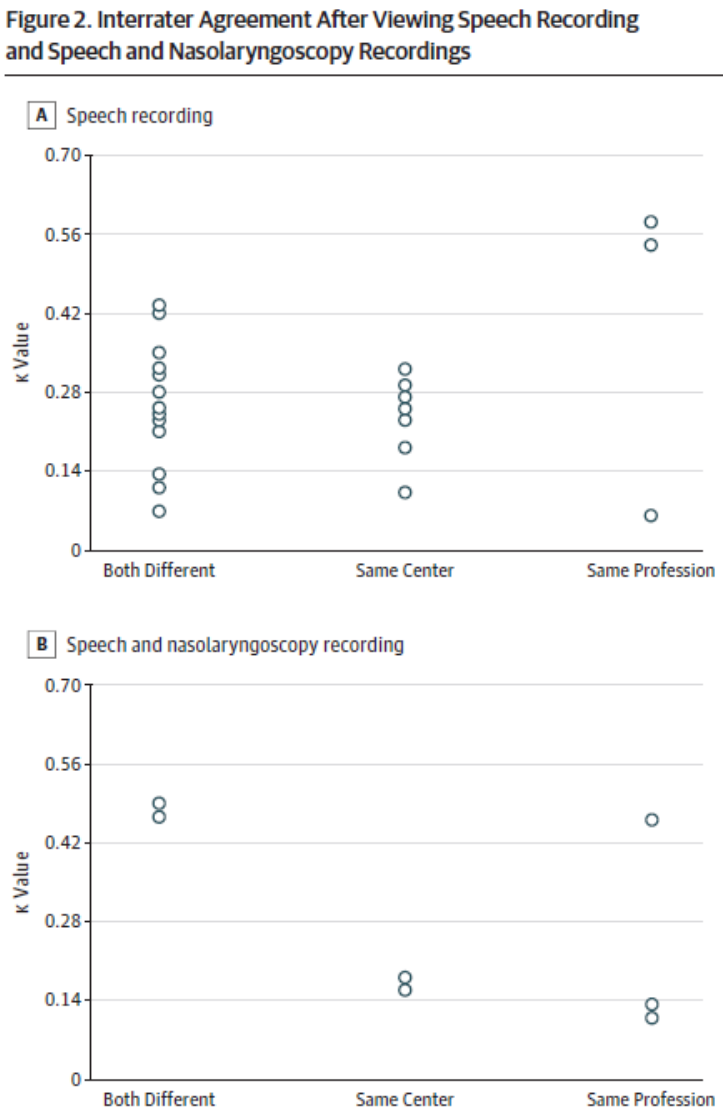
Diagnostic Criteria

Laryngeal dystonia – DC
Blepharospasm - DC
Cervical Dystonia – DC (subtypes)
Limb dystonia

Task-specific dystonia
musicians' dystonia

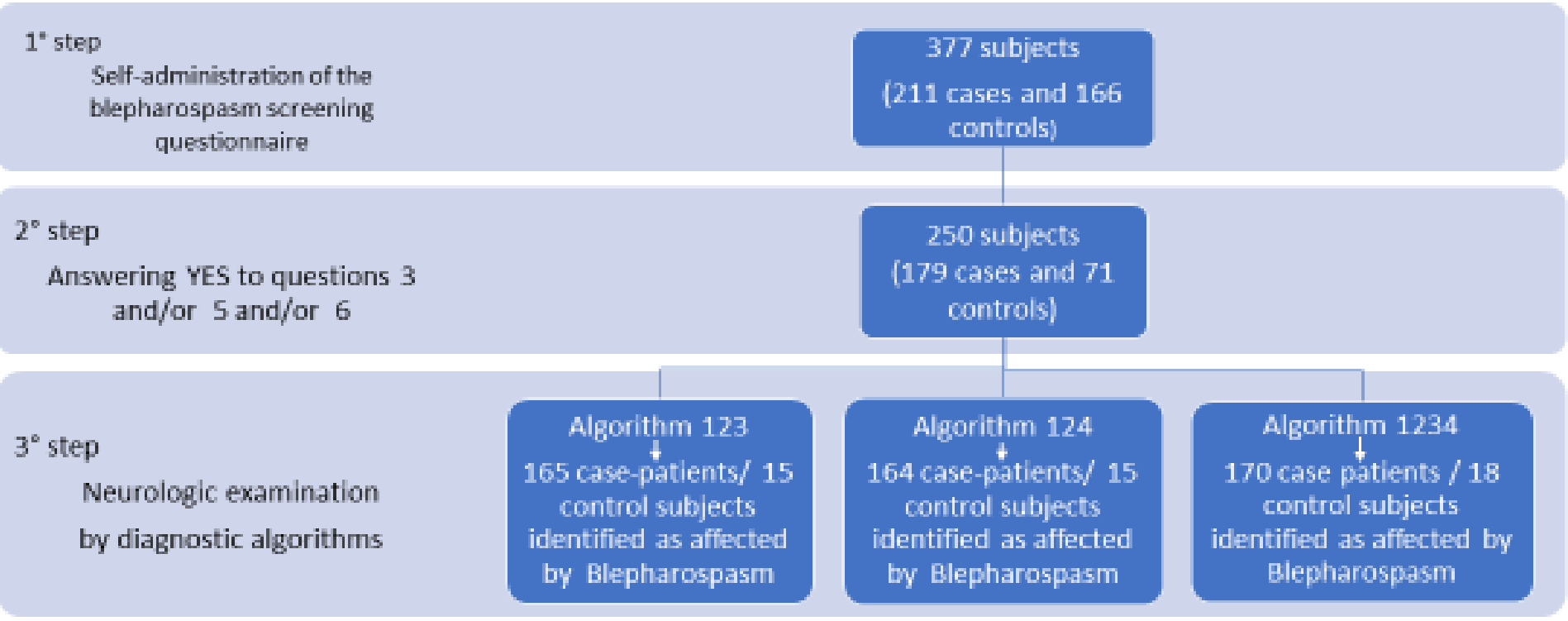
Laryngeal Dystonia: Diagnosis-DC





Ludlow C, et al, JAMA Otolaryng 2018

Blepharospasm: DC



Sensitivity	78% (165/211)	78% (164/211)	81% (170/211)
Specificity	91% (151/166)	91% (151/166)	83% (138/166)

DeFazio G, et al, submitted

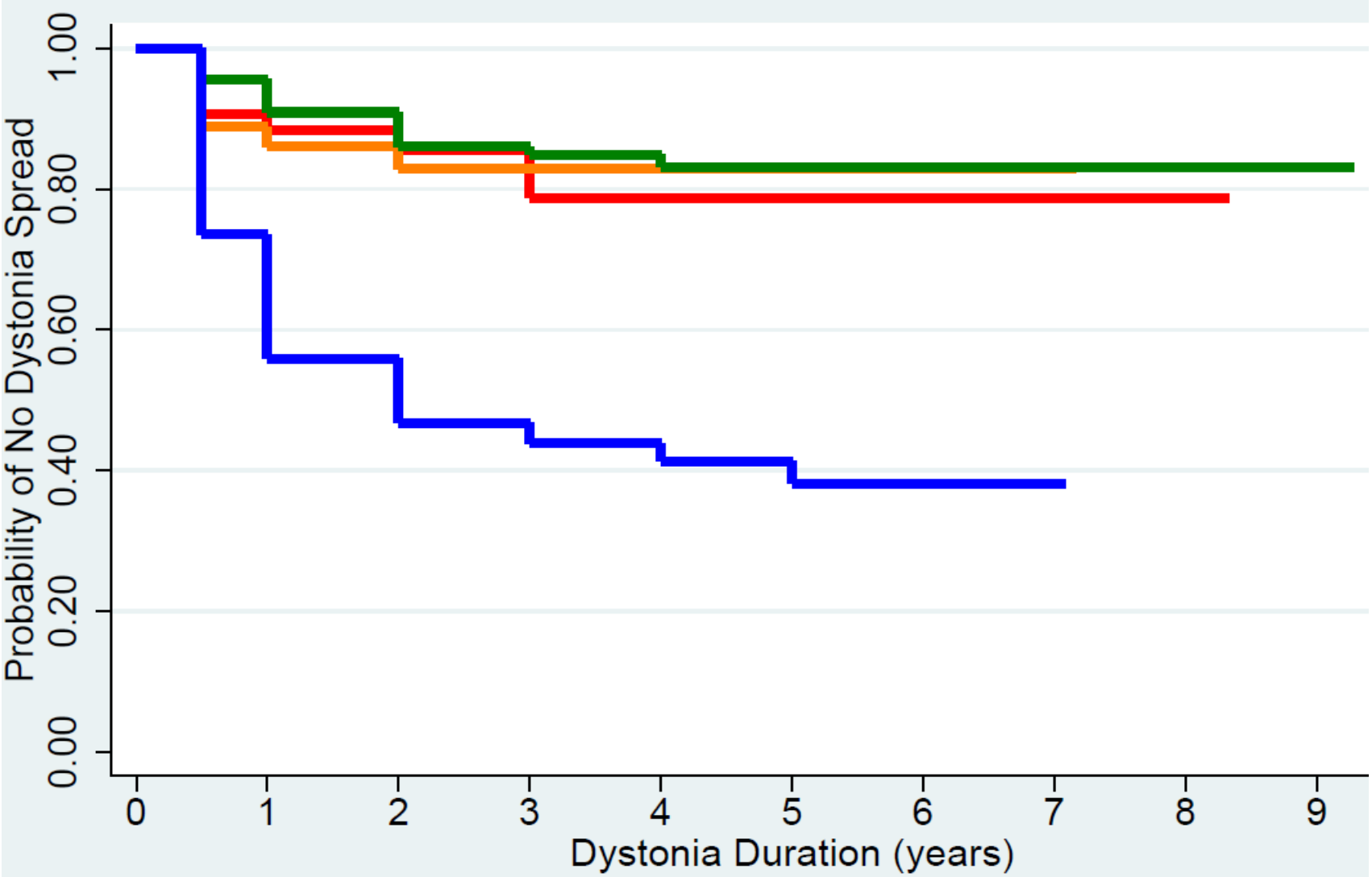
Metrics of Severity (severity vs spread)

General dystonia ratings

Specific rating scales

- Cervical Dystonia
- Blepharospasm
- Laryngeal dystonia

Natural History: Spread - DC



Berman B et al, JNNP 2020

Factors related to progression-DC

Table 3. Influence of BoNT on HR-QoL within 1 yr

	Group	Time	Group*Time
General Health (n=72)	p = .18	p = .73	p = .610
Physical Functioning (n=72)	p = .51	p = .27	p = .58
Physical Role Functioning (n=72)	p = .93	p = .01	p = .54
Pain (n=71)	p = .98	p = .56	p = .17
Energy/ Fatique (n=72)	p = .60	p = .01	p = .46
Emotional Well-being (n=72)	p = .004	p = .02	p = .54
Emotional Role Functioning (n=71)	p = .30	p = .07	p = .79
Social Functioning (n=72)	p = .03	p = .02	p = .68

Junker J et al, submitted

Metrics of Severity: Effects of Interventions

Transient: Chemodenervation

yo-yo

Long term: Surgical

but still time dependent

A Biomarker

Objectively measured indication of normal biologic process, pathogenic process or drug response

Fleming et al, Ann Intern Med, 1996

Biomarkers

Diagnostic - DC
Metric of Severity - DC
Prediction of progression - DC
Endpoints of a clinical study
surrogate endpoints

What is a Primary Endpoint of a clinical study?

Clinically important event:

- -- death, stroke or MI
- -- disability, quality of life

Categorical (e.g. need assistive walking device)

Continuous (e.g. time to walk a specified distance)

Bucher, et al: JAMA 1999; 282: 771-777

Power of a Clinical Trial Depends on:

- Clinically relevant effect of intervention on the Primary Clinical Endpoint
  - Sample size
  - Variance of measurement
  - Duration of Study
  - Effect Size

Surrogate Endpoint

A biomarker that can substitute for a clinically meaningful endpoint

Validation of a Biomarker as a Surrogate Endpoint

- **Biomarker & clinical outcome:**
  - **Strong, consistent & independent**
  - **Biomarker response must be strong enough to predict**
- **Biomarker predicts efficacy & toxicity**

Therapeutic Candidates

- Rationale
- Safety
- Efficacy
- Dose
- Target Engagement
- Phase 1, 2, 3 trials

Acknowledgments

frontiers in Neurology

REVIEW
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Check for updates

The Dystonia Coalition: A Multicenter Network for Clinical and Translational Studies

*Gamze Kilic-Berkmen[1], Laura J. Wright[2], Joel S. Perlmutter[3], Cynthia Comella[4], Mark Hallett[5], Jan Teller[6], Sarah Pirio Richardson[7], David A. Peterson[8], Carlos Cruchaga[9], Codrin Lungu[10] and H. A. Jinnah[1,11]**

NIH (NINDS, NCATS), PAGS (DMRF, NSDA, etc)

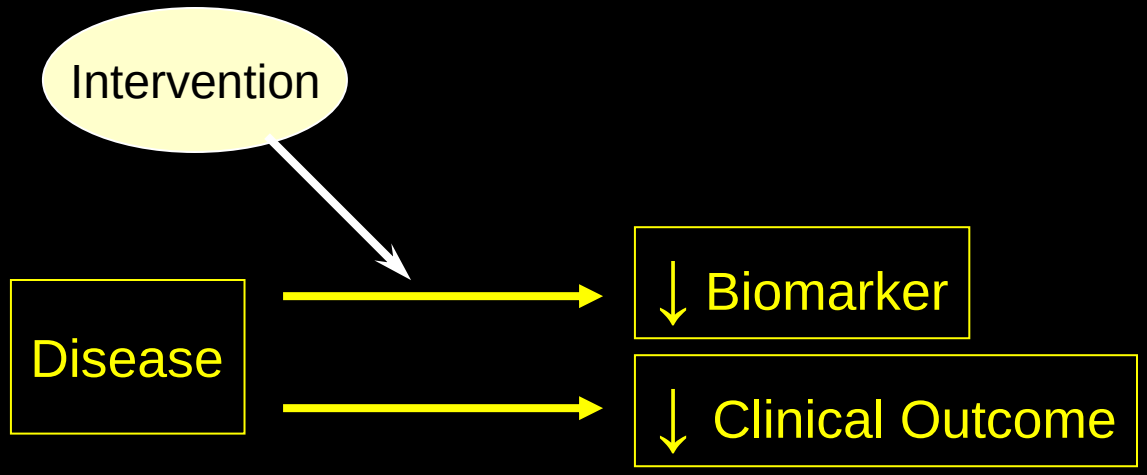
The Important Issue of the Primary Endpoint

- The Primary Clinical Endpoint should be chosen for its clinical importance to patients, **NOT** to minimize the sample size or duration of the study

Why use a surrogate endpoint?

- **If treatment effect is greater or measurement variability is less then sample size or study duration decreases**

Failures of Biomarkers as Surrogate Endpoints



The biomarker is not in the causal pathway of the disease process that affects outcome

Fleming, T. R. et. al. Ann Intern Med 1996;125:605-613

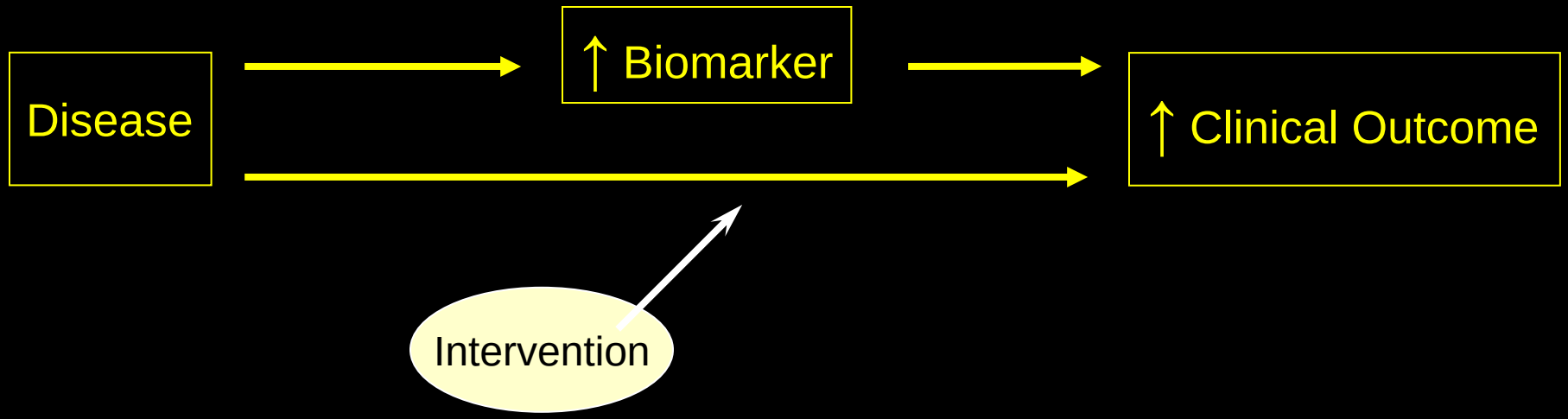
Failure of a Biomarker as Surrogate Endpoint

Efficacy of encainide after myocardial infarction

(CAPS Am J Cardiol 1988; 61:501-9; CAST NEJM 1991; 324:781-8)

	Encainide	Placebo
VPC Suppression	**79%**	**37%**
Mortality	7%	3%

Failure of biomarkers as Surrogate Endpoints



The biomarker is not in the pathway of the intervention effect on the disease process

Fleming, T. R. et. al. Ann Intern Med 1996;125:605-613

Failure of biomarkers as Surrogate Endpoints

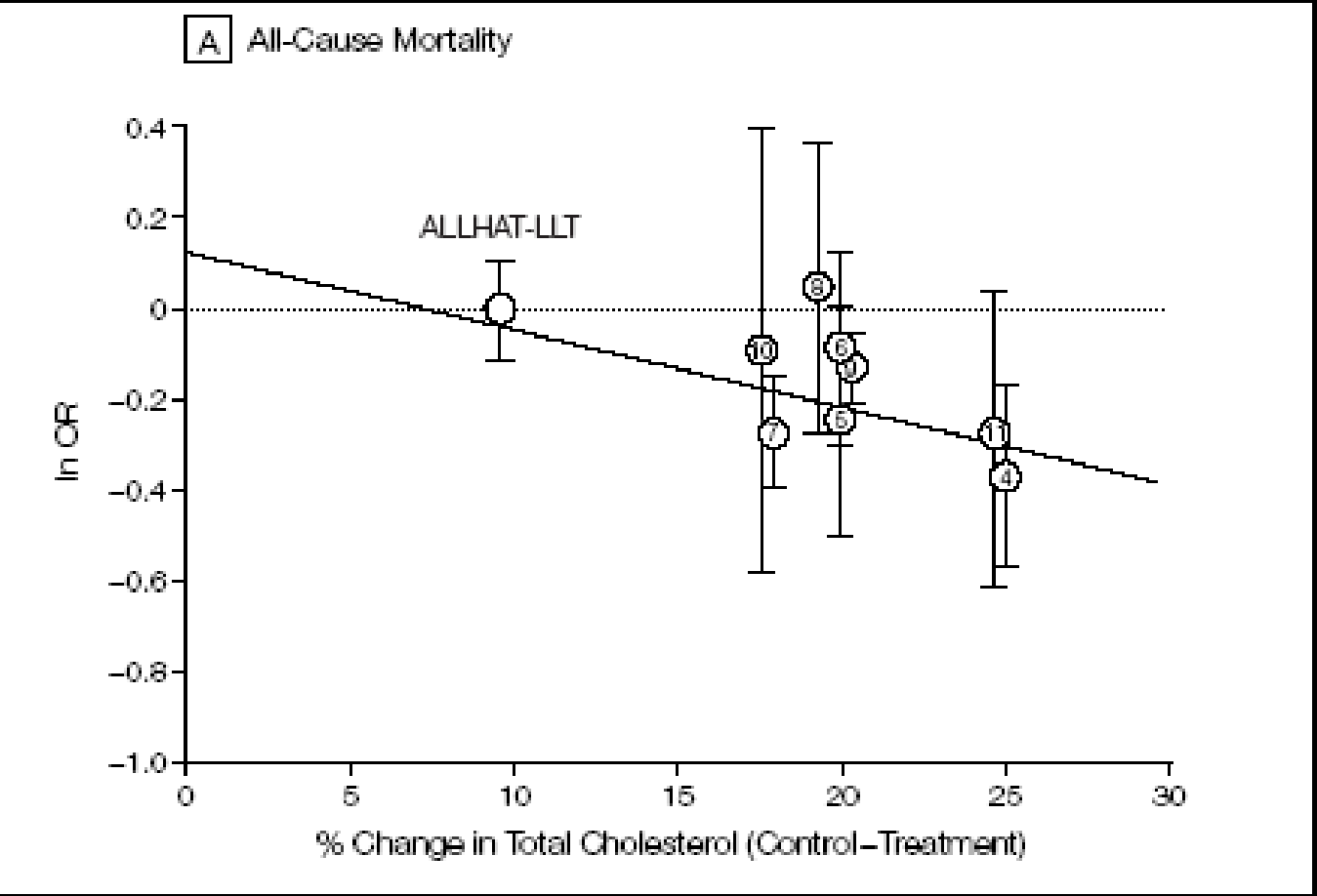
The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT)

JAMA 2002;288:2998-3007

	Treatment Group		
	Pravastatin 40 mg/day	Usual Care	p value
Cholesterol	177.6±33.8	195.5±37.3	< .0005
All Deaths	631	641	.88

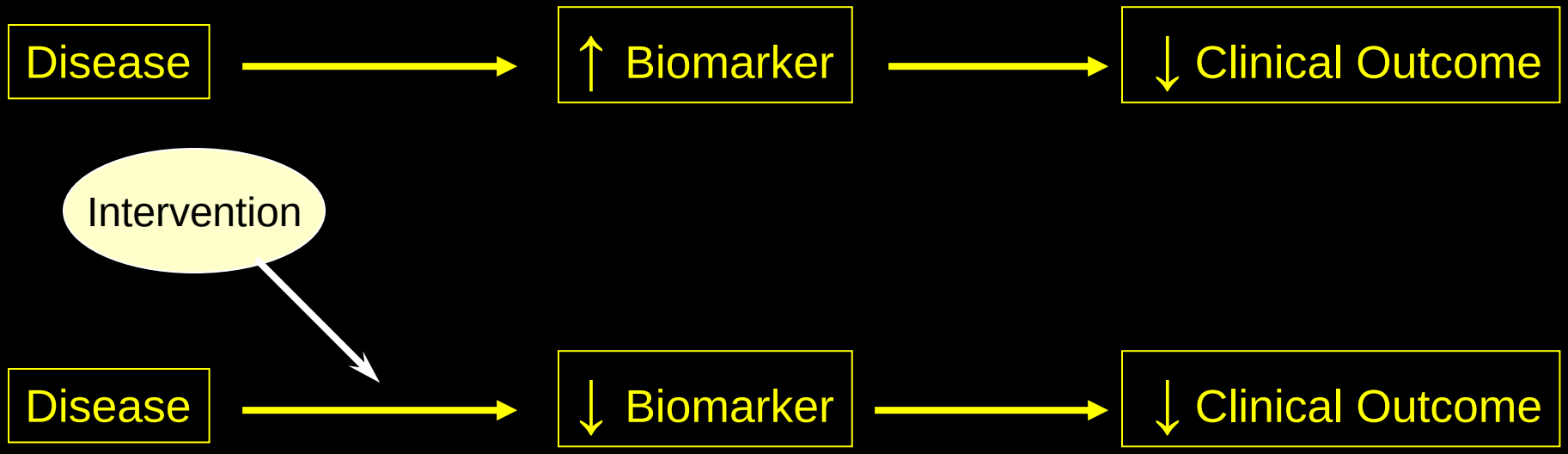
Reductions in Mortality vs Total Cholesterol Difference

JAMA 2002;288:2998-3007.



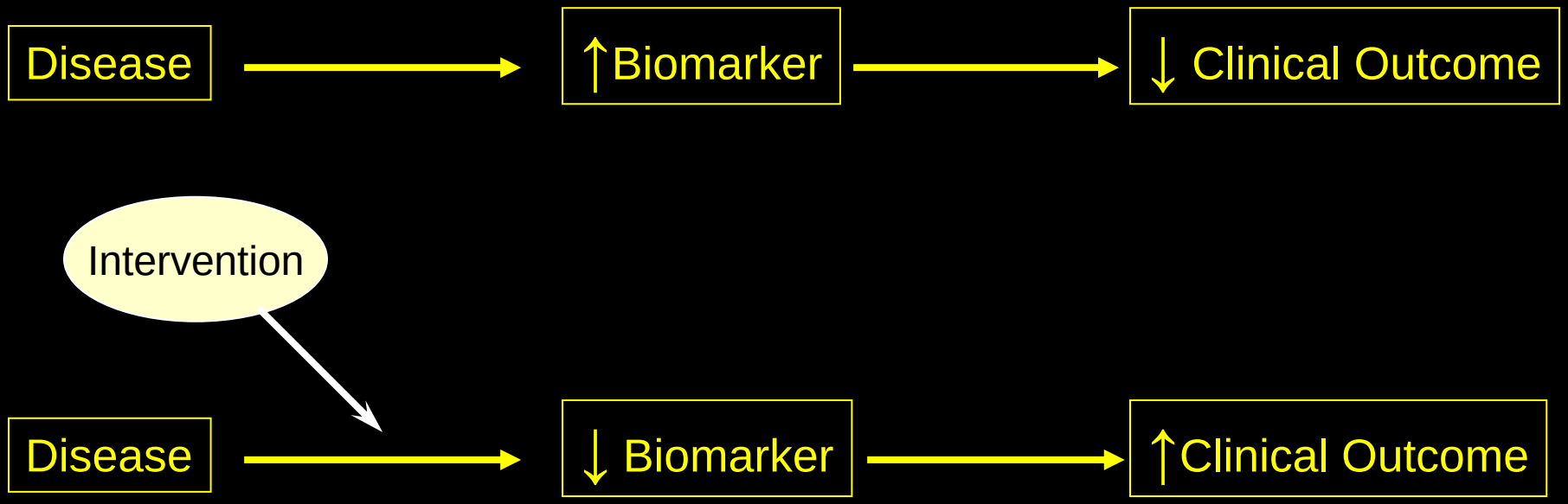
Log odds ratios (ln OR) and 95% confidence intervals for active treatment vs control for 9 large statin trials are compared with regression lines (solid) from meta-analyses of 45 long-term trials using statins and other cholesterol-lowering interventions published before December 31, 2000

Failure of biomarkers as Surrogate Endpoints



A statistically significant change in the biomarker may not be of sufficient magnitude to produce a change in clinical outcome

Optimal situation for a biomarker to be a valid surrogate endpoint



Changes in the biomarker mediate all of the effect of the intervention on clinical outcome

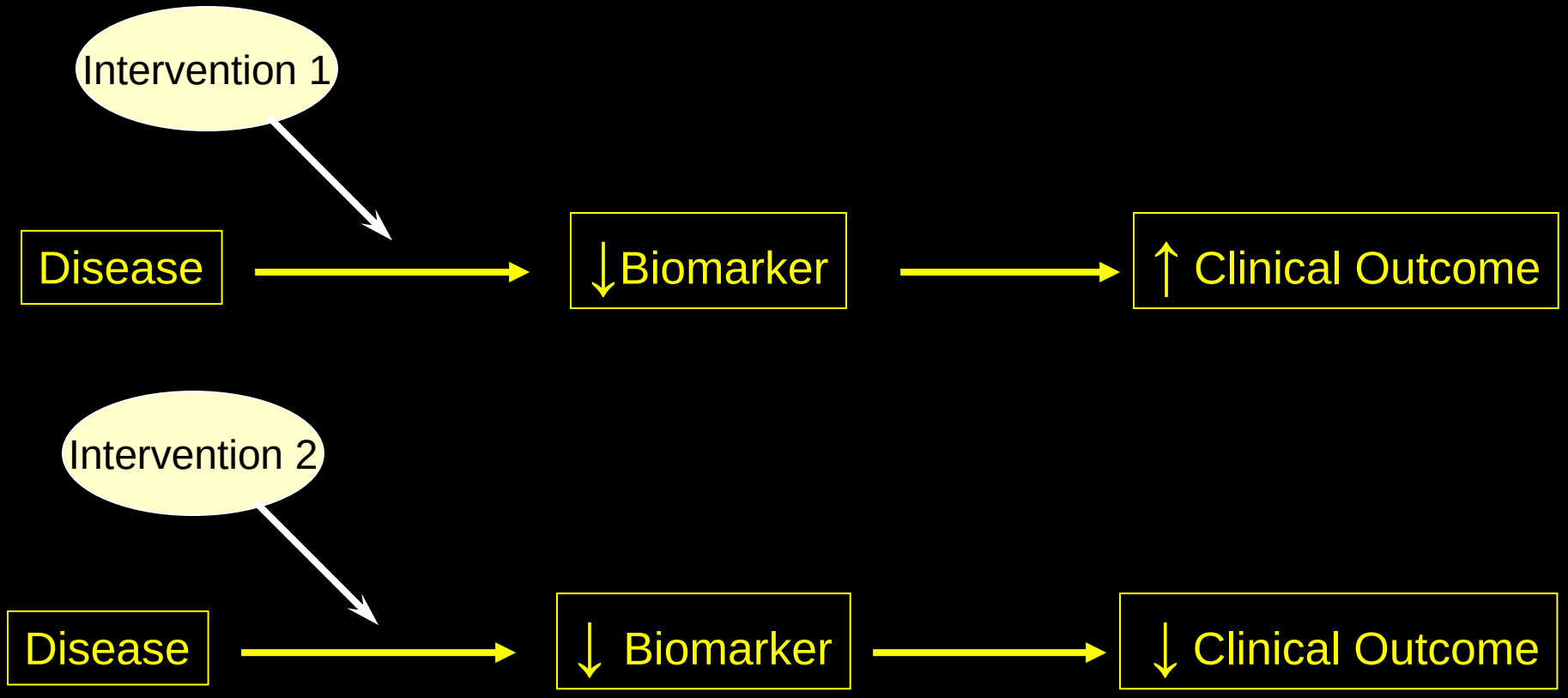
Fleming, T. R. et. al. Ann Intern Med 1996;125:605-613

Aspirin v. aspirin + clopidogrel for prevention of stroke

(CARESS Circulation 2005; 1112233-2240; MATCH Lancet 2004; 364:7331-337)

	ASA	ASA + CPD
7 days		
TCD Cerebral Emboli at 7 days	73%	44%
18 months		
Stroke	9%	8%
Life threatening Bleeding	1%	3%

Some reasons for failures of Biomarkers as Surrogate Endpoints



A biomarker that is a valid surrogate endpoint for one therapeutic mechanism/drug class may not be valid for a different therapeutic mechanism/drug class

Clinical Trial Endpoints

Clinically meaningful

Surrogate endpoints

Primary Endpoint

- **Primary Clinical Endpoints can be**
  - **Life Events (e.g. need assistive device to walk)**
  - **Quantitative Measurements (e.g. time to walk a specified distance)**

Take Home Message

Biomarker of Efficacy:

- **reflect action of therapy**
- **reflect relevant pathophysiology**

Classification Scheme

Axis 1: clinical features

- **age of onset**
- **body distribution**
- **temporal pattern**
- **associated features**
  - **isolated**
  - **combined**

Albanese A, et al, Mov Disord 2013

Classification Scheme

Axis 2: etiology

- **CNS pathology**
- **inherited or acquired**
  - **inherited**
  - **acquired**
  - **idiopathic**

Albanese A, et al, Mov Disord 2013