Decision Analytic Models for Alzheimer's Disease: State of the Art and Future Directions*

Joshua T. Cohen, Ph.D.

The Center for the Evaluation of Value and Risk
Institute for Clinical Research and Health Policy Studies
Tufts Medical Center

* This talk is based in large part on an article of the same title by JT Cohen and PJ Neumann. The article is in press at *Alzheimer's and Dementia*.

Types of Models

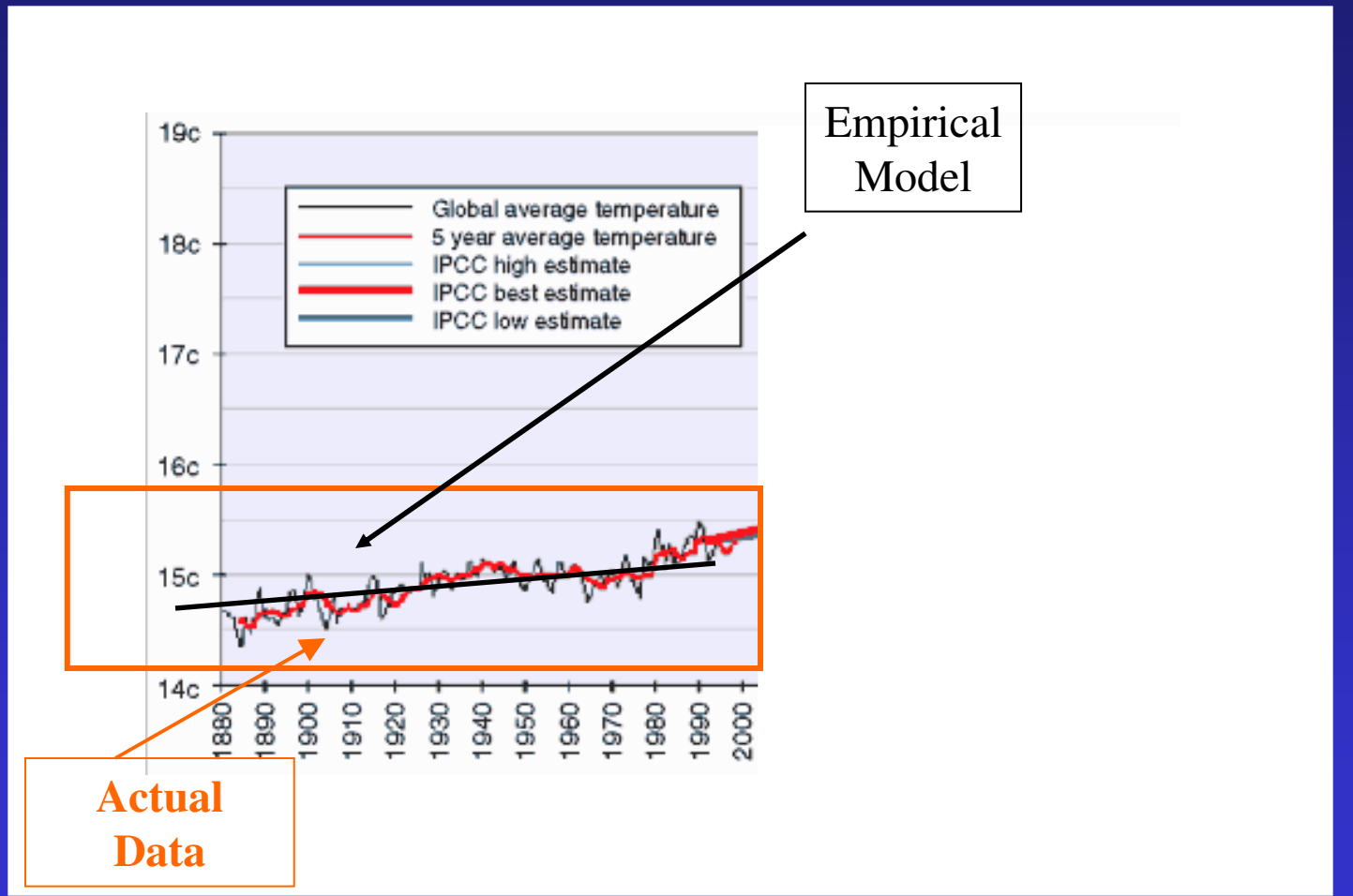
- Empirical
- Mechanistic
- Decision Analytic

Empirical Models

"… describe relationships between predictive factors and outcomes without attempting to explain the underlying mechanism that gives rise to these relationships."

Cohen JT, Neumann PJ. (in press). *Alzheimer's and Dementia*

Empirical Model Example: Global Warming

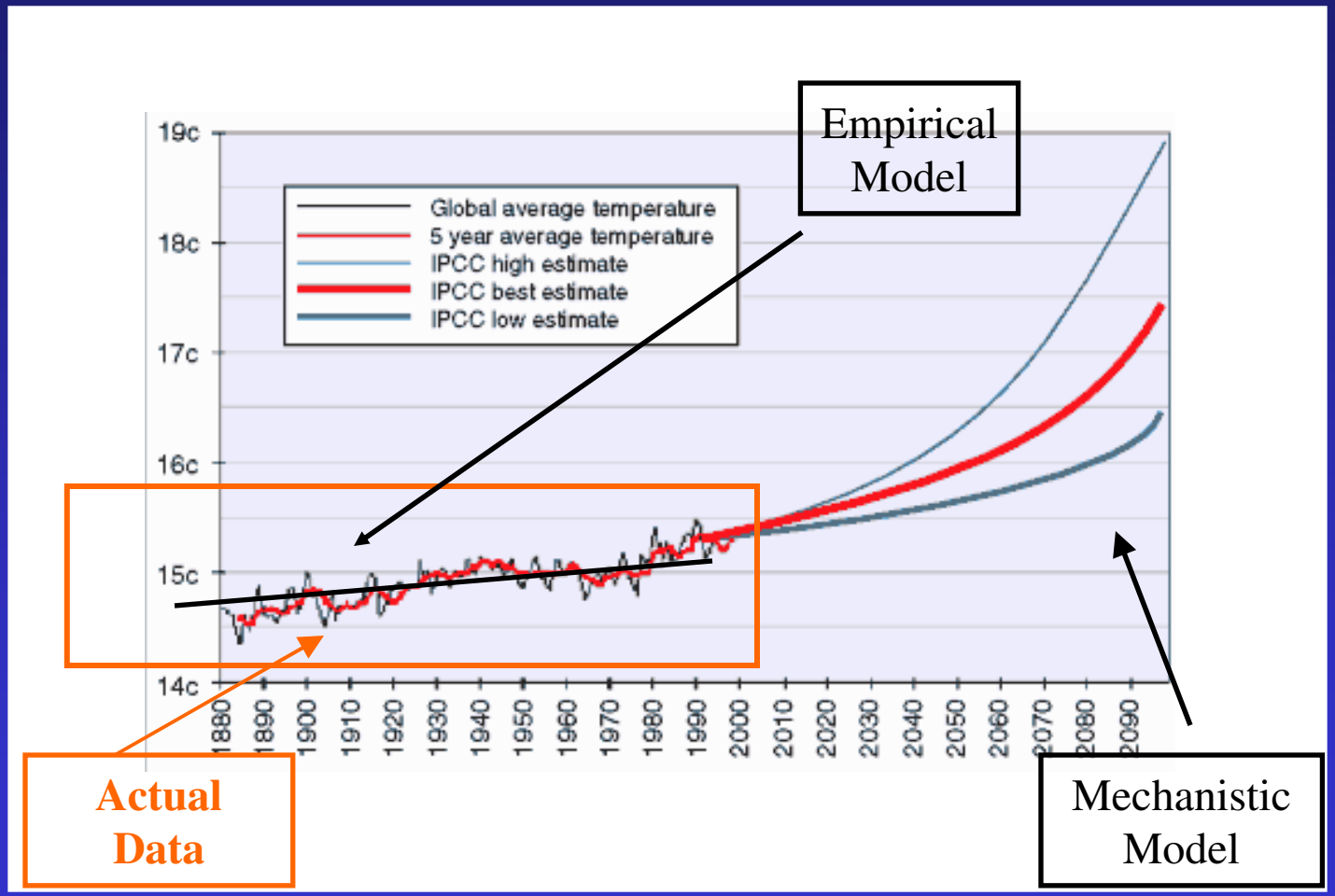


Mechanistic Model

"… extrapolate beyond existing data by incorporating judgments to systematically integrate multiple datasets."

Cohen JT, Neumann PJ. (in press). *Alzheimer's and Dementia*

Extrapolation Using Mechanistic Models

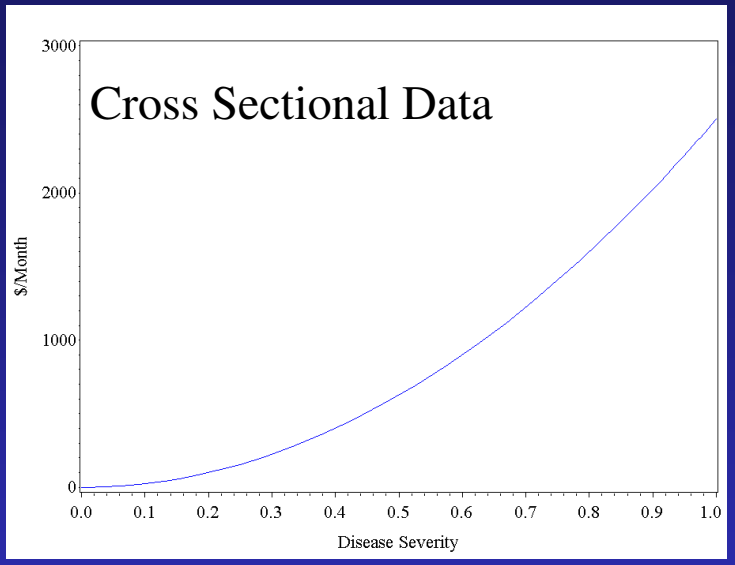


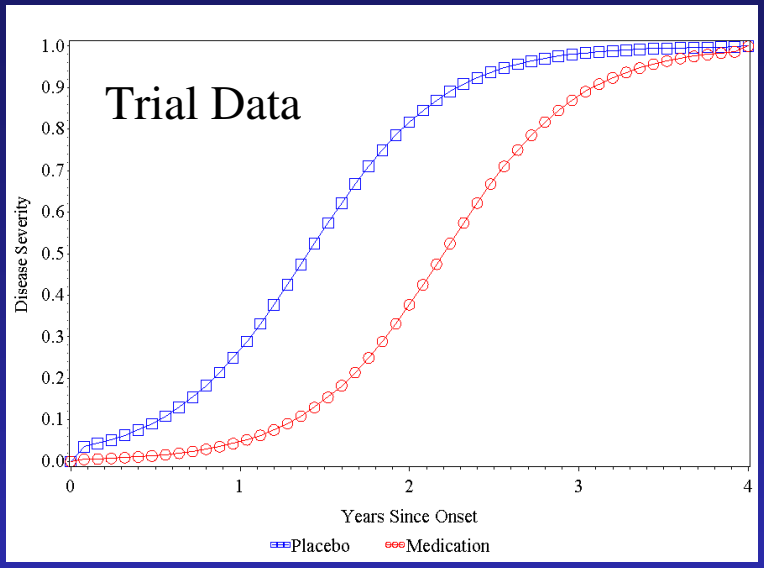
Decision Analytic Models

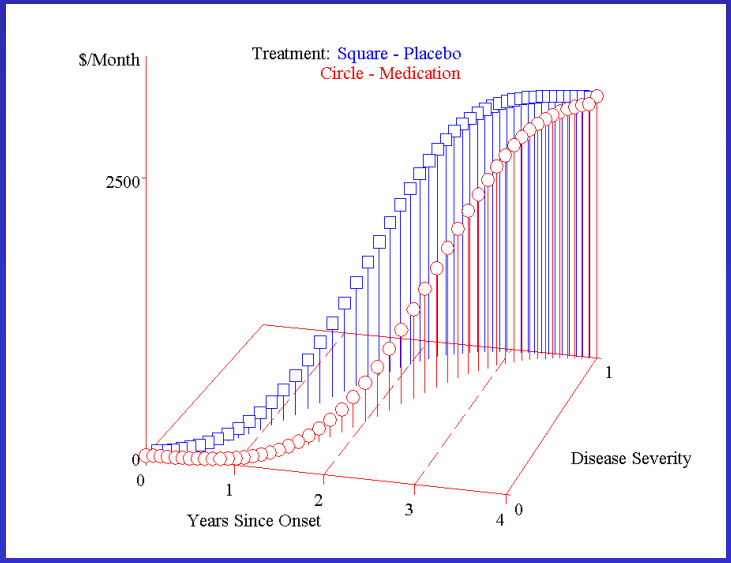
- Make "predictions for the purpose of comparing alternative courses of action."
  - Clinical endpoints of interest (not just more sensitive intermediate measures)
  - Economic costs
- Conceptually – can be mechanistic or empirical, but typically mechanistic
- Empirical models often inadequate
  - Trials often lack adequate follow-up
  - Do not record all relevant costs or quality of life impacts

Cohen JT, Neumann PJ. (in press). *Alzheimer's and Dementia*

Estimating the Impact of Alzheimer's Disease Treatment on Societal Cost – Hypothetical Example







Methods

- Identified 27 articles published since 1997 describing 13 distinct decision analysis models for AD

- Recorded
  1. Measures used to characterize disease severity
  2. Continuous vs. discrete disease severity measure
  3. Outcomes predicted
  4. Types of interventions evaluated

(1) Characterizing Disease Severity

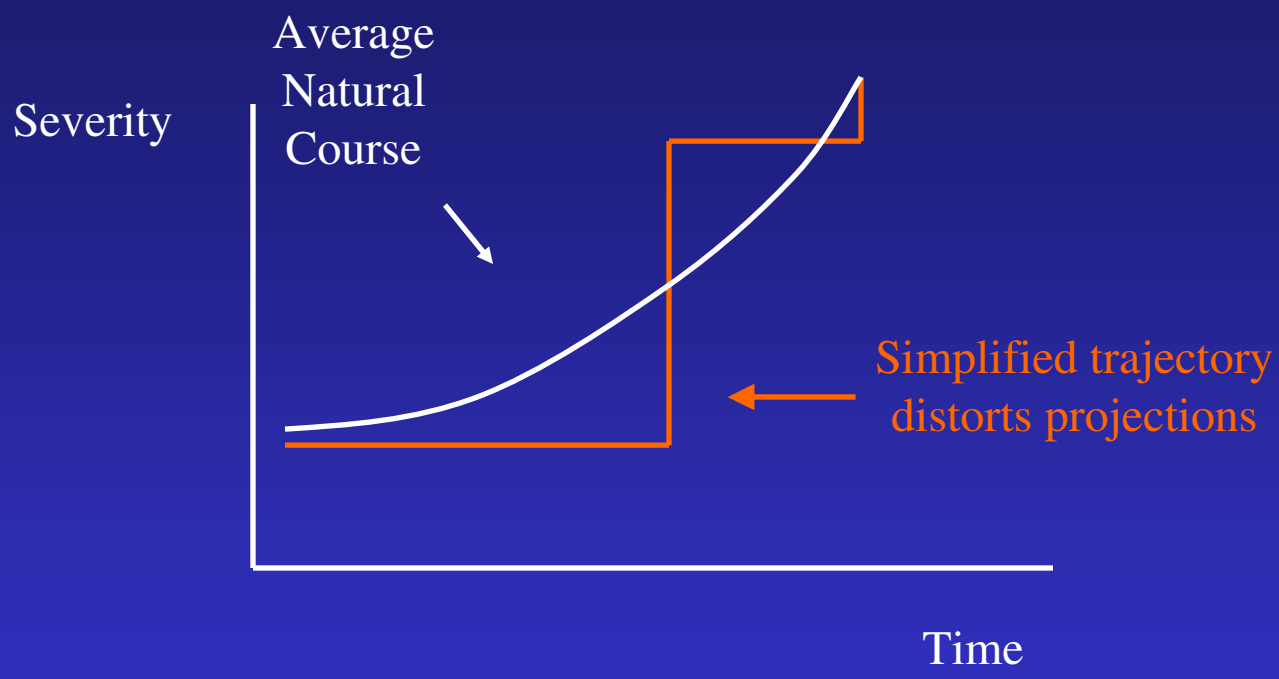
- Measures – cognition, function, behavior, aggregate measure (e.g., CDR)

- Results
  - 8 models focus on cognition
  - 2 models focus on CDR
  - 1 model (Kinosian et al.) – cognition, function, and behavior
  - 1 model (AHEAD) – full time care (FTC) required
  - 1 model (Jones et al.) – cognition and function

Use of Cognition Alone: Limitations

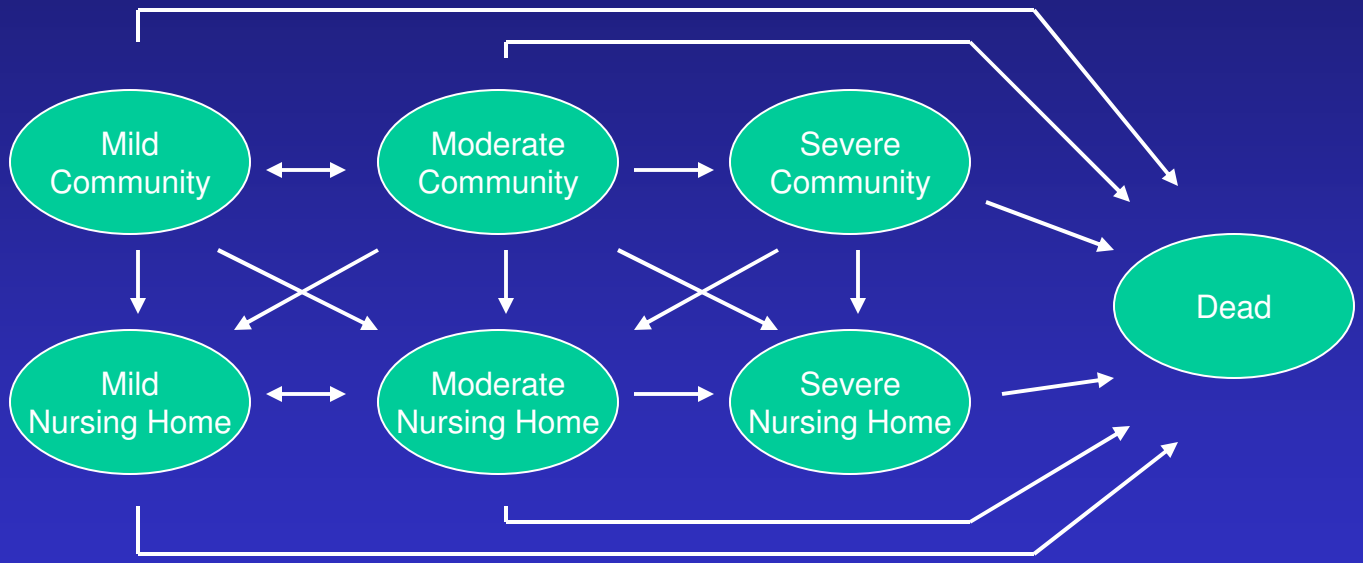
- Cognition used in clinical trials to establish efficacy for AD pharmaceuticals
- Cognition alone not a good indicator of value
  - Disease burden likely to depend strongly on function and on neuropsychiatric behavior
  - UK NICE rejected use of cognition-only models in their coverage deliberations

(2) Continuous vs. Discrete Progression



- "Discrete" means 5 or fewer states
- CDR global score is "discrete" but CDR sum of boxes is "continuous"

Discrete Model Example
Neumann et al. (1999)

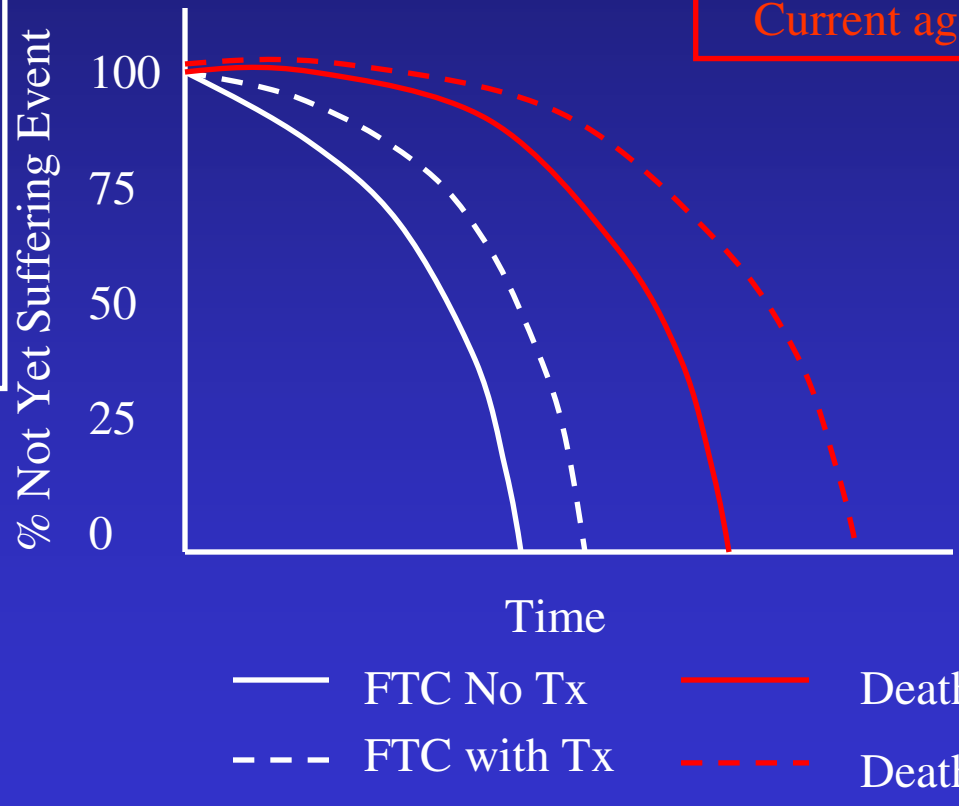


Neumann et al. (1999). Neurology. 52:1138-45

AHEAD Model

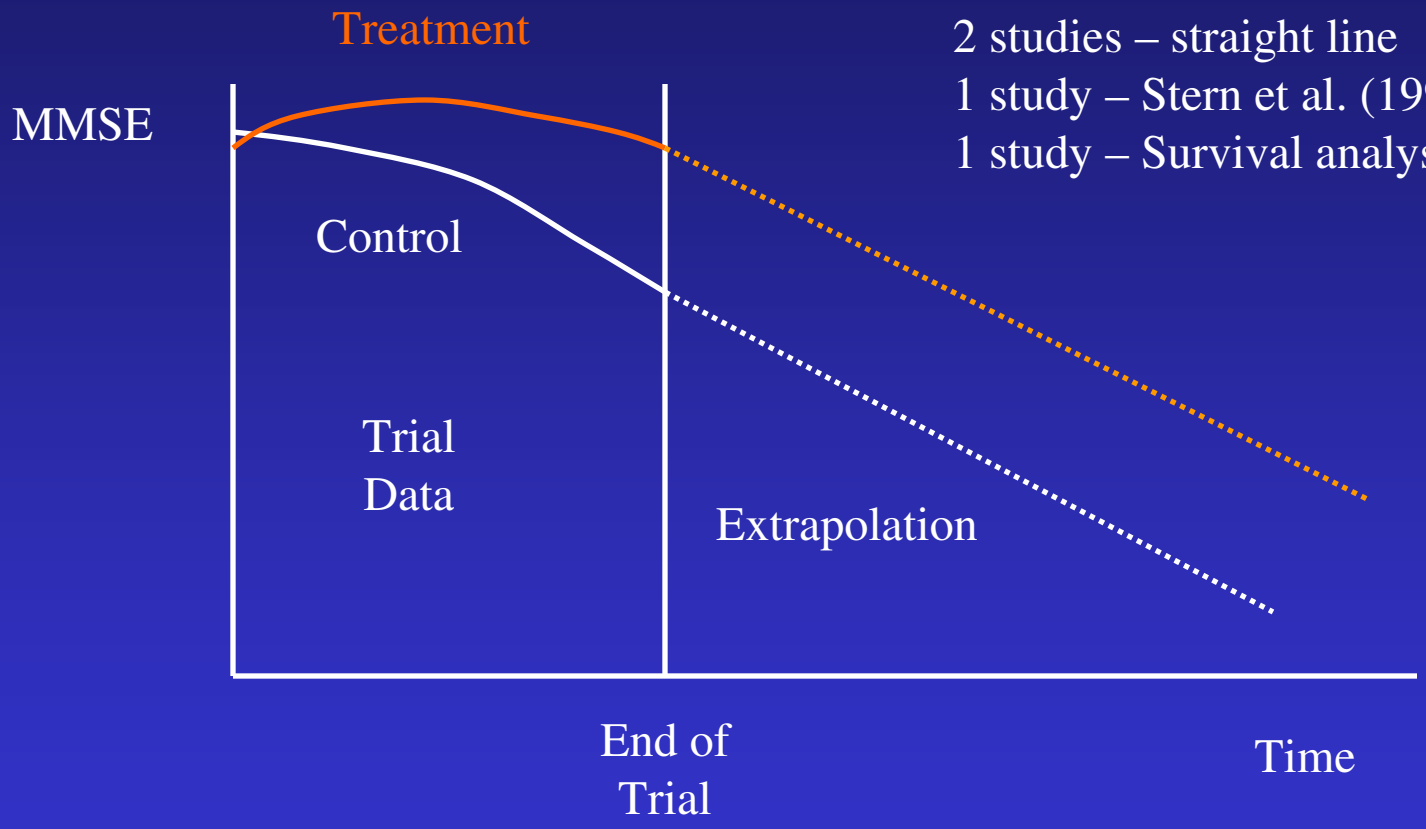
Death determinants
- Gender
- Extrapyramidal symptoms
- Modified MMS
- AD duration
- Current age 73 or less

FTC determinants
- Psychotic symptoms
- Extrapyramidal symptoms
- Modified MMS
- AD duration
- Age at onset 65 or less
- Current age 73 or less



Based on Fig. 3 from Caro JJ et al. (2001). Neurology. 57:964-971

Continuous vs. Discrete Progression: 4 of 13 Continuous



2 studies – straight line
1 study – Stern et al. (1994)* quadratic
1 study – Survival analysis

*Stern RG et al. (1994). Am J. Psychiatry. 151:390-396.

Continuous Model Based on Cognition: Fenn and Gray (1999)

- Model predicts time until loss of 1, 2, 3, 4, 5 MMSE points, controlling for
  - Baseline AD severity (MMSE)
  - Demographic characteristics
  - Treatment
- Survival curves allow for extrapolation beyond end of trial

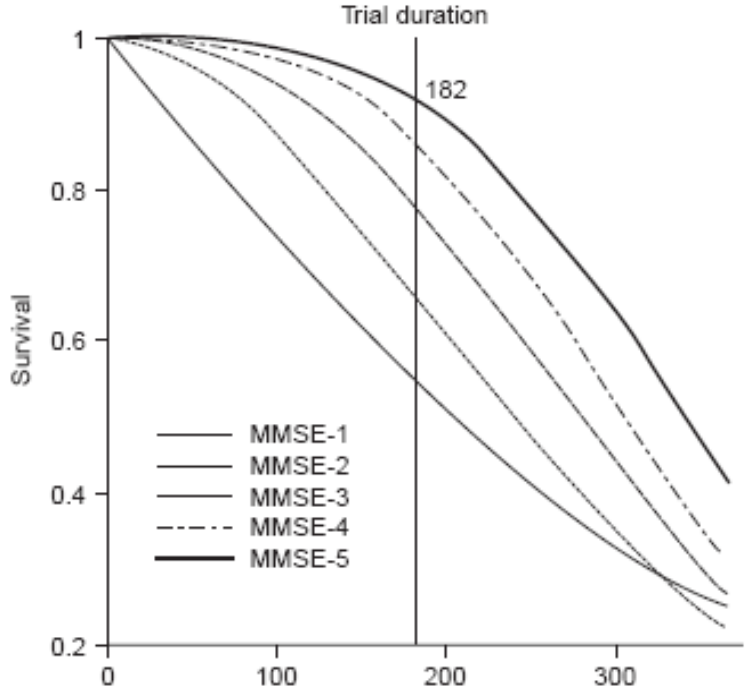


Fig. 2. Survival curves relative to MMSE thresholds. Data are based on a patient aged 73, with a baseline MMSE of 25, who was treated with placebo. **MMSE** = Mini-Mental State Exam; **MMSE-1 to -5** = point reductions in MMSE from baseline value.

Outcomes Predicted (3)

Endpoint	Number of Models out of 13 Total
Institutionalization	11
Life years	8
Years spent in severe AD state	4
Quality adjusted life years (QALYs)	4
Monetary cost	12

(4) Types of Interventions Evaluated

- Most of the 27 studies evaluated medication treatments

- Other types of interventions evaluated
  - 2 studies: diagnostic imaging
  - 1 study: treatment based on patient family risk
  - 1 study: Assistance for family caregiver

Models Should Address a Broader Range of Interventions

- Treatment cost-effectiveness depends on diagnostic characteristics
  - Resources needed to identify patients to be treated
  - False positive rate
- Treatment benefits are incremental to costs and quality of life in absence of treatment

Paucity of AD Screening Evaluation Studies

- US Preventive Services Task Force (USPSTF) concluded evidence for dementia screening is insufficient to support recommendation

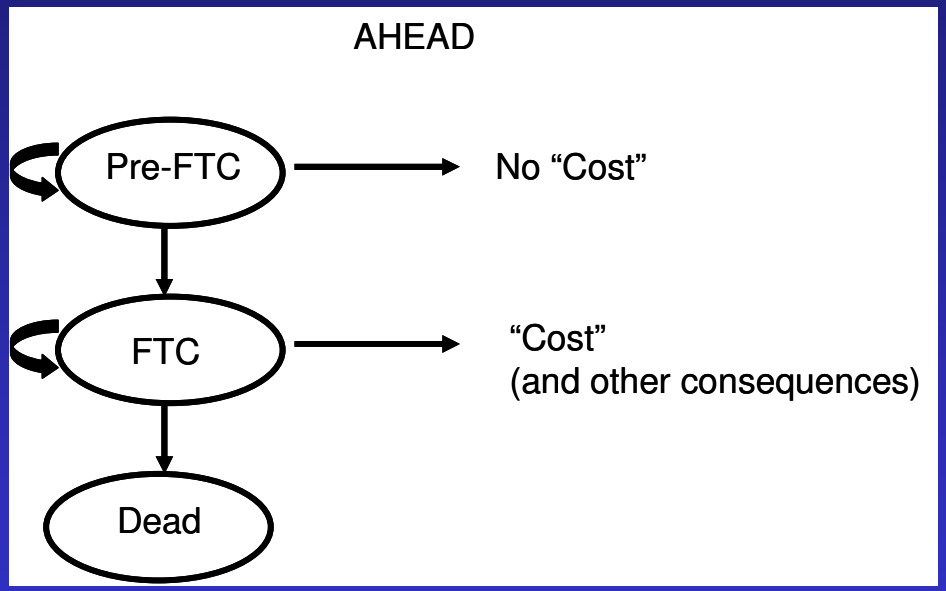
- Availability of even limited therapies can make marginal screening worthwhile (Fillit, 2006)

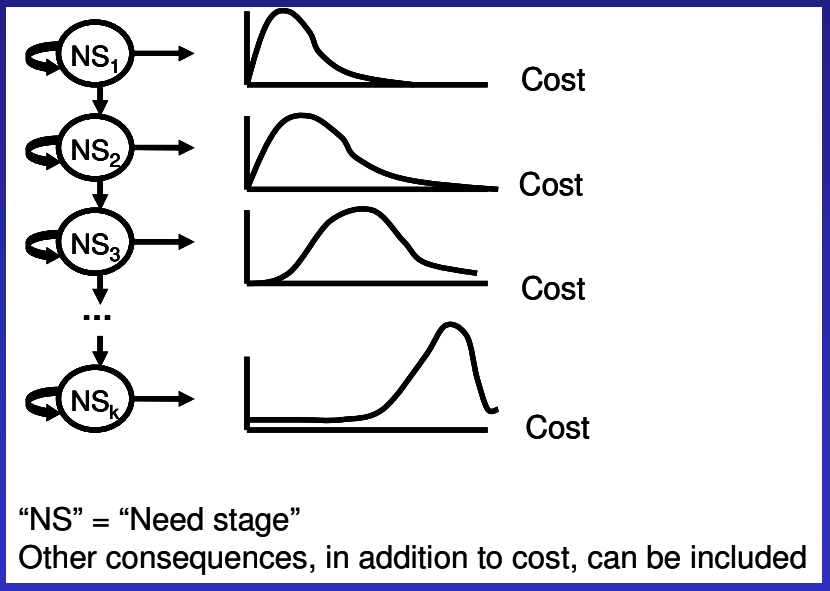
Fillit et al. (2006). Am J. Geriatric Pharmacotherapy. 4(Suppl A):S9-S24.

Summary of Findings

- Most models rely heavily on cognition to characterize AD severity
- Most models characterize AD severity using a limited number of discrete states
- Outcomes
  - Most models predict institutionalization and monetary cost
  - Length of life predicted by some models
  - Quality of life receives limited attention
- Vast majority of studies evaluate medications
  - Alternative treatments and base case interventions receive limited attention

Future Directions (1): Richer Description of Progression





Future Directions (2): Use More Indicators of Disease Progression

- Fagnani (2004) – Used MMSE to predict impacts
  - Residential status
  - Caregiver time
- Expand to include other indicators?
  - Function
  - Neuropsychiatric behavior
  - Other?

Fagnani et al. (2004). Dement Geriatr Cogn Disord. 17:5-13

Future Directions (3): Address More Interventions / Realistic Setting

- Process of identifying patients
  - Cost
  - False positives
- Alternative and complementary interventions
- Other factors influencing disease impact
  - E.g., comorbidity