MCI Conundrums: A Regulator's Perspective

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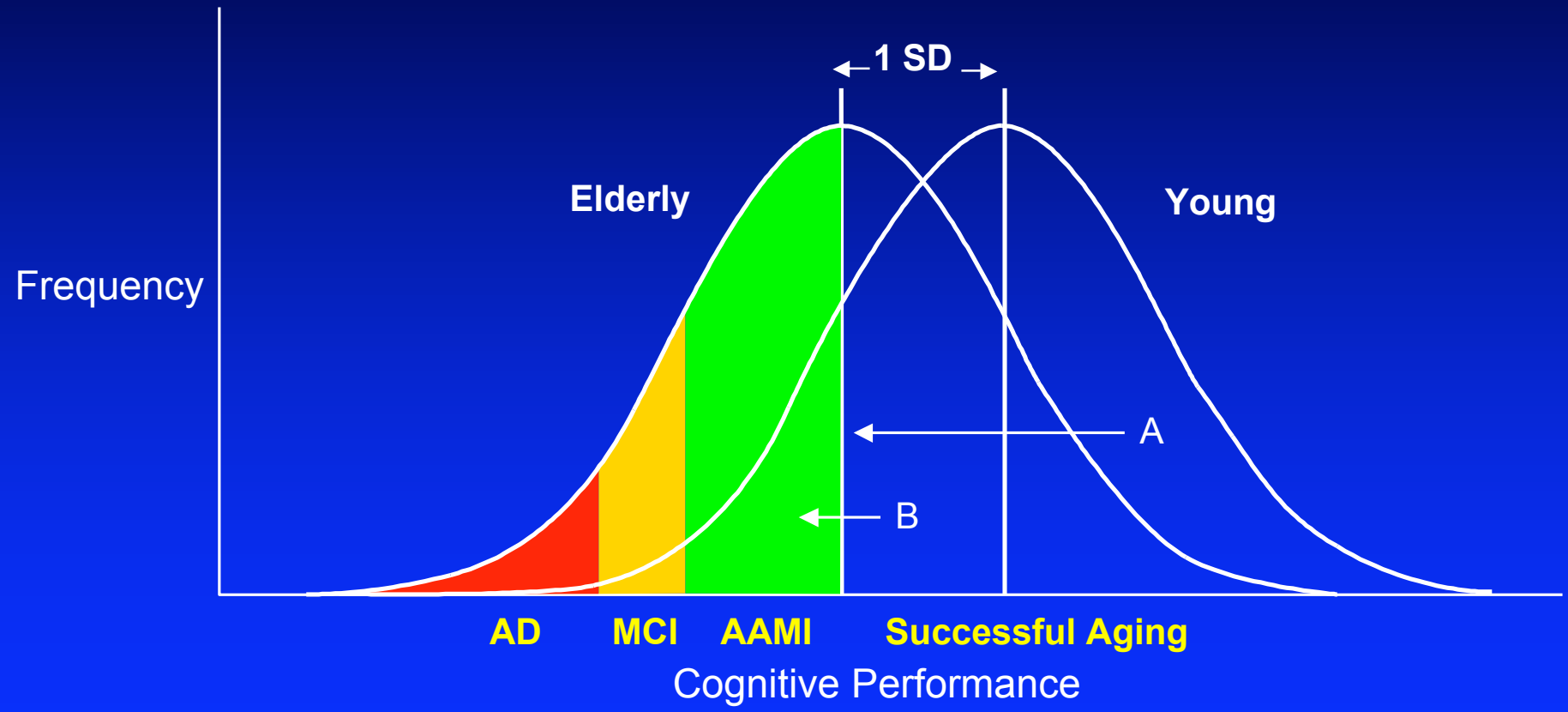
Disclosure: I am not a regulator

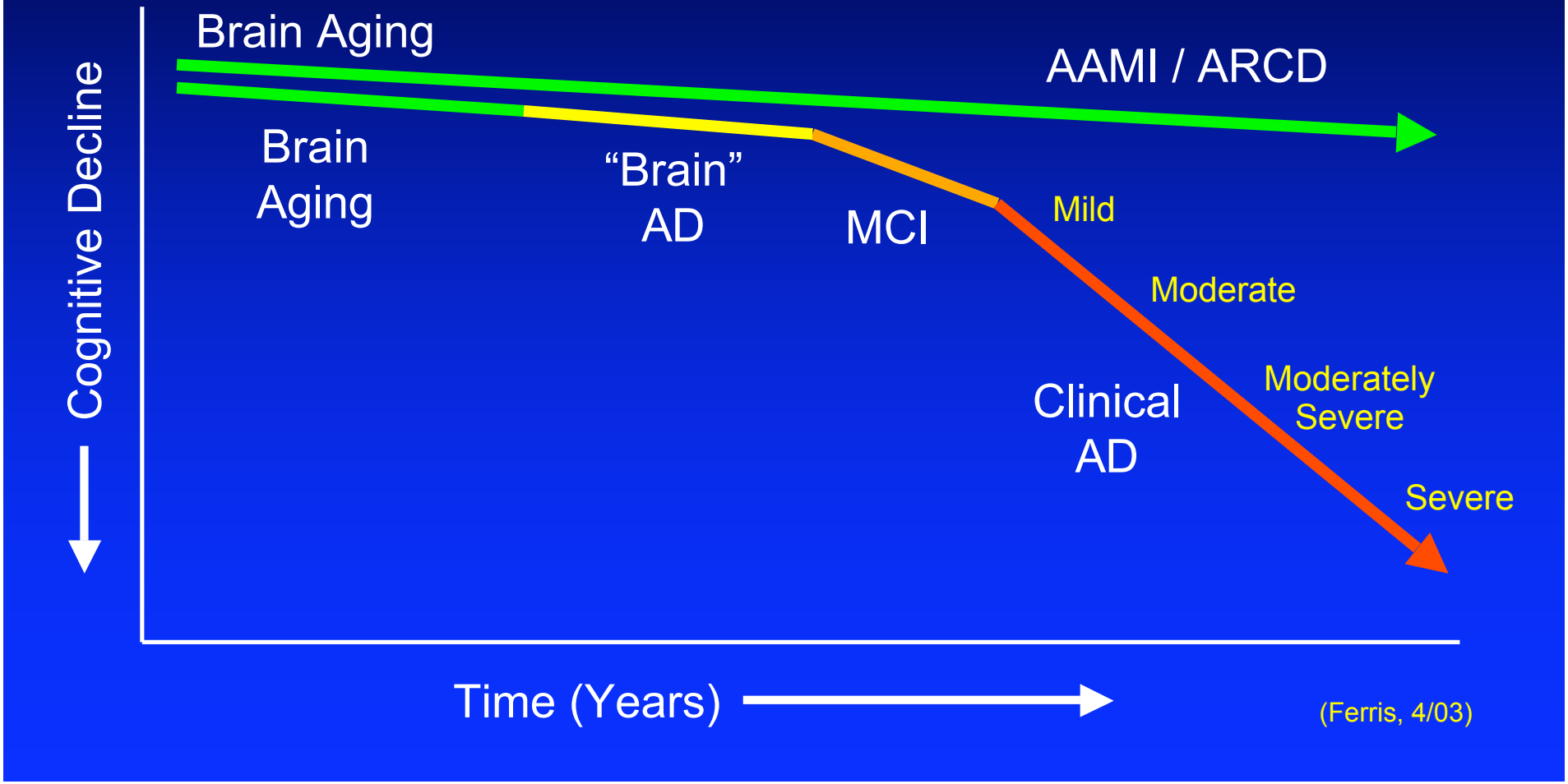
Aging, AAMI (ARCD), MCI, and AD



Adapted from Ferris and Kluger. *Aging, Neuropsychology and Cognition*, 1996.

(Ferris, 8/03)

Course of Aging, MCI and AD



Evolution of MCI Concept: Mild, *Abnormal* Cognitive Impairment

- Deficit relative to *age norms*
  - BSF (Kral, 1962): Most cases developed dementia
  - MCI Concept recognized in GDS and CDR (1982)
  - MCI: Described as group at risk for conversion to dementia (Flicker, et al. 1991; Peterson, et al., 1995)
  - AACD (Levy, et al., 1994): Similar to MCI
  - CIND (Canada): Broader concept, not age dependent
- Decline relative to *young norms*: Brain aging
  - AAMI (Crook, et al., 1986)
  - ARCD (DSM IV)

MCI: Heterogeneous Syndrome vs. Specific Disease

Syndrome

Normal Aging → MCI → Dementia

Disease

Normal Aging → MCI of AD Type → Alzheimer's Disease

(Ferris, 4/02)

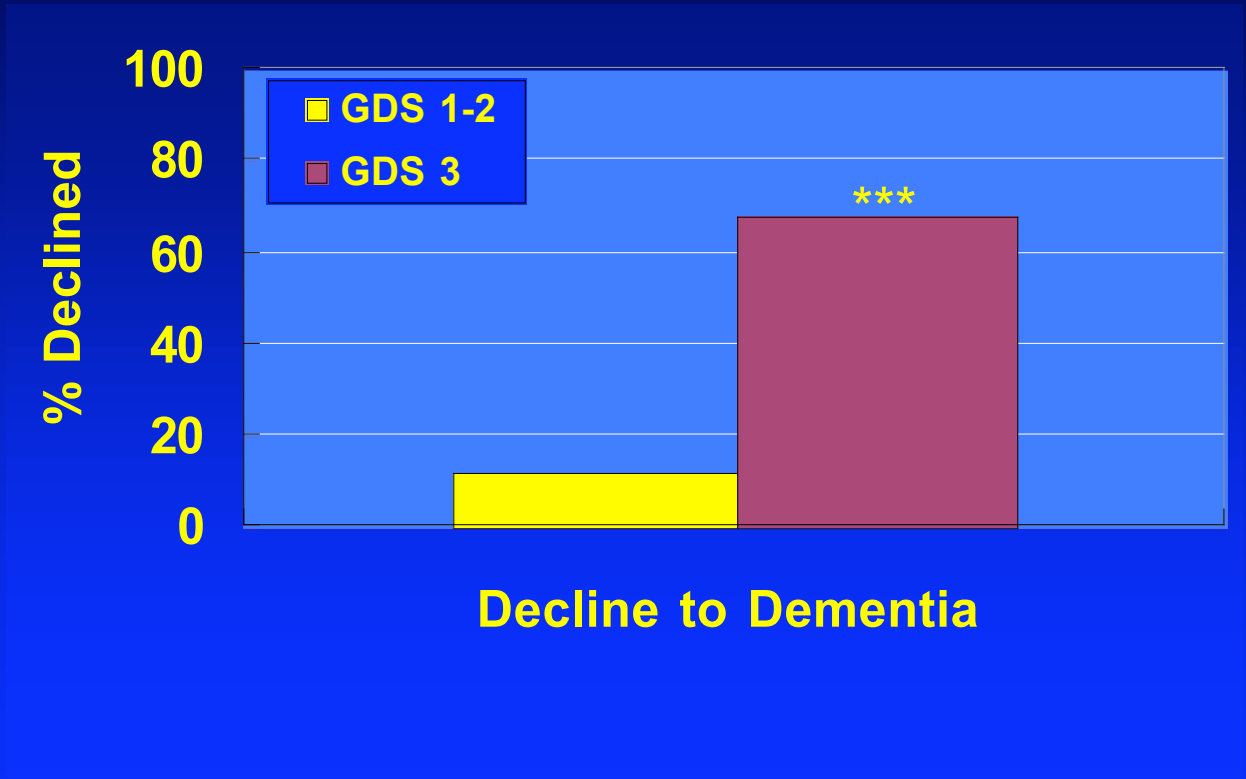
Syndrome of MCI

- Mild cognitive decline that is worse than typical for age but less severe than in dementia (Flicker, et al, 1991)
  - Mild memory impairment
  - Other cognitive domains[1]
- Common activities of daily living (ADL) are intact
  - may be subtle impairment in very complex ADL[1]
- Often a very early stage of dementia
  - 10 - 15% / year progress to dementia
  - 80% over 10 years
- Prodromal AD if apply "AD" inclusion/exclusion criteria
  - 80% hippocampal atrophy
  - 75% AD neuropathology

[1]Differs from Petersen criteria

(Ferris, 4/02)

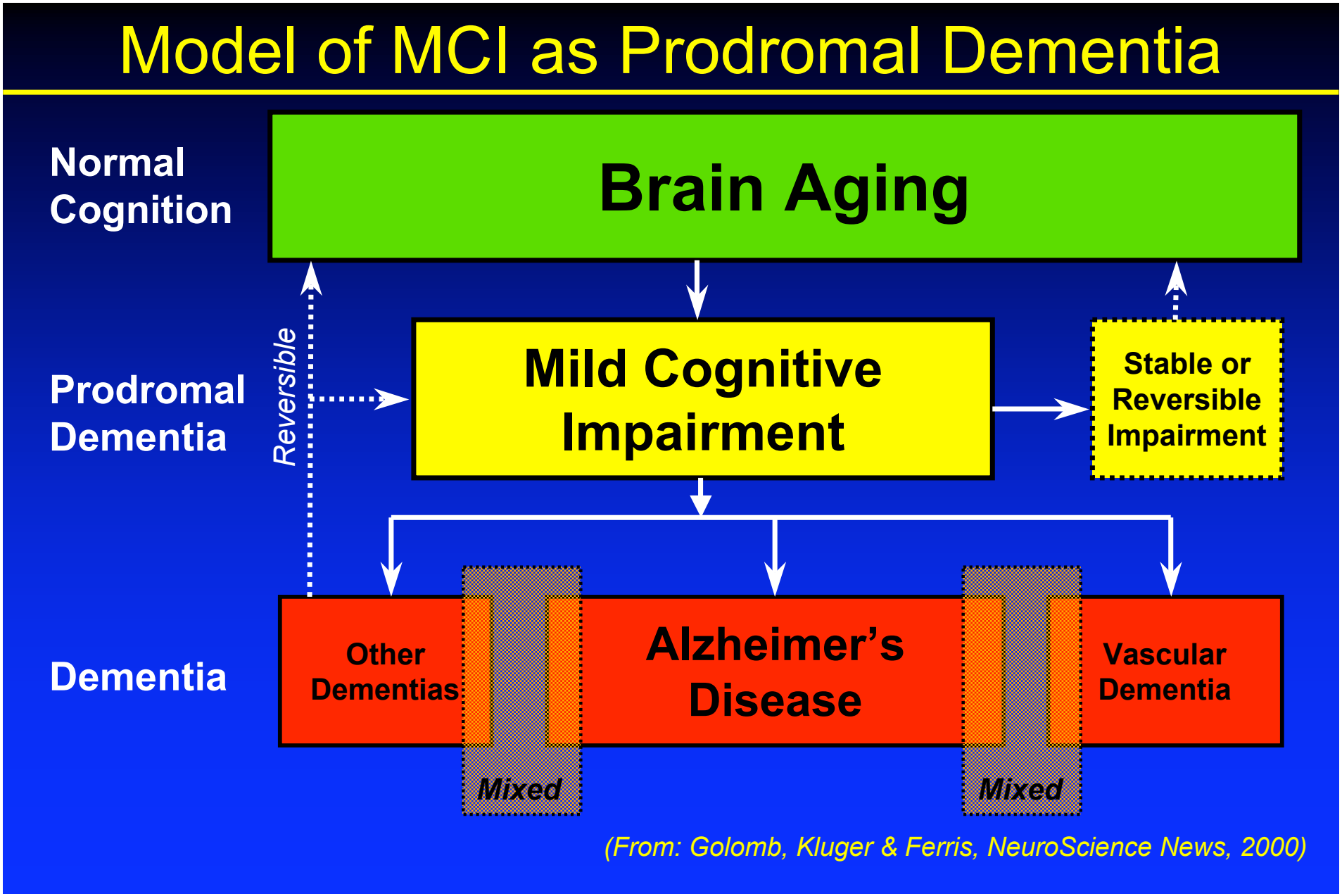
Decline To Dementia Among Nondemented Elderly (N=213)[1]



***p < .001 (5.7- fold increase in risk for decline to dementia, $\bar{x}$ = 3.9 yrs.)

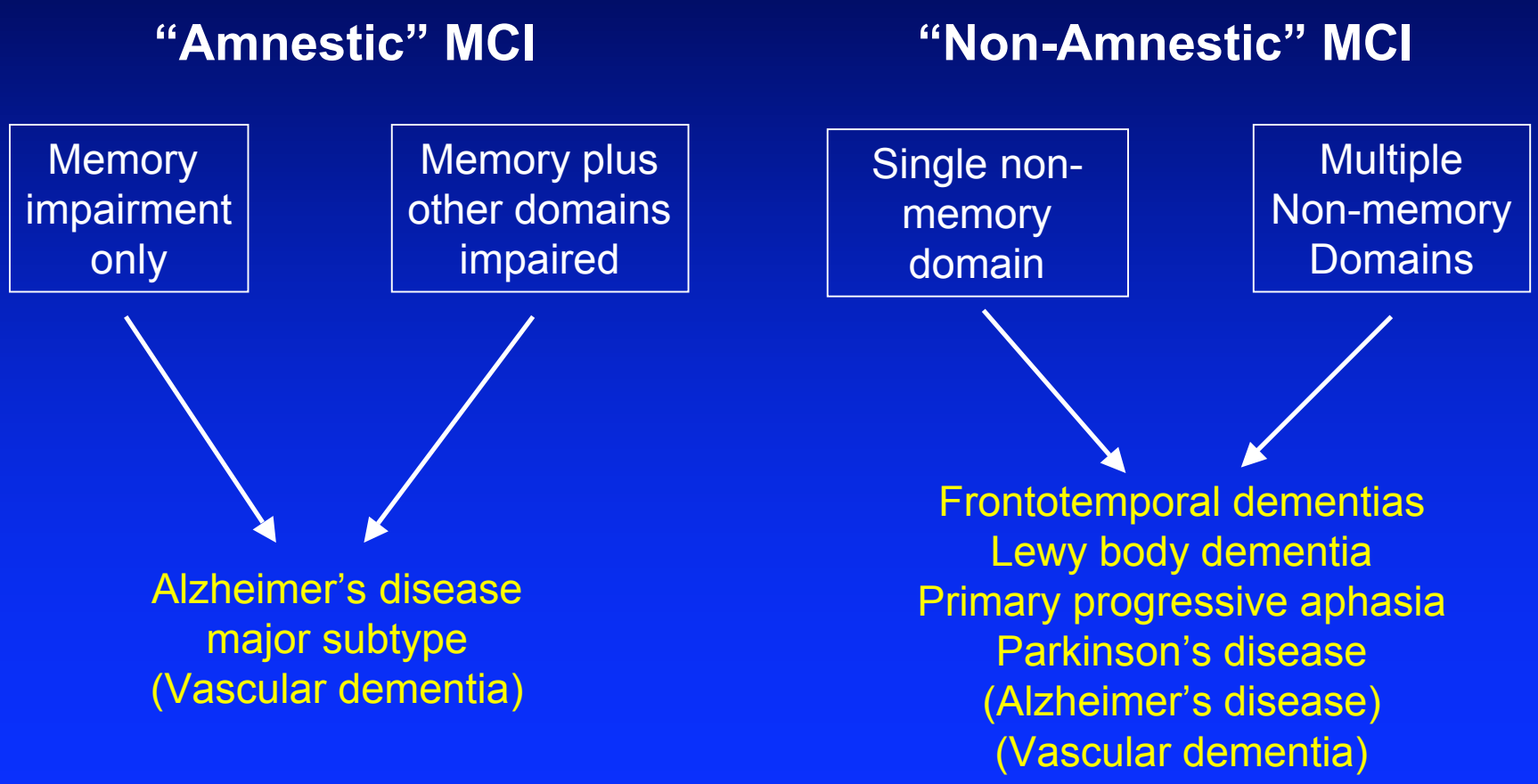
[1]Adapted from Kluger, Ferris, Golomb et al, *J. of Geriatric Psychiatry and Neurology*, 1999

Model of MCI as Prodromal Dementia



(From: Golomb, Kluger & Ferris, NeuroScience News, 2000)

EADC/ADCS Consensus on MCI Sub-types



(Ferris, 7/04)

Research Diagnostic Criteria: MCI of AD Type ("Amnestic" MCI)

- Mild cognitive decline reported by subject and/or informant
- Globally, GDS = 3 or CDR = 0.5
- Memory impairment confirmed objectively
  - Relative to age norms _ May have other impairments
- Cognitive and ADL impairment is insufficient for diagnosis of dementia
  - may be decline in complex ADL
- Inclusion and exclusion criteria for AD, except for severity of cognitive and ADL impairment

Regulatory Issues

- What aspects of current requirements for labeling for symptomatic treatment of AD would overlap with requirements for MCI?
- What is the regulatory attitude towards an MCI label?
- Why are regulators against the diagnosis?
- What will it take to change their mind?
- What would be the efficacy and safety requirements for this label?

Regulatory Issues

1. What aspects of current requirements for labeling for *symptomatic* treatment of AD would overlap with requirements for MCI?
   a. Similar trial design: Randomized, parallel groups, placebo controlled, 6-month duration with clinical outcomes
   b. Dual efficacy criteria: Cognitive performance battery and measure of clinical relevance (CIBIC+ or ADL)
   c. Two pivotal trials: Generally required

Regulatory Issues

2. What is the regulatory attitude towards an MCI label?
3. Why are regulators against the diagnosis?

FDA Advisory Meeting on MCI[1]

- Acceptance of syndrome by field?
- Ability to diagnose and measure outcome?
- Reliability of diagnosis in community settings?
- Heterogeneity of outcome and underlying disease
- Reluctance to reify a new diagnostic entity
- Bottom line:
  - Focus on MCI of AD type (very early AD)
  - Extension of AD labeling rather than new label
  - Current trials and results will help define guidelines

[1]March 13, 2001

(Ferris, 4/02)

Regulatory Issues

4. What will it take to change their mind?
   a. Improve consensus on MCI subtypes and clinical outcomes
   b. Focus trials on relatively homogeneous subtype (e.g., AD)
   c. Show clinical efficacy in accordance with regulatory guidelines for symptomatic treatment of AD
   d. Educate primary care setting to improve recognition and diagnostic accuracy

Regulatory Issues

5. What would be the efficacy and safety requirements for this label?
    a. Efficacy in accordance with AD symptomatic guidelines
    b. Relatively favorable safety profile
    c. Potential for slowing disease progression will effect risk/benefit ratio

Is MCI an "Approvable" Indication?

- FDA is reluctant to "reify" a new diagnostic entity
- A heterogeneous syndrome (analogous to dementia)
  - Multiple underlying dementia etiologies (prodromal stages of each subtype)
  - Subset of MCI is stable or reverses
  - Questionable reliability and validity in community
  - If MCI is just prodromal AD, then indication already exists (very early stage of AD)

Is MCI an "Approvable" Indication?

- Conclusion: For FDA, efficacy in AD-type ("amnestic") MCI would not lead to unique "MCI" label
  - Extension of AD label to include the MCI stage
- Similar conclusion for EU