

# The Case for MCI

By

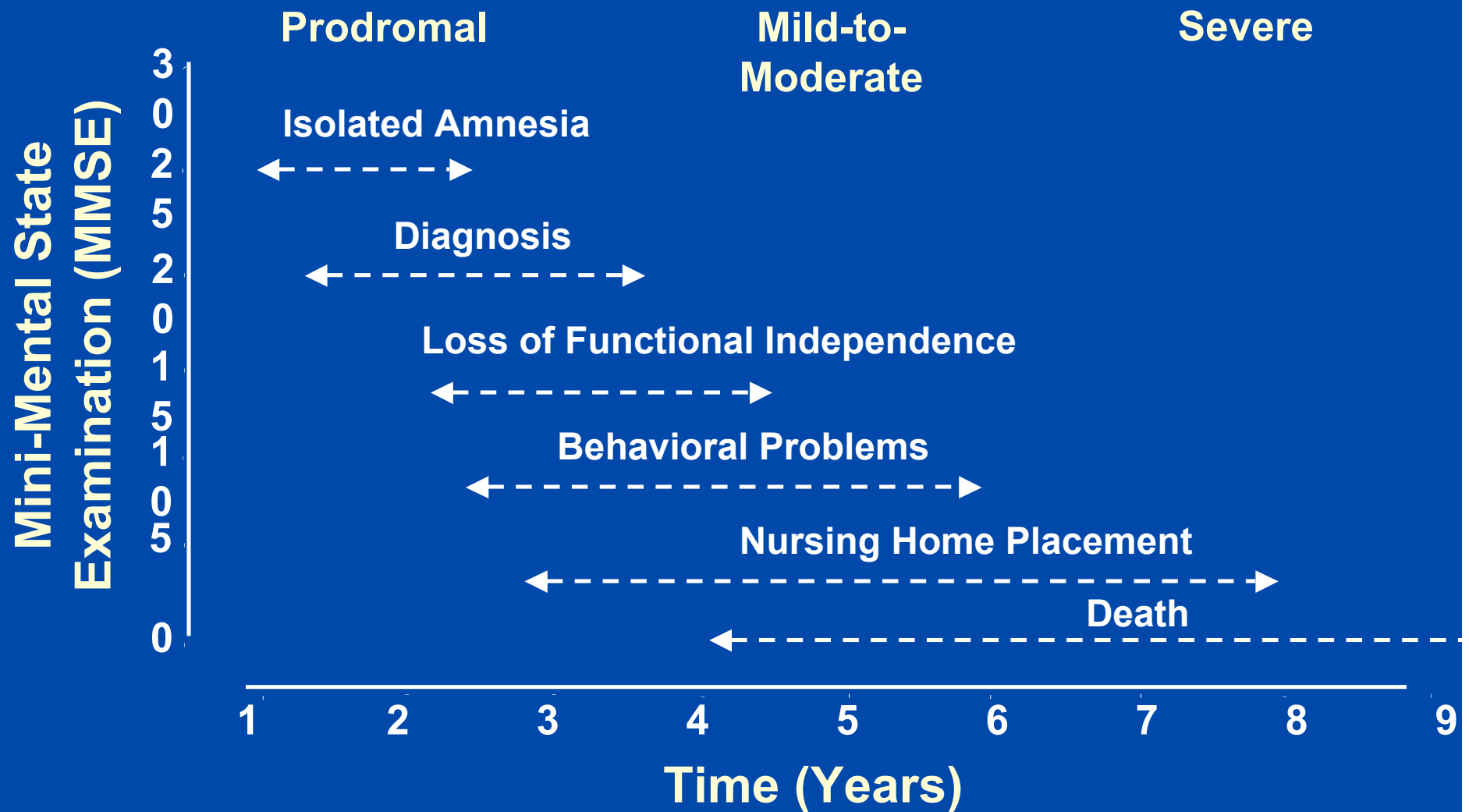
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# Natural History of Alzheimer's Disease



# Cascade of Pathophysiologies in AD

Amyloid deposition

Abnormal phosphorylation of tau

Cholinergic loss

Inflammation

Free radical toxicity

Calcium homeostasis

Synaptic loss

Neuronal loss

Norepinephrine loss

Serotonin loss

Normal



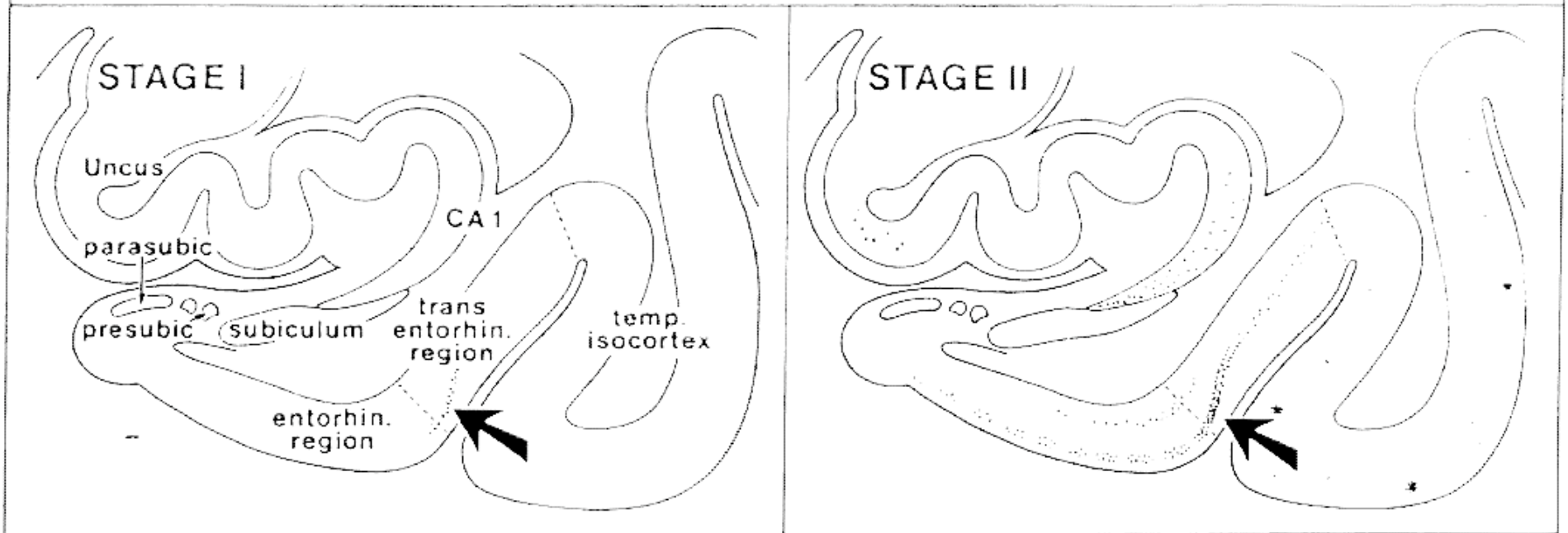
MCI



AD

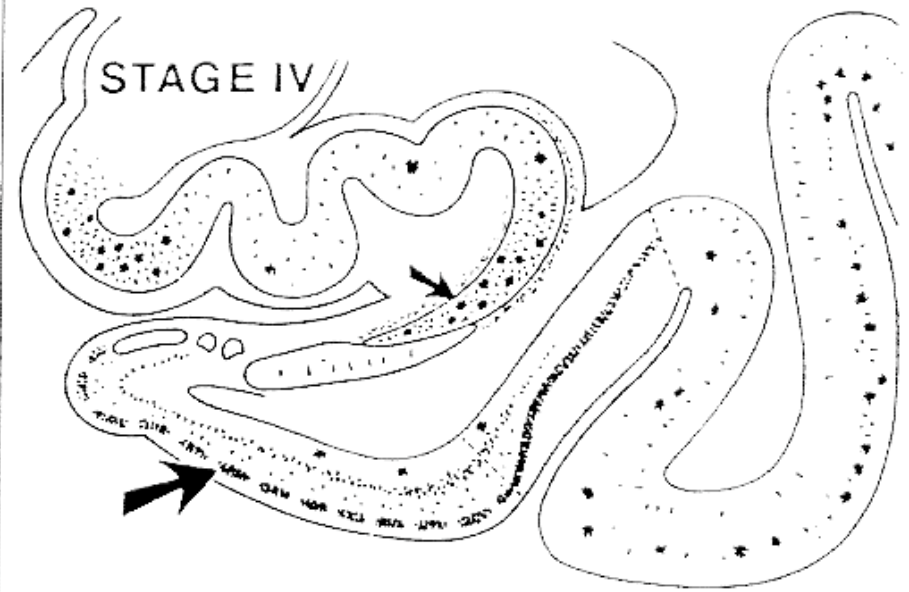
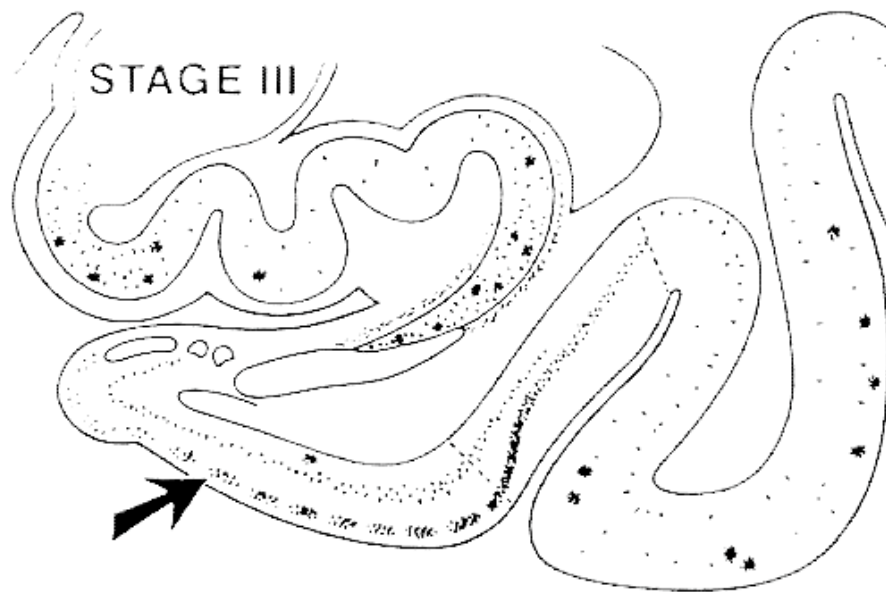
# Braak Staging

## transentorhinal stages



# Braak Staging

limbic stages



# Neuropathological Diagnoses and Hippocampal ChAT Activity in NCI, MCI, & AD

## ROS Clinical Diagnostic Group:

|                                | NCI             | MCI              | AD              |
|--------------------------------|-----------------|------------------|-----------------|
| <u>NIA-Reagan Diagnosis</u>    |                 |                  |                 |
| (1) High Likelihood of AD      | 1 (3%)          | 2 (11.2%)        | 2 (14.2%)       |
| (2) Intermediate Likelihood    | 7 (27%)         | 8 (44.4%)        | 6 (42.9%)       |
| (3) Low Likelihood             | 12 (62%)        | 8 (44.4%)        | 6 (42.9%)       |
| (4) Not AD                     | 2 (8%)          | 0                | 0               |
| <u>Ratio ChAT / NIA-Reagan</u> |                 |                  |                 |
| Mean $\pm$ STD                 | 1.29 $\pm$ 1.00 | 2.98 $\pm$ 2.87* | 1.24 $\pm$ 0.86 |

\*p = 0.01

*Thus: ChAT levels are HIGHEST in MCI, and there is no difference in pathology of MCI and AD*

# Mild Cognitive Impairment (MCI)



# What's in a name?

- Many names for cognitive impairment in later life, depending on the country, the definition, the possible pathobiology, and other factors.
- AACD      Age-Associated Cognitive Decline
- AAMI      Aged Associated Memory Impairment
- ARCD      Age-Related Cognitive Decline
- CIND      Cognitive Decline, Not Demented
- MCI      Mild Cognitive Impairment
- PDP      Possible Dementia Prodrome (CERAD)
- VCI      Vascular Cognitive Impairment
- PID      Possible Incipient Dementia

# Prevalence of MCI and Related Concepts

- Cognitive Impairment No Dementia (CIND)
  - *1,800 (Canadian) community cases: 16.8% have CIND, 8% dementia, 5.3% “circumscribed memory loss”<sup>1</sup>*
- Age-Associated Memory Impairment (AAMI)
  - *202 Germans ages 60-64: 13.5% AAMI, 6.5% Age-Consistent Memory Impairment (ACMI), 23.5% Age-Associated Cognitive Decline, 1.5% Late-Life Forgetfulness (LLF)<sup>2</sup>*

<sup>1</sup>Graham JE, Rockwood K, Beattie BL, et al. Lancet 1997(June 21):349(9068):1793-1796

<sup>2</sup>Kratz B, Schroder J, Pantel J, et al. Nervenarzt. 1998(Nov);69(11):975-982

# Prevalence of MCI and Related Concepts

- AAMI: 1,049 cases age 60-78 in Finland: 53.8% have AAMI
- AAMI, ACMI and LLF: 523 cases ages 55 to 98, overall AAMI rate of 50%, ACMI rate = 15.3%, LLF rate = 3.3%

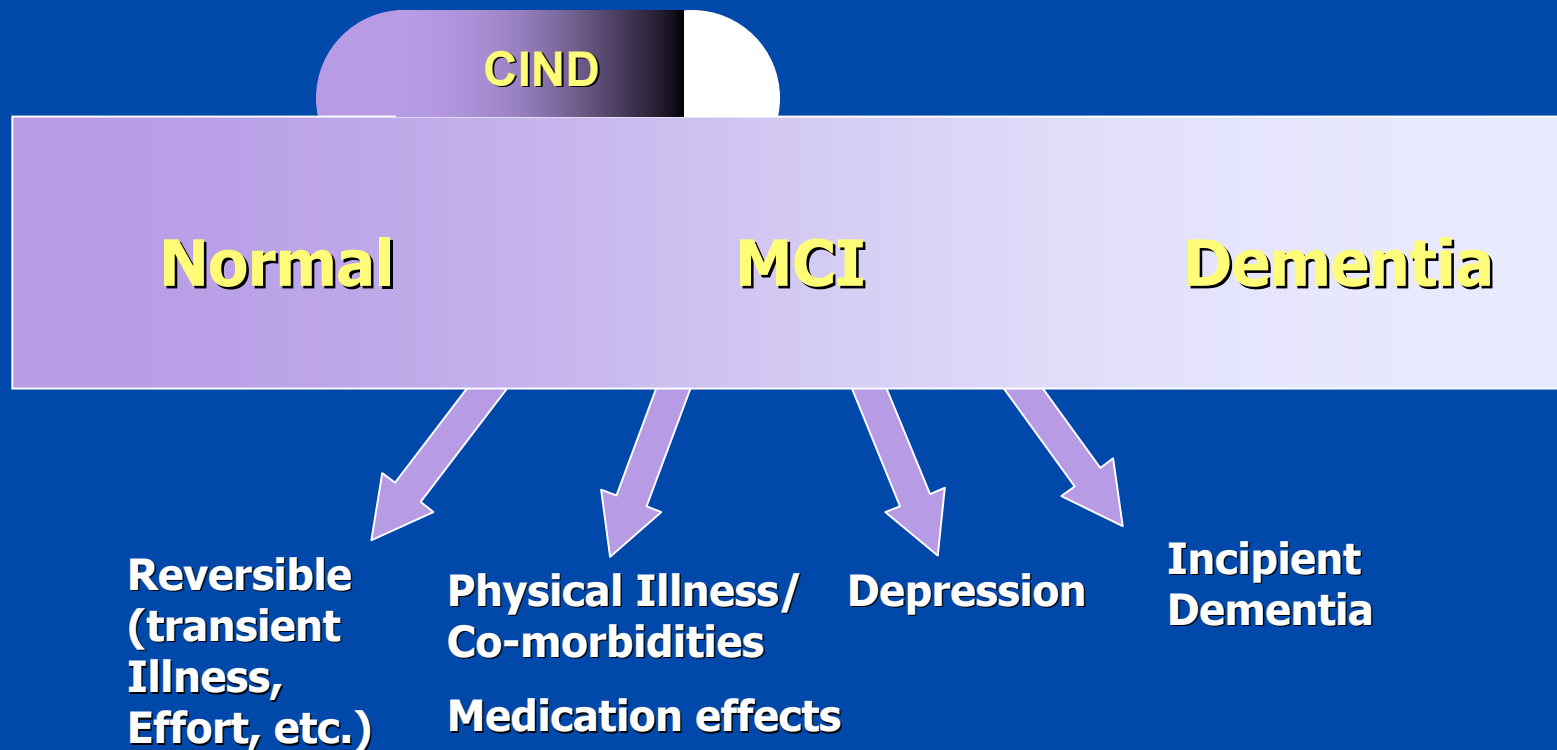
Koivisto K, Reini Kainen KJ, Hanninen T, et al. Neurology. 1995(April);45(4):741-747

Smith G, Ivnik RJ, Peterson RC, et al. Psychol Aging. 1999(Dec);6(4):551-8

# MCI may herald many diseases

- Alzheimer's Disease
- Frontotemporal Dementias
- Focal Cortical Degenerations (PPA, etc.)
- Vascular dementia
  
- If MCI is to be useful in categorization of subjects for interventional studies, it must be validated as specific for a disease or group of known responsive diseases

# The Continuum of Cognitive Changes in Aging



*How should the categorizations be made?  
What is the pathology at each stage?*

# MCI Defined

- Memory complaint
- Objective neuropsychological memory assessment showing dysfunction
- No impairment in daily living skills
- If memory impairment is not present, 1 other cognitive domain shows dysfunction

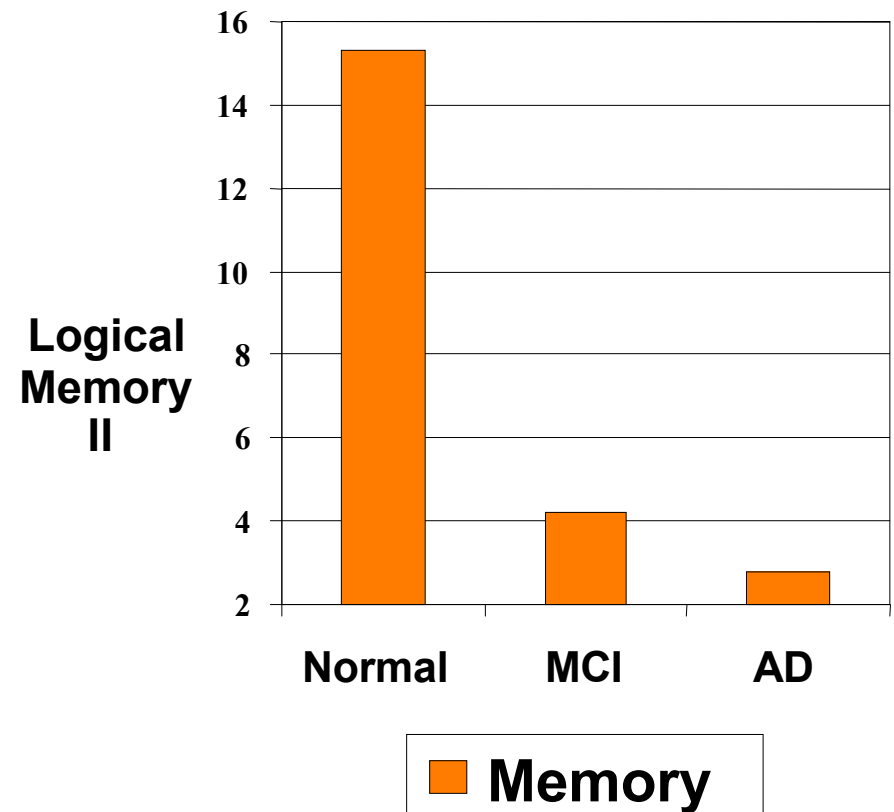
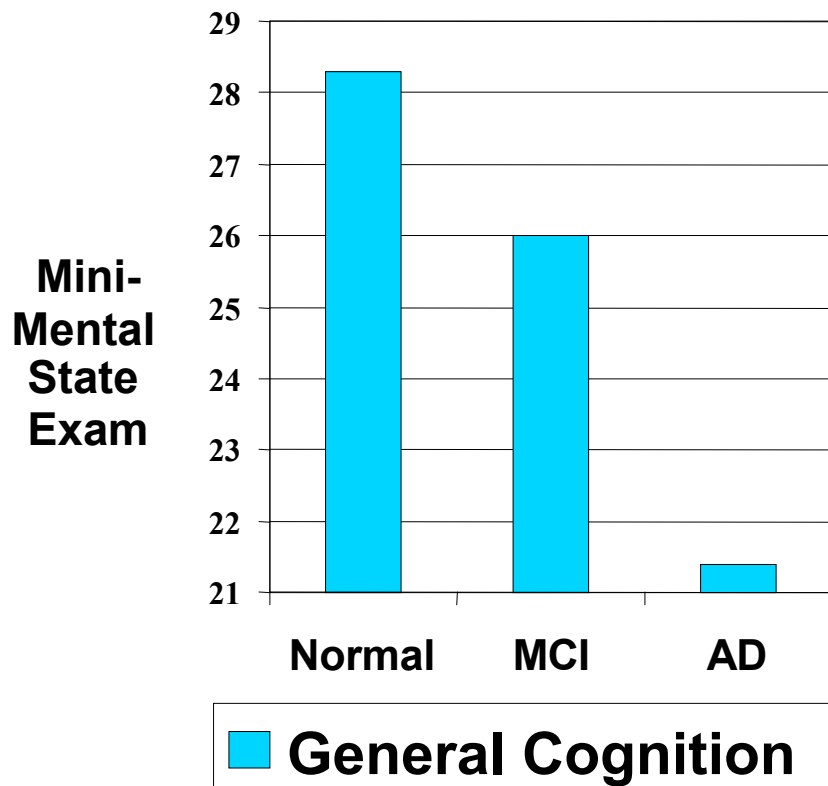
# Mild Cognitive Impairment:

- Two *definitions of MCI*
  - “MCI-amnestic”:
    - (essentially) *Isolated amnestic disorder (“Petersen”) or CDR 0.5; (“Morris”)*
  - “MCI-other” [*“MCI Multiple Cognitive Domains”*]:
    - *deficits in two or more areas of cognition > 1.5 standard deviations below the mean, controlling for age and education*
      - *Recent memory function usually declined, but does not cross threshold before other domains fail*

# Mild Cognitive Impairment (“Petersen Criteria”)

- Memory complaint
- Memory impairment
- Normal general cognitive function
- Normal daily function
- Does not have Alzheimer’s disease
- Requires “clinical judgment”  
of the clinician

# Clinical Profile of Amnestic MCI



## Clinical Dementia Rating Worksheet

This is a semi-structured interview. Please ask all of these questions. Ask any additional questions necessary to determine the subject's CDR. Please note information from the additional questions.

### Memory Questions for Informant:

1. Does he/she have a problem with his/her memory or thinking?  Yes  No
- 1a. If yes, is this a consistent problem (as opposed to inconsistent)?  Yes  No
2. Can he/she recall recent events?  Usually  Sometimes  Rarely
3. Can he/she remember a short list of items (shopping)?  Usually  Sometimes  Rarely
4. Has there been some decline in memory during the past year?  Yes  No
5. Is his/her memory impaired to such a degree that it would have interfered with his/her activities of daily life a few years ago (or pre-retirement activities)? (collateral sources opinion)  Yes  No
6. Does he/she completely forget a major event (e.g., trip, party, family wedding) within a few weeks of the event?  Usually  Sometimes  Rarely
7. Does he/she forget pertinent details of the major event?  Usually  Sometimes  Rarely
8. Does he/she completely forget important information of the distant past (e.g., birthdate, wedding date, place of employment)?  Usually  Sometimes  Rarely
9. Tell me about some recent event in his/her life that he/she should remember. (For later testing, obtain details such as location of the event, time of day, participants, how long the event was, when it ended and how the subject or other participants got there).

Within 1 week:

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

Within 1 month:

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

10. When was he/she born? \_\_\_\_\_
11. Where was he/she born? \_\_\_\_\_
12. What was the last school he/she attended? \_\_\_\_\_
  - Name \_\_\_\_\_
  - Place \_\_\_\_\_
  - Grade \_\_\_\_\_
13. What was his/her main occupation/job (or spouse's job if subject was not employed)? \_\_\_\_\_
14. What was his/her last major job (or spouse's job if subject was not employed)? \_\_\_\_\_
15. When did he/she (or spouse) retire and why? \_\_\_\_\_

## Clinical Dementia Rating Worksheet

### Orientation Questions for Informant:

How often does he/she know of the exact:

1. Date of the Month?

Usually    Sometimes    Rarely    Don't Know

2. Month?

Usually    Sometimes    Rarely    Don't Know

3. Year?

Usually    Sometimes    Rarely    Don't Know

4. Day of the Week?

Usually    Sometimes    Rarely    Don't Know

5. Does he/she have difficulty with time relationships (when events happened in relation to each other)?

Usually    Sometimes    Rarely    Don't Know

6. Can he/she find his/her way about familiar streets?

Usually    Sometimes    Rarely    Don't Know

7. How often does he/she know how to get from one place to another outside his/her neighborhood?

Usually    Sometimes    Rarely    Don't Know

8. How often can he/she find his/her way about indoors?

Usually    Sometimes    Rarely    Don't Know

## Clinical Dementia Rating Worksheet

### Judgment and Problem Solving Questions for Informant:

1. In general, if you had to rate his/her abilities to solve problems at the present time, would you consider them:

- As good as they have ever been
- Good, but not as good as before
- Fair
- Poor
- No ability at all

2. Rate his/her ability to cope with small sums of money (e.g., make change, leave a small tip):

- No loss
- Some loss
- Severe loss

3. Rate his/her ability to handle complicated financial or business transactions (e.g., balance check-book, pay bills):

- No loss
- Some loss
- Severe loss

4. Can he/she handle a household emergency (e.g., plumbing leak, small fire)?

- As well as before
- Worse than before because of trouble thinking
- Worse than before, another reason (why) \_\_\_\_\_

5. Can he/she understand situations or explanations?

- Usually
- Sometimes
- Rarely
- Don't Know

6. Does he/she behave\* appropriately [i.e., in his/her usual (premorbid) manner] in social situations and interactions with other people?

- Usually
- Sometimes
- Rarely
- Don't Know

\*This item rates behavior, not appearance.

## Clinical Dementia Rating Worksheet

### Community Affairs: Questions for Informant:

#### Occupational

1. Is the subject still working?  Yes  No  N/A  
 If not applicable, proceed to item 4  
 If yes, proceed to item 3  
 If no, proceed to item 2
2. Did memory or thinking problems contribute to the subject's decision To retire? (Question 4 is next)  Yes  No  D/K
3. Does the subject have significant difficulty in his/her job because of problems with memory or thinking?  
 Rarely or Never  Sometimes  Usually  Don't Know

#### Social

4. Did he/she ever drive a car?  Yes  No  
 Does the subject drive a car now?  Yes  No  
 If no, is this because of memory or thinking problems?  Yes  No
5. If he/she is still driving, are there problems or risks because of poor thinking?  Yes  No
- \*6. Is he/she able to independently shop for needs?  
 Rarely or Never (Needs to be accompanied on any shopping trip)  Sometimes (Shops for limited number of items; buys duplicate items or forgets needed items)  Usually  Don't Know
7. Is he/she able to independently carry out activities outside the home?  
 Rarely or Never (Generally unable to perform activities without help)  Sometimes (Limited and/or routine, e.g., superficial participation in church or meetings; trips to beauty parlor)  Usually (Meaningful participation in activities, e.g., voting)  Don't Know
8. Is he/she taken to social functions outside a family home?  
 If no, why not? \_\_\_\_\_  Yes  No
9. Would a casual observer of the subject's behavior think the subject was ill?  Yes  No
10. If in nursing home, does he/she participate well in social functions (thinking)?  Yes  No

#### IMPORTANT:

Is there enough information available to rate the subject's level of impairment in community affairs?

**If not, please probe further.**

Community Affairs: Such as going to church, visiting with friends or family, political activities, professional organizations such as bar association, other professional groups, social clubs, service organizations, educational programs.

\*Please add notes if needed to clarify subject's level of functioning in this area.

## Clinical Dementia Rating Worksheet

### Home and Hobbies Questions for Informant:

- 1a. What changes have occurred in his/her abilities to perform household chores? \_\_\_\_\_  
\_\_\_\_\_
- 1b. What can he/she still do well? \_\_\_\_\_  
\_\_\_\_\_
- 2a. What changes have occurred in his/her abilities to perform hobbies? \_\_\_\_\_  
\_\_\_\_\_
- 2b. What can he/she still do well? \_\_\_\_\_  
\_\_\_\_\_
3. If in nursing home, what can he/she no longer do well (H and H)? \_\_\_\_\_  
\_\_\_\_\_

### Everyday Activities (Blessed):

- |                                       |         |     |             |
|---------------------------------------|---------|-----|-------------|
|                                       | No Loss |     | Severe Loss |
| 4. Ability to perform household tasks | 0       | 0.5 | 1           |

Please describe: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

5. Is he/she able to perform household chores at the level of:  
(Pick one. Informant does not need to be asked directly).

- No meaningful function.  
(Performs simple activities, such as making a bed, only with much supervision)
- Functions in limited activities only.  
(With some supervision, washes dishes with acceptable cleanliness; sets table)
- Functions independently in some activities.  
(Operates appliances, such as a vacuum cleaner; prepares simple meals)
- Functions in usual activities but not at usual level.
- Normal function in usual activities.

### IMPORTANT:

Is there enough information available to rate the subject's level of impairment in HOME & HOBBIES?  
If not, please probe further.

Homemaking Tasks: Such as cooking, laundry, cleaning, grocery shopping, taking out garbage, yard work, simple care maintenance, and basic home repair.

Hobbies: Sewing, painting, handicrafts, reading, entertaining, photography, gardening, going to theater or symphony, woodworking, participation in sports.

## Clinical Dementia Rating Worksheet

### Personal Care Questions for Informant:

\*What is your estimate of his/her mental ability in the following areas:

|                                |                          |                                      |   |                                    |
|--------------------------------|--------------------------|--------------------------------------|---|------------------------------------|
|                                | Unaided                  | Occasionally misplaced buttons, etc. | Wrong sequence commonly forgotten items | Unable to dress                    |
| A. Dressing (Blessed)          | 0                        | 1                                    | 2                                       | 3                                  |
|                                | Unaided                  | Needs prompting                      | Sometimes needs help                    | Always or nearly always needs help |
| B. Washing, grooming           | 0                        | 1                                    | 2                                       | 3                                  |
|                                | Cleanly; proper utensils | Messily; spoon                       | Simple solids                           | Has to be fed completely           |
| C. Eating habits               | 0                        | 1                                    | 2                                       | 3                                  |
|                                | Normal complete control  | Occasionally wets bed                | Frequently wets bed                     | Doubly incontinent                 |
| D. Sphincter control (Blessed) | 0                        | 1                                    | 2                                       | 3                                  |

\*A box-score of 1 can be considered if the subject's personal care is impaired from a previous level, even if they do not receive prompting.

## Clinical Dementia Rating Worksheet

### Memory Questions for Subject:

1. Do you have problems with memory or thinking?  Yes  No
2. A few moments ago your (spouse, etc.) told me a few recent experiences you had. Will you tell me something about those? (Prompt for details, if needed such as location of the event, time of day, participants, how long the event was, when it ended and how the subject or other participants got there).

Within 1 week

1.0 – Largely correct  
0.5  
0.0 – Largely incorrect

\_\_\_\_\_

\_\_\_\_\_

Within 1 month

1.0 – Largely correct  
0.5  
0.0 – Largely incorrect

\_\_\_\_\_

\_\_\_\_\_

3. I will give you a name and address to remember for a few minutes. Repeat this name and address after me: (Repeat until the phrase is correctly repeated or to a maximum of three trials).

| Elements | 1    | 2      | 3  | 4              | 5       |
|----------|------|--------|----|----------------|---------|
| John     | John | Brown, | 42 | Market Street, | Chicago |
| John     | John | Brown, | 42 | Market Street, | Chicago |
| John     | John | Brown, | 42 | Market Street, | Chicago |

(Underline elements repeated correctly in each trial).

4. When were you born? \_\_\_\_\_
5. Where were you born? \_\_\_\_\_
6. What was the last school you attended?  
Name \_\_\_\_\_  
Place \_\_\_\_\_ Grade \_\_\_\_\_
7. What was your main occupation job (or spouse if not employed)? \_\_\_\_\_
8. What was your last major job (or spouse if not employed)? \_\_\_\_\_
9. When did you (or spouse) retire and why? \_\_\_\_\_

10. Repeat the name and address I asked you to remember:

| Elements | 1    | 2      | 3  | 4              | 5       |
|----------|------|--------|----|----------------|---------|
| John     | John | Brown, | 42 | Market Street, | Chicago |

(Underline elements repeated correctly in each trial).

Subject Initials \_\_\_\_\_

## Clinical Dementia Rating Worksheet

### Orientation Questions for Subject

Record the subject's answer verbatim for each question

1. What is the date today?  Correct  Incorrect

\_\_\_\_\_

2. What day of the week is it?  Correct  Incorrect

\_\_\_\_\_

3. What is the month?  Correct  Incorrect

\_\_\_\_\_

4. What is the year?  Correct  Incorrect

\_\_\_\_\_

5. What is the name of this place?  Correct  Incorrect

\_\_\_\_\_

6. What town or city are we in?  Correct  Incorrect

\_\_\_\_\_

7. What time is it?  Correct  Incorrect

\_\_\_\_\_

8. Does the subject know who the informant is (in your judgment)?  Correct  Incorrect

\_\_\_\_\_

## Clinical Dementia Rating Worksheet

### Judgment and Problem Solving Questions for Subject:

Instructions: If initial response by subject does not merit a grade 0, press the matter to identify the subject's best understanding of the problem. Circle nearest response.

#### Similarities:

Example: "How are a pencil and pen alike? (writing instruments)"

How are these things alike?                      Subject's Response

1. turnip.....cauliflower \_\_\_\_\_  
(0 = vegetables)  
(1 = edible foods, living things, can be cooked, etc.)  
(2 = answers not pertinent; differences; buy them)
2. desk.....bookcase \_\_\_\_\_  
(0 = furniture, office furniture; both hold books)  
(1 = wooden, legs)  
(2 = not pertinent, differences)

#### Differences:

Example: "What is the difference between sugar and vinegar? (sweet vs. sour)"

What is the difference between these things?

3. lie.....mistake \_\_\_\_\_  
(0 = one deliberate, one unintentional)  
(1 = one bad the other good - or explains only one)  
(2 = anything else, similarities)
4. river.....canal \_\_\_\_\_  
(0 = natural - artificial)  
(1 = anything else)

#### Calculations:

5. How many nickels in a dollar?                       Correct    Incorrect
6. How many quarters in \$6.75?                       Correct    Incorrect
7. Subtract 3 from 20 and keep subtracting 3 from each new number all the way down.                       Correct    Incorrect

#### Judgment:

8. Upon arriving in a strange city, how would you locate a friend that you wished to see?  
  
(0 = try the telephone book, go to the courthouse for a directory; call a mutual friend)  
(1 = call the police, call operator (usually will not give address))  
(2 = no clear response)
9. Subject's assessment of disability and station in life and understanding of why she/she is present at the examination (may have covered, but rate here):  
  
 Good Insight    Partial Insight    Little Insight

CLINICAL DEMENTIA RATING (CDR)

|                                 |   |     |   |   |   |
|---------------------------------|---|-----|---|---|---|
| CLINICAL DEMENTIA RATING (CDR): | 0 | 0.5 | 1 | 2 | 3 |
|---------------------------------|---|-----|---|---|---|

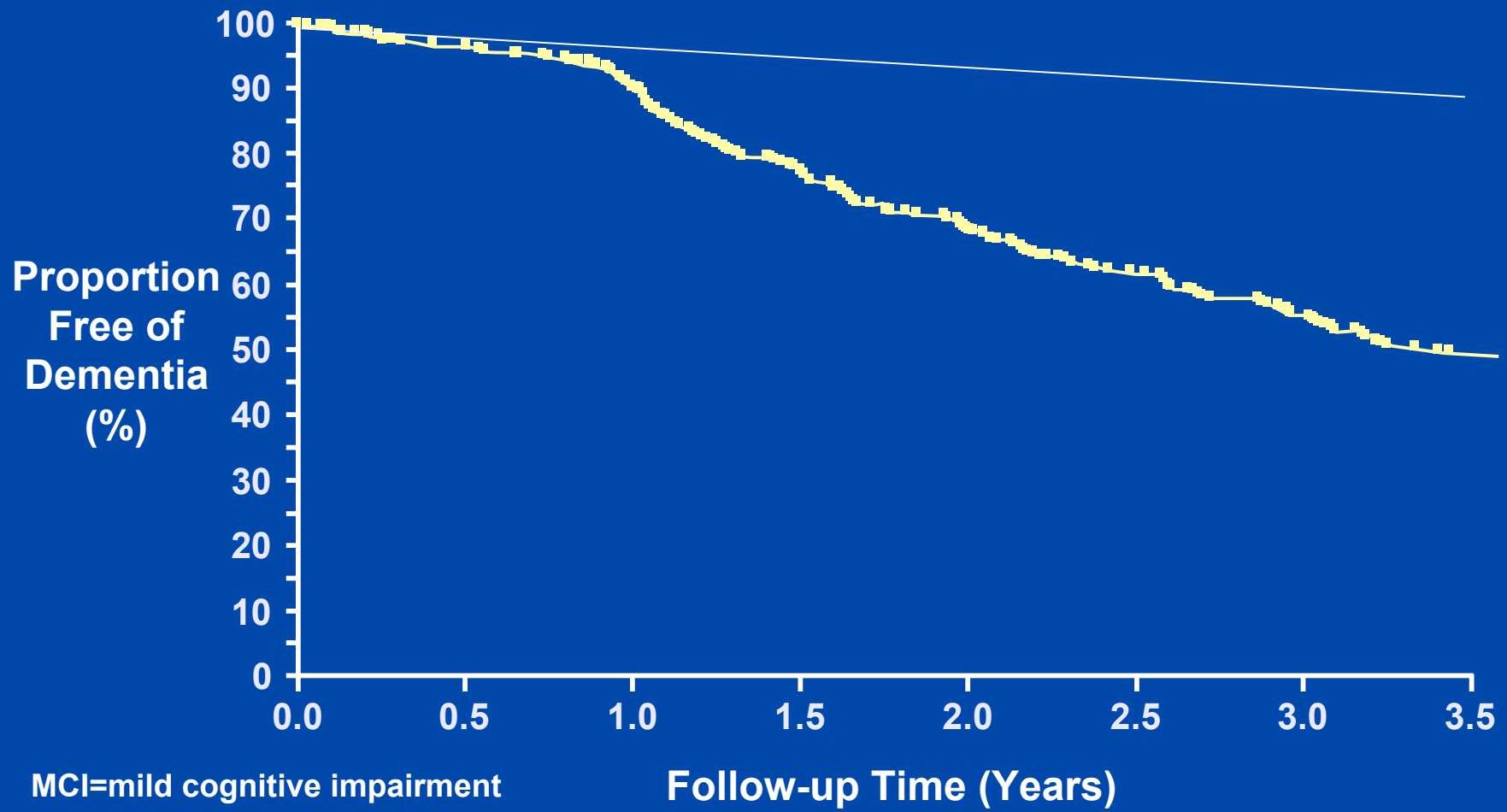
|                            | Impairment  |   |   |  |  |
|----------------------------|---|---|---|--|--|
|                            | None<br>0   | Questionable<br>0.5   | Mild<br>1   | Moderate<br>2  | Severe<br>3  |
| Memory                     | No memory loss or slight inconsistent forgetfulness   | Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness | Moderate memory loss; more marked for recent events; defect interferes with everyday activities                                     | Severe memory loss; only highly learned material retained; new material rapidly lost                                   | Severe memory loss; only fragments remain                      |
| Orientation                | Fully oriented  | Fully oriented except for slight difficulty with time relationships                     | Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere        | Severe difficulty with time relationships; usually disoriented to time, often to place                                 | Oriented to person only  |
| Judgment & Problem Solving | Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance | Slight impairment in solving problems, similarities, and differences                    | Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained                         | Severely impaired in handling problems, similarities, and differences; social judgment usually impaired                | Unable to make judgments or solve problems                     |
| Community Affairs          | Independent function at usual level in job, shopping, volunteer and social groups                                   | Slight impairment in these activities   | Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection     | No pretense of independent function outside home<br>Appears well enough to be taken to functions outside a family home | Appears too ill to be taken to functions outside a family home |
| Home and Hobbies           | Life at home, hobbies, and intellectual interests well maintained   | Life at home, hobbies, and intellectual interests slightly impaired                     | Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned | Only simple chores preserved; very restricted interests, poorly maintained   | No significant function in home                                |
| Personal Care              | Fully capable of self-care  |   | Needs prompting   | Requires assistance in dressing, hygiene, keeping of personal effects  | Requires much help with personal care; frequent incontinence   |

Score only as decline from previous usual level due to cognitive loss, not impairment due to other factors.

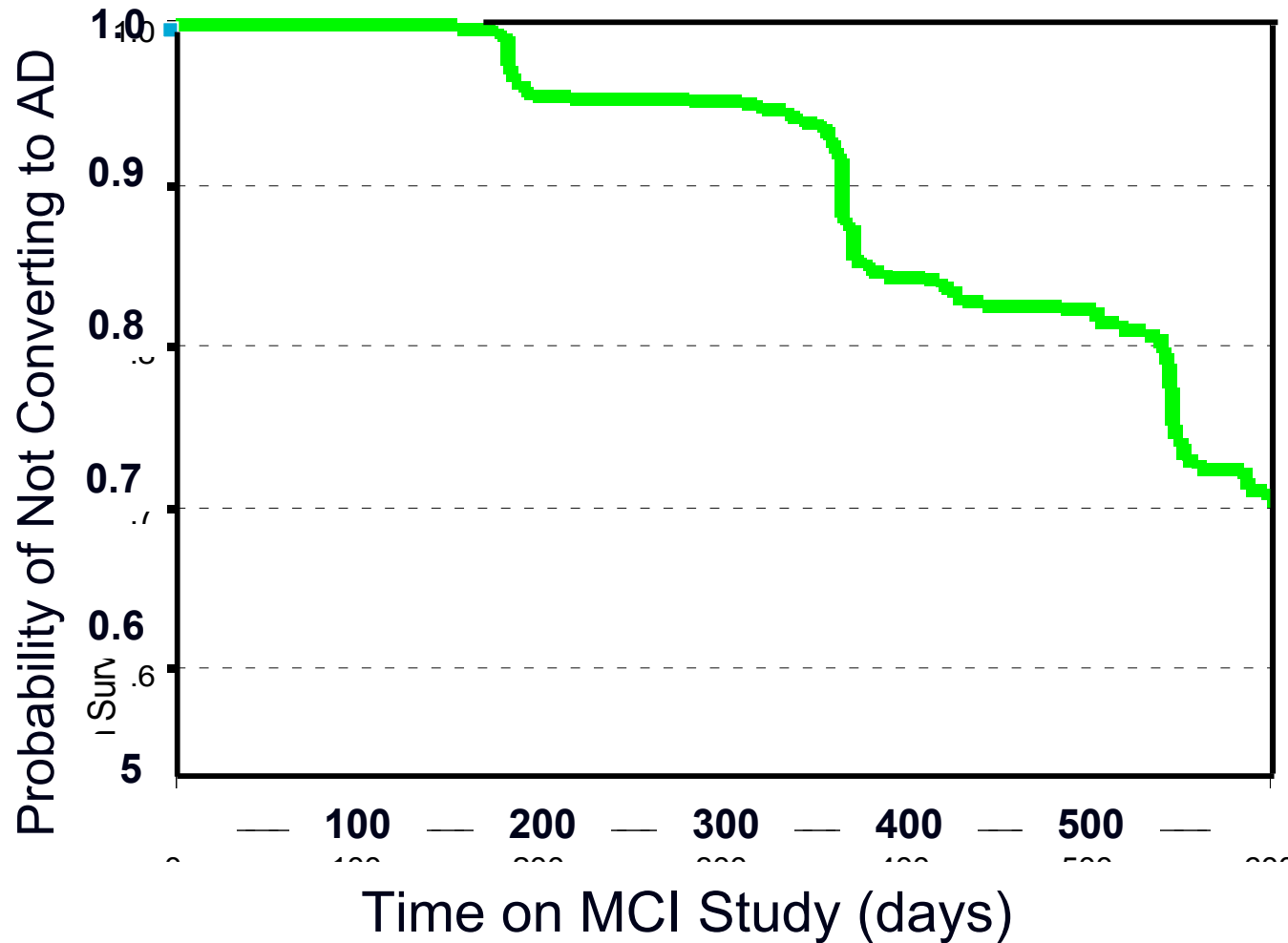
# Conversion from MCI or ? Dementia to AD

| ■ Author    | Year | Location  | Criteria     | Yrs Fol. | Conversion rate/yr |
|-------------|------|-----------|--------------|----------|--------------------|
| ■ Flicker   | 1991 | NY        | GDS 3        | 2        | 25                 |
| ■ Tierney   | 1996 | Toronto   | Mem imp      | 2        | 12                 |
| ■ Bowen     | 1997 | Seattle   | Isolated mem | 4        | 12                 |
| ■ Devenand  | 1997 | NYC       | ? Dementia   | 3        | 15                 |
| ■ Geerlings | 1999 | Amsterdam | Mem imp      | 3        | 12                 |
| ■ Petersen  | 1999 | Mayo      | MCI          | 4        | 12                 |
| ■ Daly      | 2000 | Boston    | CDR 0.5      | 3        | 6                  |
| ■ Bennett   | 2002 | ROS       | MCI          | 4.5      | 8                  |
| ■ Larrieu   | 2002 | France    | MCI          | 5        | 8                  |

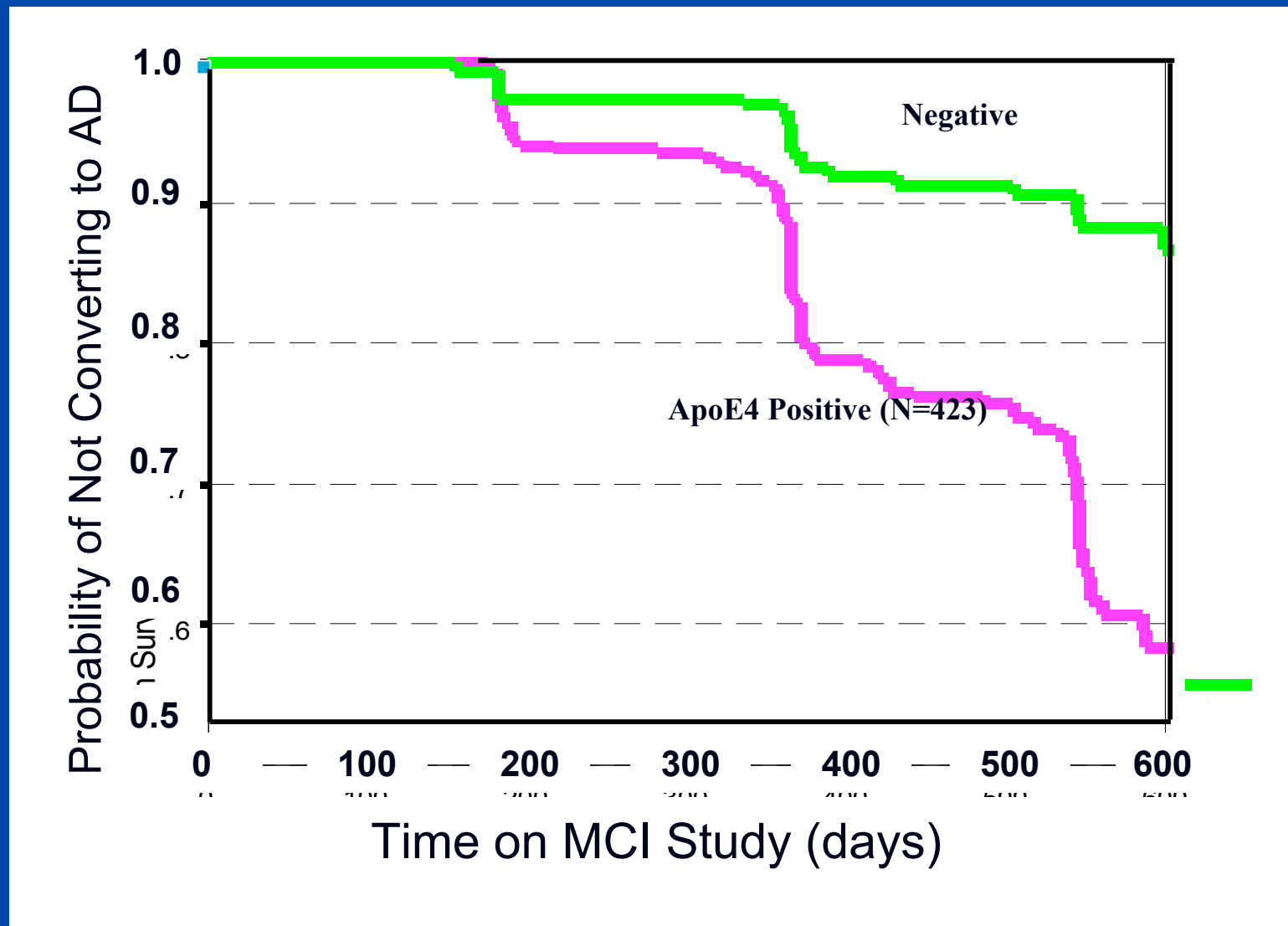
# Conversion Rate of MCI-Amnestic to Dementia (AD Cooperative Study)



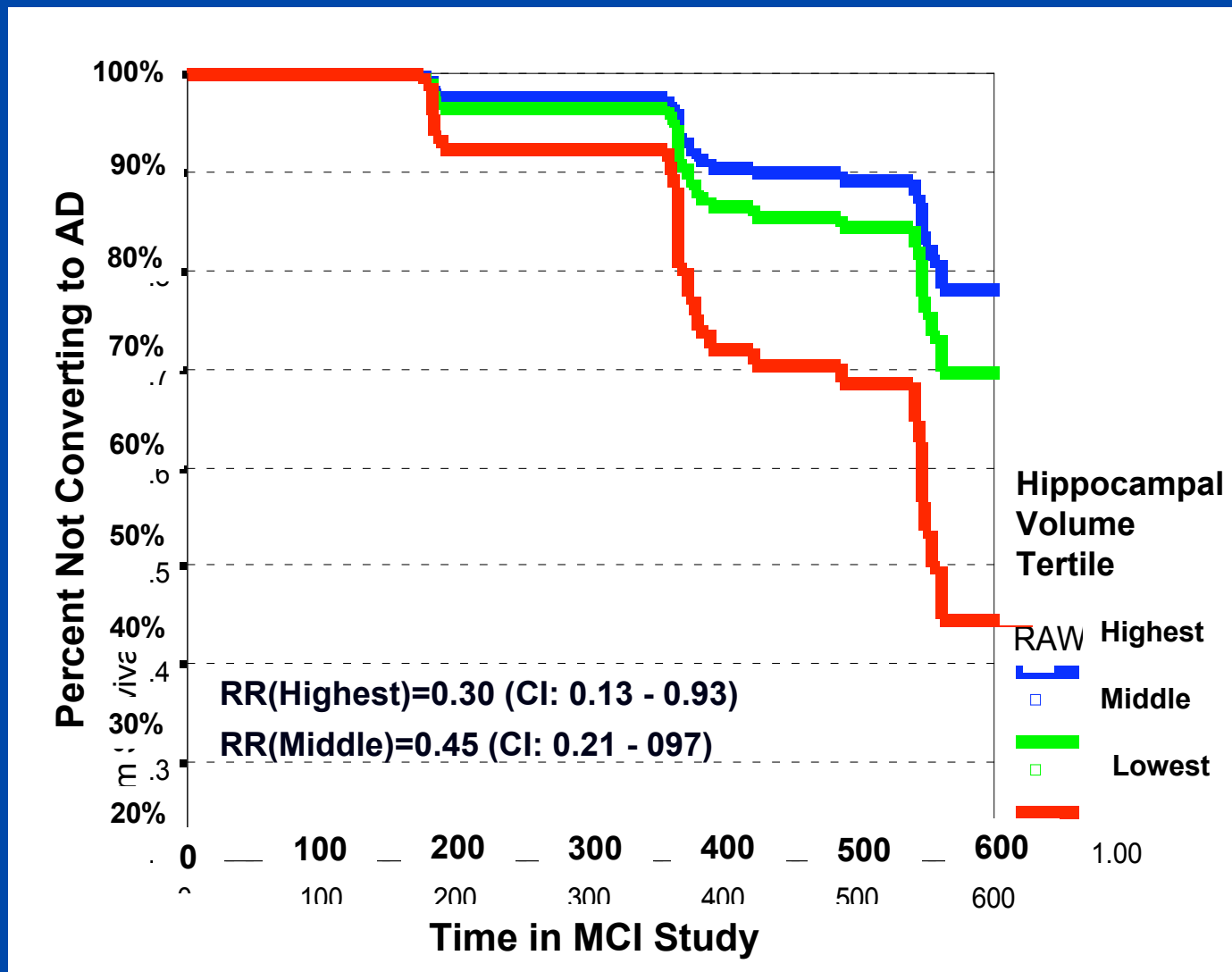
# MCI Protocol: Conversion to AD (ADCS Trial)



# MCI Protocol: Conversion to AD by ApoE4 Status (ADCS Trial)



# Conversion to AD by Baseline Hippocampal Volume Tertiles (ADCS Trial)



# ADCS MCI TRIAL

- 769 subjects baselined
- Conversion rate from MCI to AD is 12-15% per year
- Hippocampal volume at baseline is a strong predictor of rate of conversion to AD
- ApoE4 allele is a strong predictor of conversion to AD

# Problems with Mild Cognitive Impairment

- Non-specific
- Encourages generalization to a variety of late life cognitive disturbances
- Always prompts the question: “How did you define MCI?”

# MCI can be a useful concept if carefully defined

- Can be a risk state for the development of Alzheimer's disease or other dementias
- AD and Vascular Cognitive Impairment are the greatest public health problems
- AD and VCI have the most potential interventions
- A major challenge will be distinguishing them, especially early
- Desperately seeking biomarkers

# Outcome Measures

- Clinical Global
- Cognitive Testing
- Function in ADLs
- Behavior
- (Biomarkers - Structural MRI, PET, A<sub>β</sub> or Tau in CSF, A<sub>β</sub> lead by PET)
- (Conversion to AD)

# Delay to Diagnosis of MCI Paradigm

*It is unclear how mild cognitive impairment would be diagnosed by the community physician, and whether such patients would be the same and respond similarly to those in clinical trials*

- MCI criteria in clinical trials contain subjective features, that depending on interpretation give widely varying conversion rates (where are the cutoffs in cognitive testing, how much dysfunction in ADLs is allowed?)
- Likely to be very low conversion rates in first year in clinical trials as truly borderline patients will be excluded
- Conversion criteria from MCI to Dementia are not well defined in the community and may differ between clinical trials.

# SUMMARY OF MCI

- MCI ~ Remains controversial as a separable entity
- MCI ~ (amnesic form) probably best look at as prodromal AD or the earliest stage of AD
- MCI ~ rate of conversion to AD is 10-12 %/year
- MCI ~ predictors of early conversion are APOE4 genotypes and the hippocampal atrophy
- MCI ~ No therapy known to halt conversion