ADC Directors Meeting

NIA - Alzheimer's Association Working Groups: Diagnostic Approaches Across the Evolution of AD

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Overview

- Describe working groups organized several months ago by NIA and Alzheimer's Association related to diagnostic criteria for the phases of AD
- Outline the status of their recommendations, particularly as it applies to biomarkers for AD
- Describe the general timeline for these recommendations and future plans

Serve as introduction for other speakers

Background

- Three Working Groups established by the NIA and the Alzheimer's Association (Jan 2010):
  - Gp1 - Update diagnostic criteria for AD dementia (NINCDS/ADRDA criteria, 1984)
  - Gp 2 - Update diagnostic criteria for 'MCI due to AD'
  - Gp 3 - Outline research agenda for identifying biomarkers that might predict emergence of cognitive symptoms among normal individuals (needed to define presymptomatic phase of AD)

Working Group on AD Dementia

Chair: Guy McKhann
Clifford Jack
Brad Hyman
Claudia Kawas
Bill Klunk
David Knopman
Walter Koroshetz
Jennifer Manly
Richard Mayuex
Richard Mohs
John Morris
Sandra Weintraub

Sponsored by NIA and Alzheimer's Association

Working Group on ‘MCI due to AD’

Chair: Marilyn Albert
Steve DeKosky
Dennis Dickson
Bruno Dubois
Howard Feldman
Nick Fox
Anthony Gamst
Dave Holtzman
Bill Jagust
Ron Petersen
Steve Snyder

Sponsored by NIA and Alzheimer’s Association

Working Group on Presymptomatic AD

Chair: Reisa Sperling
Laurel Beckett
Dave Bennett
Suzanne Craft
Ann Fagan
Jeff Kaye
Denise Park
Tom Montine
Eric Reiman
Eric Siemers
Yaakov Stern
Christine Yaffee

Cliff Jack (ex officio)

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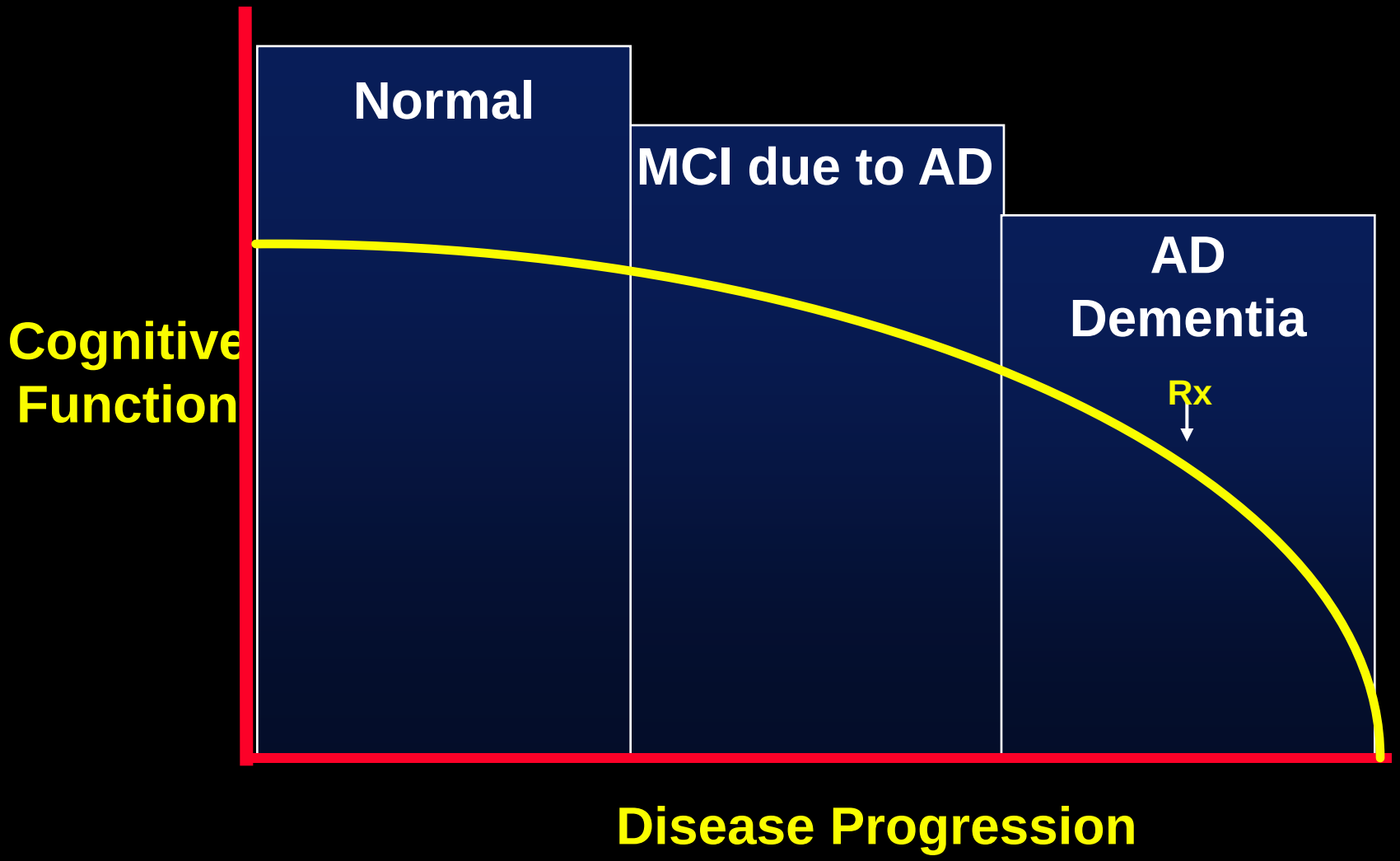
Progression of Alzheimer's Disease

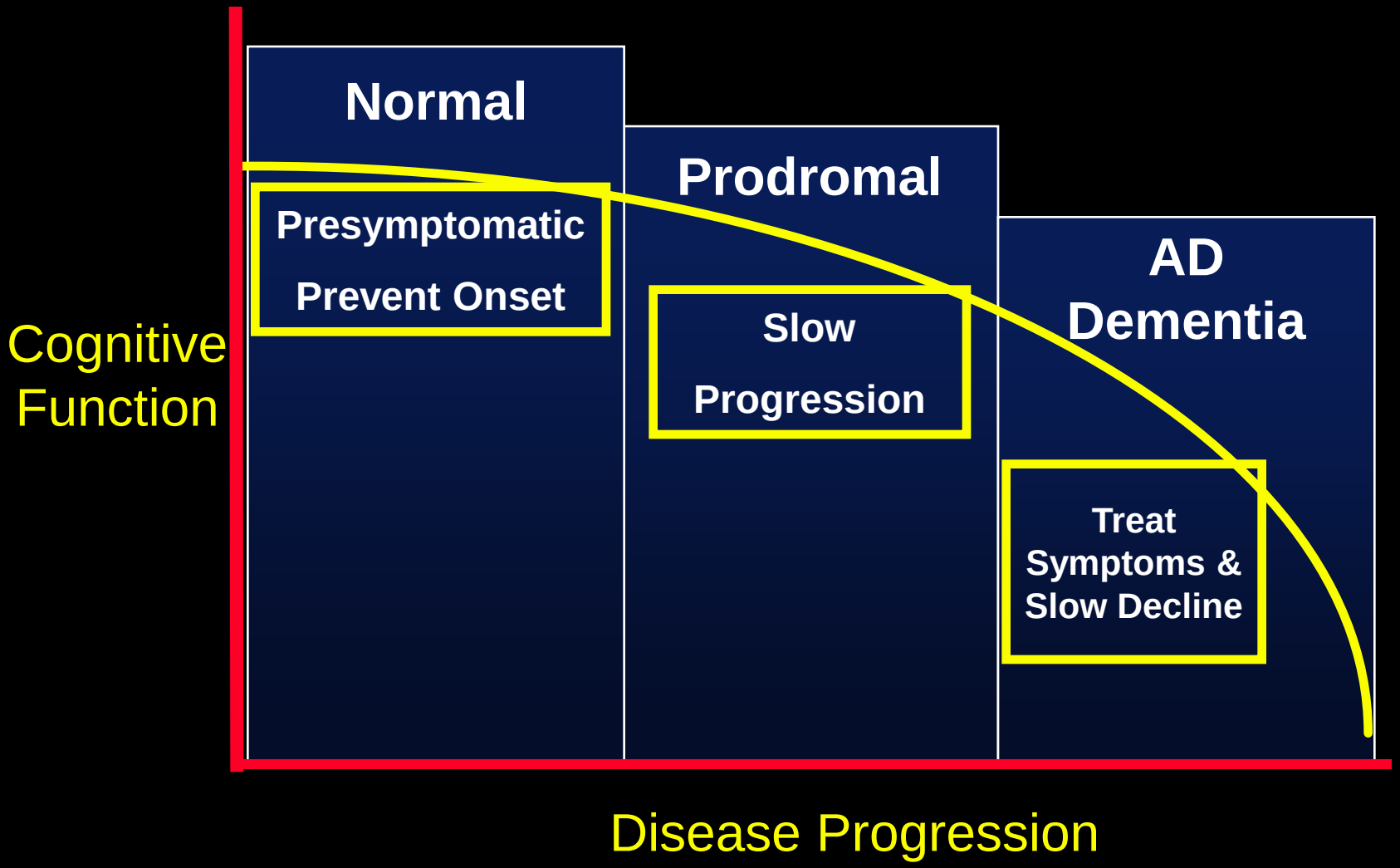
- Consensus that AD has a long prodromal phase – likely a decade or more
- Consensus that individuals are symptomatic for many years prior to dementia (MCI)
- Consensus that AD pathology exists (without neuronal loss) among some individuals with normal cognition
- Increasing concern that late intervention may be less effective, hope that biomarkers can increase certainty of diagnosis so early intervention may be feasible

WGs built on consensus in field

Progression of Alzheimer's Disease



Therapeutic Implications of Disease Course



Interim Status

- Recommendations not complete but general direction is clear:
  - Focus on AD – describe other disorders primarily for purposes of differential diagnosis (AD dementia, ‘MCI due to AD’, presymptomatic AD)
  - AD and MCI Criteria - Separate but overlapping criteria for clinician in community and for researchers (similar nomenclature and concepts)
  - Most novel aspect of diagnostic criteria will be emphasis on biomarkers for increasing level of certainty for the diagnosis (AD dementia and ‘MCI due to AD’)
  - Will recommend criteria and/or research plan that must evolve as more data are acquired
  - Decisions reflect the impact of the knowledge that has emerged from the last three decades of research

Interim Status

- Incorporation of biomarkers will emphasize amyloid hypothesis, recognizing that this may need to change if not supported by evidence:
  - The AD and MCI Working Groups will establish criteria that will incorporate clear testable hypotheses regarding the levels of certainty conferred by categories of biomarkers
  - The Working Group on the presymptomatic phase of AD will not outline criteria for this phase of disease, but rather the information needed to some day establish criteria for presymptomatic AD.

Framework for Biomarkers

Biomarkers of Molecular Neuropathology of AD

- CSF Aβ 42
- CSF tau / phospho tau
- PET amyloid imaging

Downstream Measures of Structural Change

- Hippocampal Volume or Medial Temporal Lobe Atrophy
- Rate of Brain Atrophy
- Less well validated biomarkers (e.g., diffusion tensor imaging, voxel-based and multivariate MRI measures)

Working Group on MCI

Jagust, Holtzman, Fox

Framework for Biomarkers
(cont)

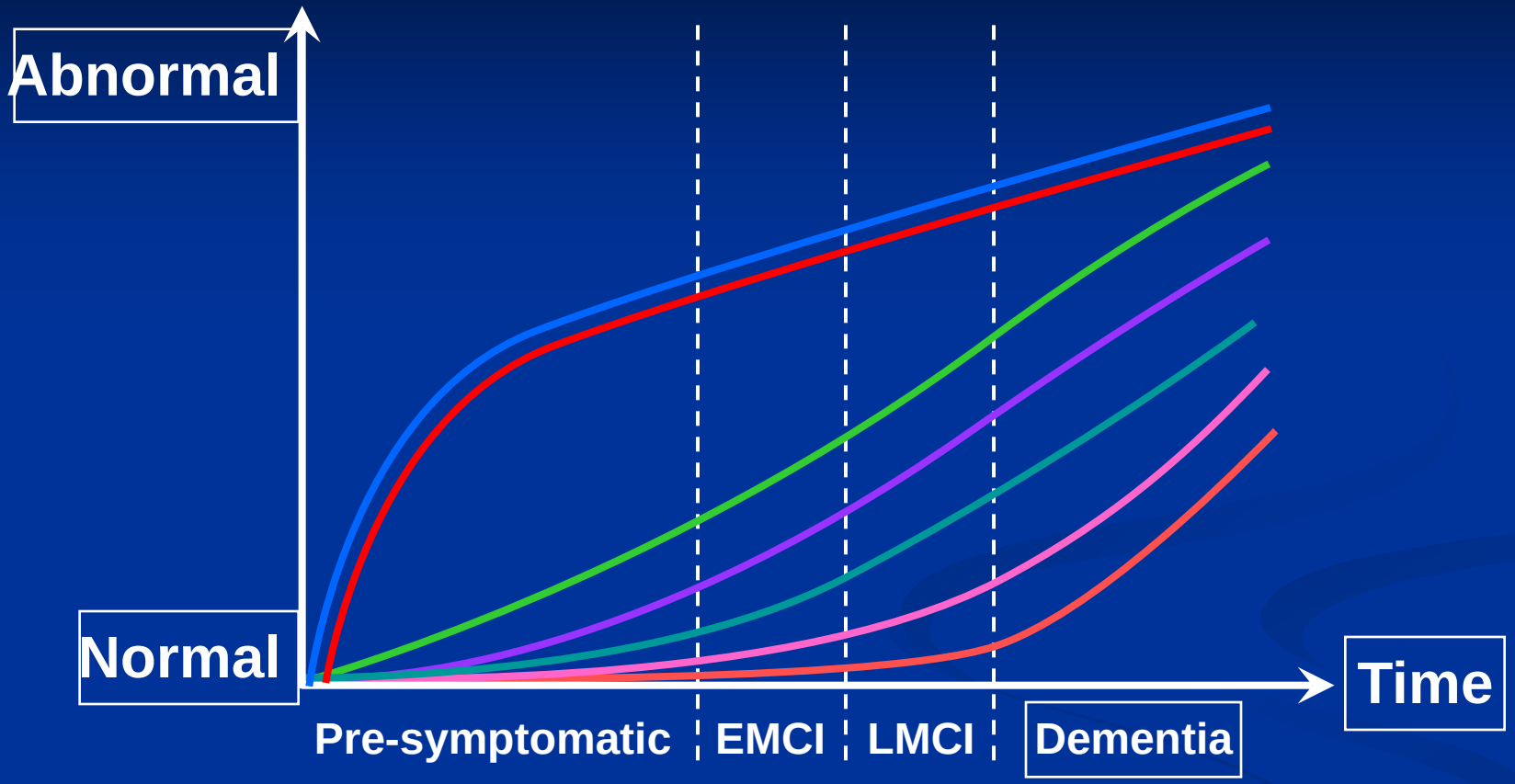
Downstream Measures of Functional Change

- FDG PET Imaging
- SPECT perfusion imaging
- Less well validated biomarkers: fMRI activation studies, resting BOLD connectivity, MRI perfusion, MR spectroscopy

Associated Biochemical Change

- Inflammatory biomarkers
- Oxidative stress (isoprostanes)
- Other markers of neurodegeneration

Hypothetical Model of Biomarkers



Jack et al., 2010

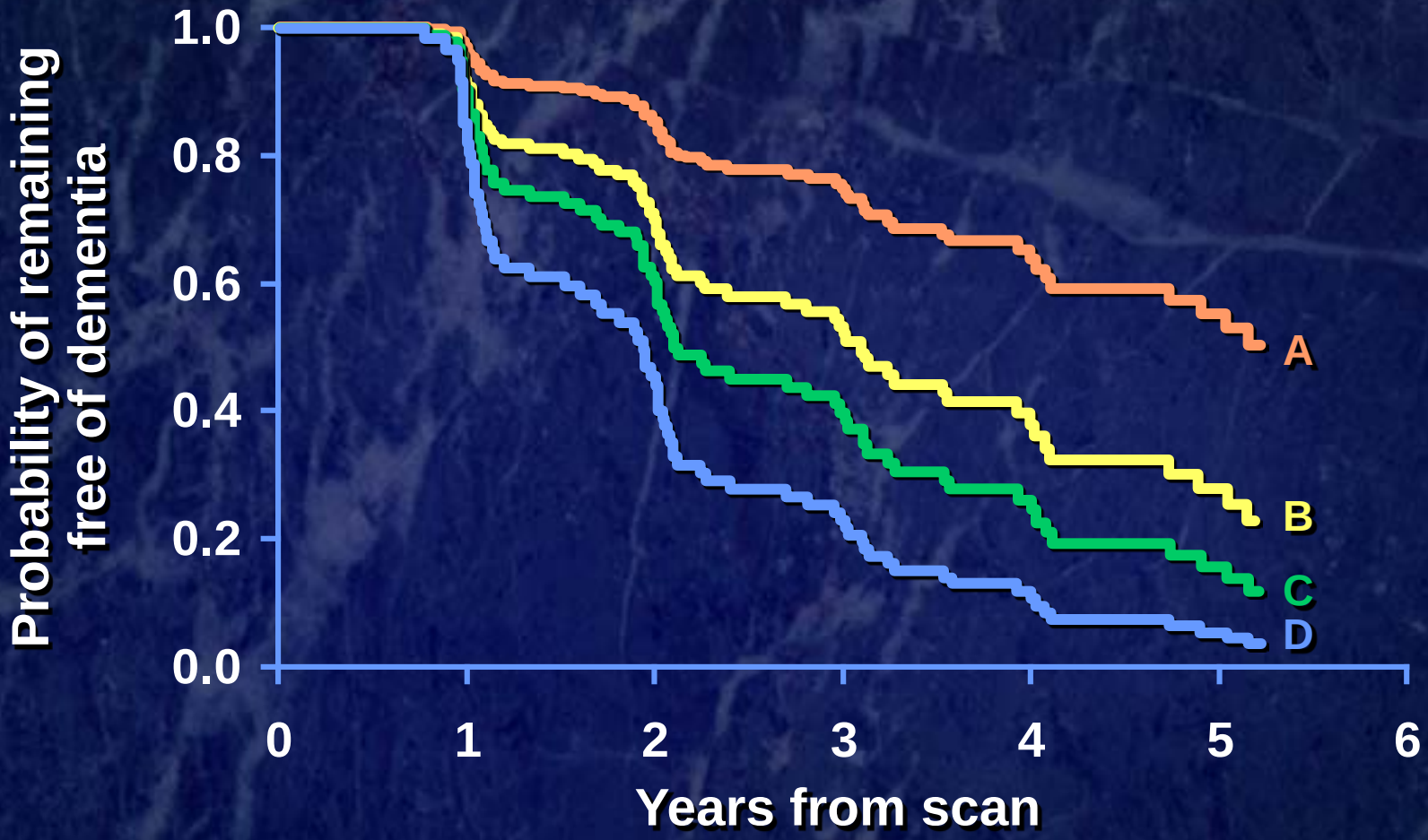
Example of Use of Biomarkers in Diagnosis

- Highly Probable – subject meets clinical and cognitive criteria for the disorder plus positive findings on molecular biomarker
- Probable – subject meets clinical and cognitive criteria for the disorder plus positive findings on a downstream biomarker (MRI, FDG PET)
- Low Probability – subject has clinical, cognitive and/or biomarker evidence to suggest another disorder

Application of Biomarkers in Diagnosis

- Application of biomarkers for diagnosis in community will require much more information about normative values, laboratory to laboratory variation, etc.
- Lack of clarity for how to handle competing results from biomarkers (positive finding on one biomarker but negative or ambiguous finding on another)
- Utility of combinations of biomarkers need to be clarified

Combinations of Biomarkers for Prediction



A = base rate; B = with hippocampal atrophy;
C = with hippocampal atrophy + abnormal MRS;
D = with hippocampal atrophy + abnormal MRS + cortical stroke

Kantarci et al: Neurology (in press)

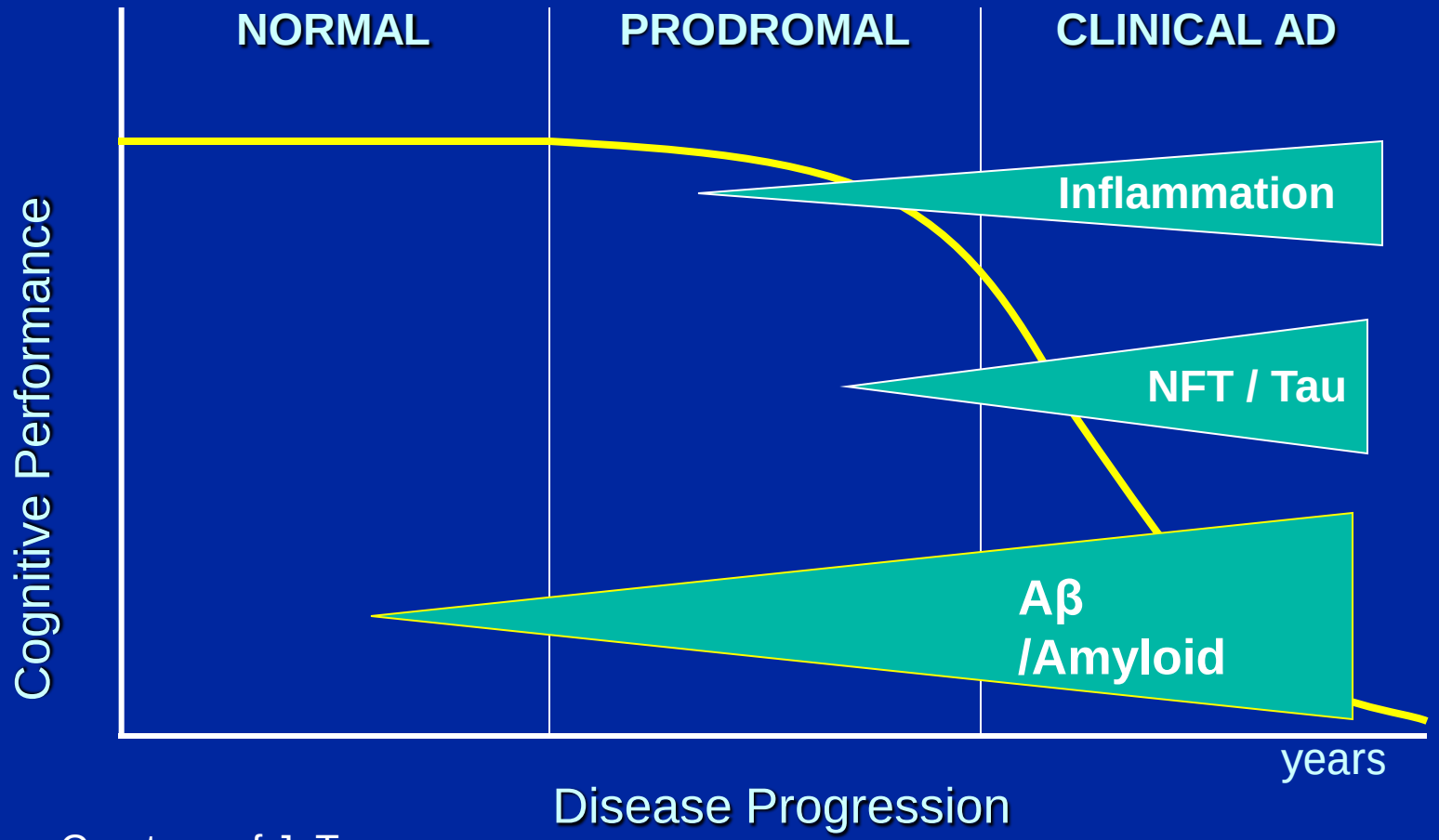
Application of Biomarkers in Clinical Trials

- Inclusion of biomarkers in clinical trials
  - already being used to enrich samples with subjects likely to meet criterion of interest
  - problems such as appropriate norms, laboratory to laboratory variation less of an issue
  - Do not need to give someone a diagnosis with high specificity in order to enroll them in a clinical trial (e.g., MCI vs. prodromal AD)

Summary

- Recommendations of Working Groups will be presented at ICAD – will be open to input from the community at large and modified, as needed
- Diagnostic criteria for AD dementia and ‘MCI due to AD’ likely to require revision over time, as we learn more about the role of biomarkers in diagnosis and prediction (from work such as the speakers on this panel)
- It is, nevertheless, rewarding to see so many years of work by so many people begin to come to fruition.

Evolution of Pathology in Alzheimer's Disease



Courtesy of J. Troncoso