NIA / Alzheimer's Association Working Groups Diagnostic Guidelines for AD

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General Background

- Concept behind formation of working groups sponsored by the NIA and Alzheimer's Association:
  - The development of AD pathology occurs across a continuum of time (years) and level of impairment
  - Increasing percentage of individuals have AD pathology as one goes across the continuum from: clinically normal – mild cognitive impairment – dementia
  - Time was right to reconsider the diagnostic guidelines from this perspective

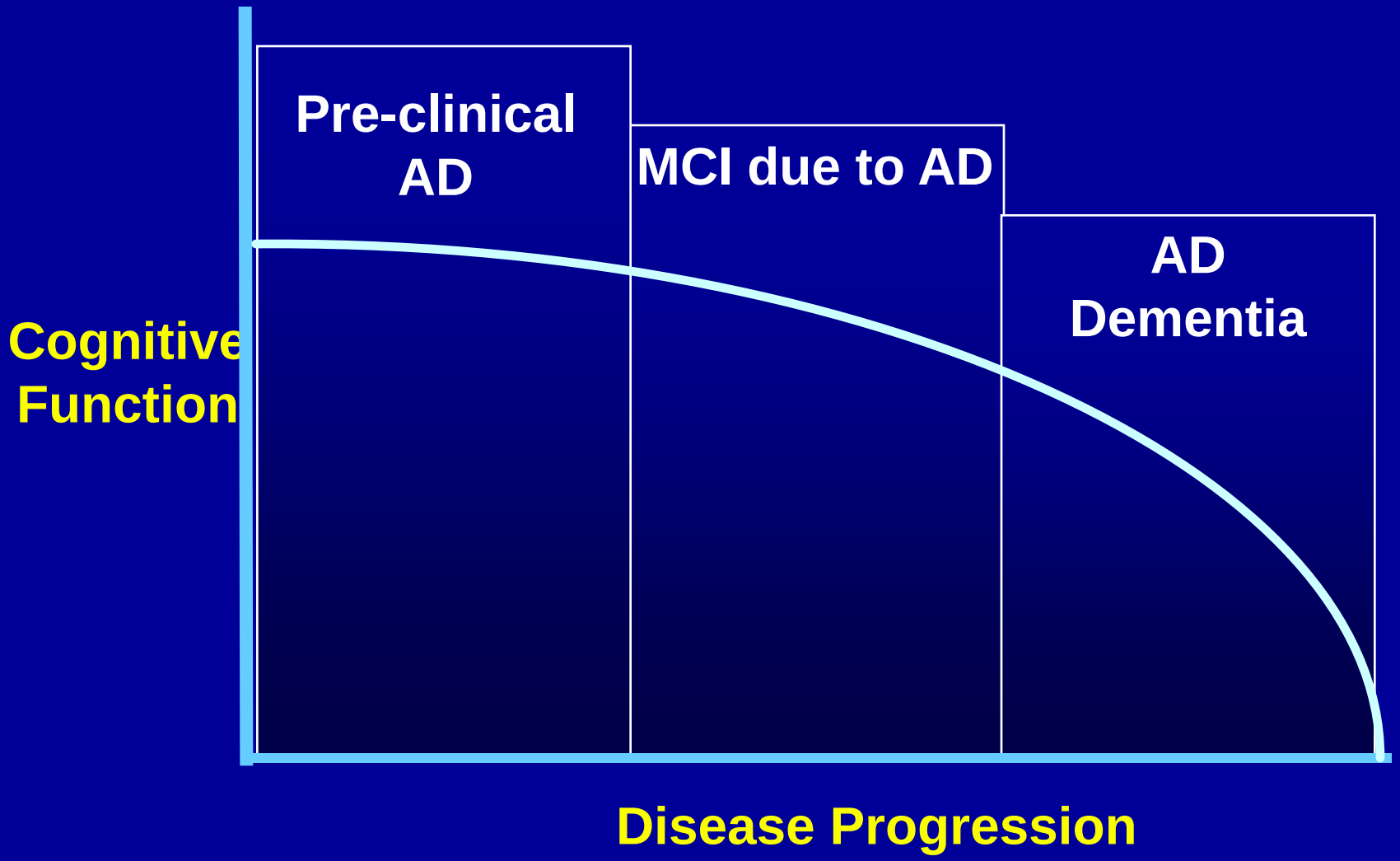
Three Working Groups

- Review diagnostic guidelines across the spectrum of Alzheimer's disease (AD):
  - Dementia of the Alzheimer type
  - Symptomatic pre-dementia phase of AD
  - Asymptomatic phase of AD

Three Working Groups

- Working Group Chairs:
  - Dementia of the Alzheimer Type – Guy McKhann, MD
  - Symptomatic Pre-dementia phase of AD– Marilyn Albert, PhD
  - Asymptomatic phase of AD – Reisa Sperling, MD

Progression of Alzheimer's Disease



AD Dementia
Working Group

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

MCI Due to AD
Working Group

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

Pre-clinical AD
Workgroup

Reisa Sperling - Chair
Laurel Beckett
David Bennett
Suzanne Craft
Anne Fagan
Jeffrey Kaye
Tom Montine
Denise Park
Eric Reiman
Eric Siemers
Yaakov Stern
Kristine Yaffe
Paul Aisen (Ex-officio)
Cliff Jack (Ex-officio)

Three Working Groups

- Key Feature of Charge to Working Groups: Encouraged to acknowledge that more needs to be learned about how to define this continuum and thus should incorporate into recommendations hypotheses to be tested:
  - Aspects of recommendations would be re-evaluated and expected to evolve over time as more information is acquired
  - Primary outcome in all three working groups: incorporation of biomarkers in recommendations that need to be tested in research settings

AD Dementia & MCI Working Groups

Common Features

- Developed core set of clinical and cognitive criteria with wide application (community clinicians, tertiary care institutions, academic researchers, clinical trials)
- Used biomarkers to increase certainty of diagnosis - for use in research settings (academic research, clinical trials)
- Applied current knowledge regarding biomarkers, even though it may be incomplete
  - Outlined areas where more information is needed
  - Incorporated testable hypotheses regarding diagnosis

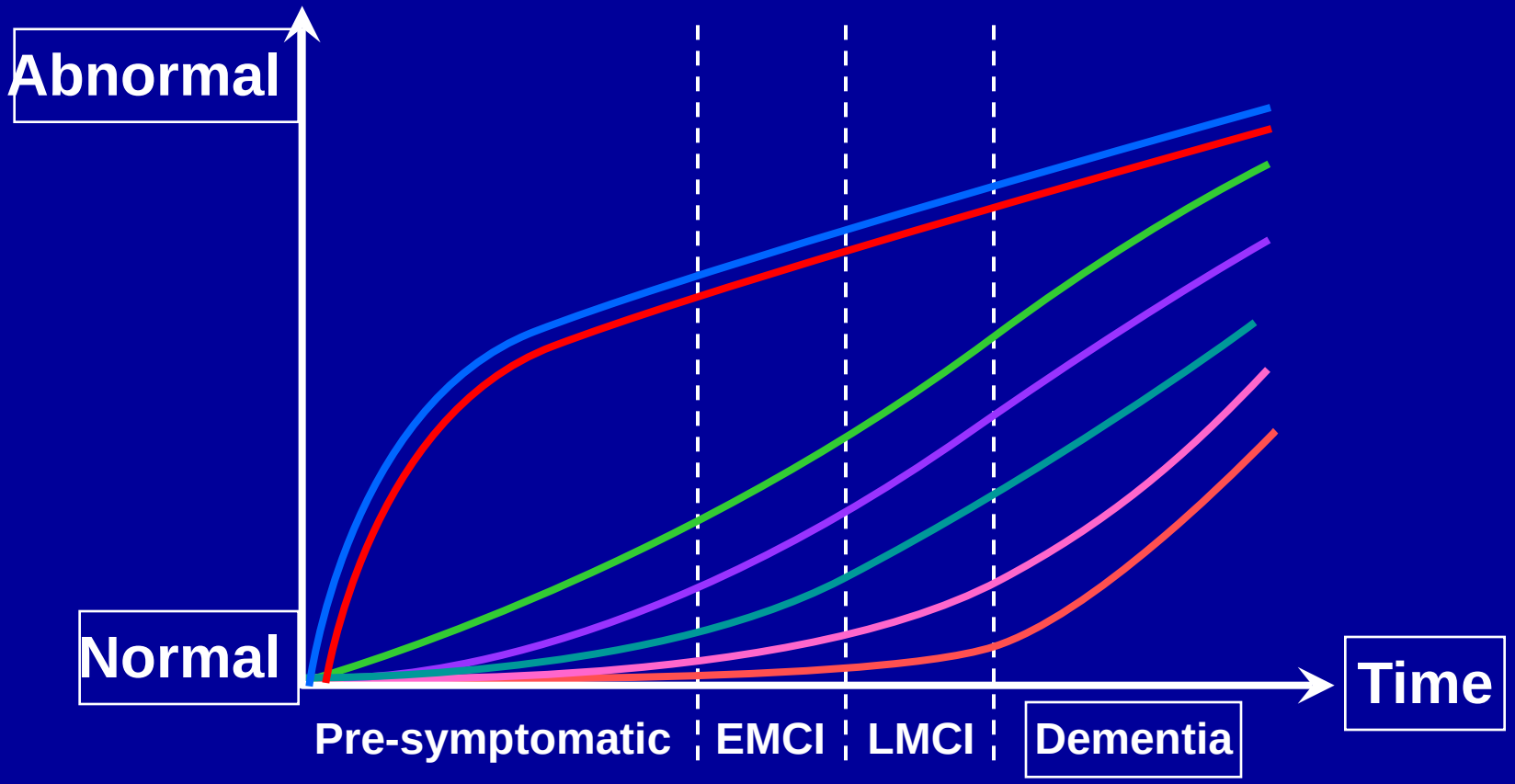
AD Dementia and MCI Working Group
Recommendations

- Described clinical and cognitive criteria for diagnosis
  - Describe general nature of evaluation
  - Outline differences from previous criteria (minimal)
- Described framework for approach to biomarkers
  - Molecular pathology of AD vs. downstream measures
  - Outline information that remains to be acquired in the future
- Criteria for AD Dementia
  - Did not indicate differing levels of certainty depending on nature of biomarker information
- Criteria for MCI due to AD
  - Three levels of certainty, depending on nature of biomarker information: (1) no biomarkers, (2) downstream biomarkers (e.g., atrophy, glucose metabolism), (3) molecular biomarkers reflecting AD pathology (e.g., CSF, amyloid imaging)

Framework for Biomarkers

- Molecular Pathology of AD
  - CSF Abeta 42
  - CSF tau/ phospho tau
  - Amyloid Imaging
- Downstream Measures of Structural Change
  - Hippocampal Volume
  - Medial Temporal Lobe Atrophy
- Downstream Measures of Functional Change
  - FDG PET
  - SPECT Perfusion

Hypothetical Model of Biomarkers in AD



Jack et al., 2010

Pre-Clinical AD Working Group

- Summarized what is known about cognitive measures and biomarkers among clinically normal individuals with substantial AD pathology
- Outlined research strategy to determine whether it is possible to identify clinically normal individuals destined to develop MCI and/or AD dementia
- Intended ONLY for research purposes
  - NO application to clinicians in community at the present time

Pre-clinical AD Working Group

- Described studies showing cognitive testing may differ among clinically normal individuals destined to develop MCI or AD dementia and test performance associated with AD pathology on autopsy
- Emphasized importance of using biomarkers to determine if AD pathology is present
  - Focused on molecular biomarkers that assess presence of AD pathology (e.g., CSF, amyloid imaging)
  - Also described biomarker findings that may provide indirect assessment of presence of AD pathology (e.g., resting BOLD fMRI)

Working Group Presentations & Comments by Community

- Worked from January – June 2010
- Special session at ICAD in July 2010
  - Presentation by chair of each working group
  - Presentation by discussant (Steve DeKosky)
  - General discussion by attendees
- On-line comments by research community via Alzheimer's Association website – ended September 2010
- Articles and editorials in media

Major Points Raised During Comment Period

- Clarify which aspects of criteria are intended for clinicians in the community and which are intended only for research community
- Emphasize that boundary conditions offer challenges for accurate diagnosis if condition is actually a continuum of disease
- Harmonize approach to utilizing biomarkers to confer differing levels of certainty depending on whether the biomarkers reflect molecular pathology of AD vs. downstream measures of structural and functional change

Chairs of Working Groups

Major Points Raised During Comment Period

- Amyloid Hypothesis: Clarify that in using molecular markers of amyloid pathology as evidence that AD pathology is present, does not constitute proof that amyloid hypothesis is correct (diagnostic criteria as ‘trojan horse’)
- Neuropsychological Testing: Outline potential uses of neuropsychological testing (range of tests or development of new tests)
- Sub-issues: Clearly identifiable sections on potential role of genetics and current limitations for how to incorporate cultural differences and application to individuals of extreme old age

Major Points Raised During Comment Period

- Consistency of approach to discussion of disorders other than AD
  - Impact of vascular disease
  - Key features that suggest another disorder is present (FTLD, DLB, CJD, etc)
- Terminology for major diagnostic categories
  - AD dementia - highly probable
  - Prodromal Alzheimer's dementia – probable MCI of the AD type
  - Preclinical AD - asymptomatic

Next Steps for Working Groups

- Discuss comments with members of each working group
  - Reach consensus on changes to incorporate
- Prepare three articles summarizing recommendations
- Prepare Introduction that would summarize overarching issues common to all three groups
  - Evolution of pathology across the spectrum of cognitive impairment (normal, MCI, dementia)
  - Challenges of boundary conditions for disorder that is continuum
  - Why biomarkers are important to include in research strategy
  - Challenges for use of biomarkers in clinical practice (e.g., lack of standardization, lack of access, cost)
  - Disclaimer regarding proof that amyloid is causative agent

Next Steps for Working Groups

- Reconsider terminology
  - Each group has received comments about terminology that was recommended
  - Appears to be emotionally charged issue

Summary

- Working Group Recommendations:
  - Clinical criteria for clinicians in community – minimal change from prior criteria for AD dementia or MCI
  - Most novel aspect of diagnostic criteria is emphasis on biomarkers for increasing level of certainty for the diagnosis
  - Research plan for pre-clinical phase of disease
  - Recommendation that 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 - consensus by working group members

Criteria for MCI due to AD

Clinical and Cognitive Criteria - Evaluation

- Evidence of progressive decline
  - Encourage longitudinal assessment, when possible
- Role of genetics – special considerations
  - Individuals with mutation in AD genes
  - Genes that increase risk for AD (ApoE)
- Emphasize that diagnosis requires clinical judgment, taking all information into account
  - Re-emphasize this point in discussion of biomarkers

Criteria for MCI due to AD

Clinical and Cognitive Criteria - Differences

- Concern about cognitive change can be identified by any source:
  - Patient, informant, skilled clinician
- Independence of function:
  - Can have evidence of functional change
  - Must maintain independence of function with minimal aids or assistance

Criteria for MCI due to AD

Clinical and Cognitive Criteria - Differences

- Cognitive domains impaired:
  - Emphasize primary impairment is generally episodic memory
  - Acknowledge that other domains can be impaired
  - Allow for impairments in more than one cognitive domain
  - Do not use terms - ‘amnestic’ and ‘non-amnestic’ MCI

Role of Biomarkers

- Clarify nature of underlying pathology:
  - Evidence of amyloid burden considered of primary importance in confirming that pathology of AD is present
- Prediction of progression from MCI to Alzheimer's dementia:
  - Acknowledge that measures of structural and functional change may be more useful in prediction of progression

Use of Biomarkers in Diagnosis

- Incorporation of biomarkers in diagnosis emphasizes that accumulation of amyloid is seen first and is followed by other changes (recognizing that more work needs to be done to confirm this trajectory):
  - Different biomarkers provide different levels of certainty in diagnosis of MCI due to AD
  - Since more needs to be learned regarding biomarkers, the criteria, in essence, outline testable hypotheses regarding the levels of certainty conferred by categories of biomarkers
  - Can apply in academic research settings and clinical trials and determine utility of this framework

Diagnosis of MCI due to AD
Levels of Certainty

- MCI of a Neurodegenerative Etiology
- MCI of the Alzheimer's Type
- Prodromal Alzheimer's Dementia

Diagnosis of MCI due to AD
Levels of Certainty

- MCI of a Neurodegenerative Etiology
  - patient meets clinical and cognitive criteria for the disorder
  - biomarkers have not been tested, or
  - biomarkers have been tested and are ambiguous, or
  - molecular biomarkers are negative (likelihood of AD is low)

Diagnosis of MCI due to AD
Levels of Certainty

- MCI of the Alzheimer's Type
  - patient meets clinical and cognitive criteria for the disorder plus positive findings from a downstream biomarker of structure or function (MRI, FDG PET)
  - consistent with absence of molecular biomarkers or equivocal findings from molecular biomarkers

Diagnosis of MCI due to AD
Levels of Certainty

- Prodromal Alzheimer's Dementia – patient meets clinical and cognitive criteria for MCI due to AD plus biomarker evidence to suggest AD is underlying pathology (e.g., low CSF Abeta42, amyloid accumulation with PET imaging)
  - Consistent with absence of downstream biomarker evidence of structural or functional change (MRI, FDG PET)
  - Consistent with equivocal or normal findings from downstream biomarkers of structural or functional change (MRI, FDG PET)