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NEW CRITERIA AND GUIDELINES FOR THE DIAGNOSIS OF ALZHEIMER'S DISEASE PUBLISHED FOR FIRST TIME IN 27 YEARS

– Research Agenda Suggested for Detecting Pre–Symptomatic Alzheimer's –
– New Alzheimer's Definition Moves Researchers Closer to Early Detection and Intervention –

CHICAGO, April 19, 2011 – For the first time in 27 years, new criteria and guidelines for the diagnosis of Alzheimer's disease have been published by three expert workgroups spearheaded by the Alzheimer's Association and the National Institute on Aging (NIA) of the National Institutes of Health (NIH).

The workgroups published four articles including ready-to-use clinical diagnostic criteria for Alzheimer's disease dementia and mild cognitive impairment (MCI) due to Alzheimer's. A research agenda was proposed for preclinical Alzheimer's. The use of biomarkers in Alzheimer's dementia and MCI due to Alzheimer's was also proposed as a research agenda only, and is not intended for application in clinical settings at this time.

The articles – collectively, the National Institute on Aging/Alzheimer's Association Diagnostic Guidelines for Alzheimer's Disease – expand the definition of Alzheimer's to include two new phases of the disease: (1) presymptomatic and (2) mildly symptomatic but pre-dementia, along with (3) dementia caused by Alzheimer's. This reflects current thinking that Alzheimer's begins creating distinct and measurable changes in the brains of affected people years, perhaps decades, before memory and thinking symptoms are noticeable.

"It is our hope that incorporating scientific knowledge gained and technological advances made over the past quarter century will improve current diagnosis, bring the field closer to earlier detection and treatment, and ultimately lead to effective disease-modifying therapies," said William Thies, Ph.D., Chief Medical and Scientific Officer at the Alzheimer's Association. "Development and publication of these articles is a major landmark in the field. That said, publication of these articles is not yet the end of the process of developing new diagnostic criteria for Alzheimer's, but is another major step in the process."

"The new guidelines reflect today's understanding of how key changes in the brain lead to Alzheimer's disease pathology and how they relate to the clinical signs of mild cognitive impairment and Alzheimer's disease dementia," said Creighton Phelps, Ph.D., Program Director of the Alzheimer's Disease Centers Program at the National Institutes of Health. "We are also beginning to be able to detect these changes at a preclinical stage, long before symptoms appear in many people. With further research on biomarkers, as set forth in the new guidelines, we may ultimately be able to predict who is at risk for development of mild cognitive impairment and Alzheimer's dementia, and who would benefit most as interventions are developed."

The proposed new Alzheimer's disease diagnostic guidelines were published online today by *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*. Hard copy publication is scheduled for the May 2011 issue of the journal.

Three Stages of Alzheimer's Disease

The current diagnostic criteria for Alzheimer's⋆, for the most part, focus on reliable diagnosis when signs of problems in thinking, learning, and memory are noticeable to an individual, family, and friends. But research tells us that Alzheimer's likely begins years, maybe even decades, prior to symptoms appearing.

The new articles refer to three phases of Alzheimer's disease progression over time:

- <u>Preclinical Alzheimer's Disease</u> – Measurable changes in biomarkers (such as brain imaging and spinal fluid chemistry) that indicate the very earliest signs of disease, before outward symptoms are visible. Currently, there are no clinical diagnostic criteria for this phase, but the group provides a scientific framework to help researchers better define this stage of Alzheimer's. (See supplement 5.)
- <u>Mild cognitive impairment (MCI) due to Alzheimer's Disease</u> – Mild changes in memory and thinking abilities, enough to be noticed and measured, but not impairment that compromises everyday activities and functioning.
- <u>Dementia due to Alzheimer's Disease</u> – Memory, thinking and behavioral symptoms that impair a person's ability to function in daily life.
  (For more details, see supplement 3.)

According to the authors, in order to facilitate the possibility of future presymptomatic treatment of Alzheimer's, it was important to define the disease from the earliest changes in the brain, not only the observable, symptomatic stages of the disease. The authors propose that Alzheimer's begins with a long asymptomatic period during which detrimental changes are progressing in the brain, and individuals with biomarker evidence of these changes are at increased risk for developing cognitive and behavioral impairment and progression to Alzheimer's dementia.

A biomarker is a naturally occurring, measurable substance or condition in the body that reliably indicates the presence or absence of disease or the risk of later developing a disease; for example, blood glucose levels are a biomarker of diabetes, and cholesterol levels are a biomarker of cardiovascular disease risk. Both fluid and imaging measures are being tested as possible biomarkers for Alzheimer's. (See supplement 4.)

There was a broad consensus within the workgroups that much additional research needs to be done to validate the application of biomarkers as they are proposed in the newly-published articles. According to the authors, "The definitive studies … are likely to take more than a decade to fully accomplish. Thus, we must move quickly … and adjust our models and study designs as new data become available."

"If we can definitively determine the risk of developing Alzheimer's dementia in people who have biomarker evidence of brain changes but are not showing outward symptoms, we will open

an important window of opportunity to intervene with disease-modifying therapies, once they are developed," Thies said.

"In addition, the new criteria give us powerful tools to accelerate our knowledge in the fight against Alzheimer's disease. They give us guidelines for getting a more accurate assessment of Alzheimer's prevalence. In that way we can better assess the need for everything from research dollars to care services, to patient and caregiver education materials, to nursing home beds, to the number of gerontologists and nurses that we need. And, they give us a basis for creating the next generation of Alzheimer's treatments that will be effective in each stage of the disease," Thies said.

Moving the Field Toward Earlier Diagnosis and Treatment of Alzheimer's

The Alzheimer's Association, in its 2010 report titled "Changing the Trajectory of Alzheimer's Disease: A National Imperative," showed that a hypothetical intervention that delayed the onset of Alzheimer's dementia by five years would result in a nearly 45 percent reduction in the number of people with Alzheimer's by 2050, and reduce the projected Medicare costs of Alzheimer's from $627 billion to $344 billion dollars.

The authors of the newly-released articles write, "It is our hope that the advances in preclinical detection of Alzheimer's will enable earlier, more effective treatment, just as nearly all of therapeutic gains in cancer, cardiovascular disease, osteoporosis, and diabetes involve treatment before significant clinical symptoms are present. Screening and treatment programs instituted for other diseases … have already been associated with a decrease in mortality due to these conditions."

Thies adds, "Currently, Alzheimer's therapies are in development that may be able to slow or stop the progression of the disease. By improving early detection and risk evaluation, we will better be able to test potential therapies and eventually prescribe them for people at increased risk. Ultimately, this approach envisions for Alzheimer's what is now common practice in cardiovascular disease, where early signs of risk – for example, in genetic markers or in blood cholesterol and/or blood pressure levels – can be treated to reduce the likelihood of heart attack or stroke later on."

The challenge for Alzheimer's now is that there is currently no single, generally accepted way to identify the disease in the earliest stage – before symptoms are evident. It is hoped that the research agenda outlined in the new preclinical Alzheimer's article will correct this deficit.

Presymptomatic Disease Detection and Treatment – Not a New Idea, Except in Alzheimer's

According to the authors, "The concept of a preclinical phase of disease should not be too foreign. Medical professionals readily acknowledge that cancer can be detected at the stage of 'carcinoma in situ' and that hypercholesterolemia and atherosclerosis can result in narrowing of coronary arteries that is detectable prior to myocardial infarction. It is widely acknowledged that symptoms are not necessary to diagnose human disease. Type II diabetes, hypertension, renal insufficiency, and osteoporosis are frequently detected through laboratory tests, and effective treatment can prevent the emergence of symptoms."

"We should be open to the idea that Alzheimer's could one day be diagnosed preclinically by the presence of biomarker evidence, which may eventually guide therapy prior to the onset of symptoms. We treat people with diabetes, elevated cholesterol, hypertension and a variety of other illnesses – we do not wait for strokes, heart attacks or other long term complications that we know will occur in significant numbers of those affected. Similarly, our intention is to use these criteria to better determine an individual's risk of developing Alzheimer's disease. This diagnostic research will help us discover the drugs of the future and prepare for the day when we can administer them to those at risk in order to prevent or delay the emergence of symptoms," wrote the authors.

What Was Published

The proposed new diagnostic criteria and research agenda for Alzheimer's disease are presented in three documents, plus an introduction.

- One workgroup updated the 1984 diagnostic criteria for the dementia due to Alzheimer's disease. Guy McKhann, M.D., Johns Hopkins University School of Medicine, Baltimore, and David Knopman, M.D., Mayo Clinic, Rochester, Minn., co-chaired this panel.
- A second workgroup focused on refining the criteria for the symptomatic, pre-dementia phase, referred to as Mild Cognitive Impairment due to Alzheimer's disease. Marilyn Albert, Ph.D., Johns Hopkins University School of Medicine, Baltimore, chaired this workgroup.
- The third workgroup proposed a research agenda (NOT criteria for clinical diagnosis; this is an important distinction. See supplement 4.) for the asymptomatic, preclinical phase of Alzheimer's. Reisa Sperling, M.D, Brigham and Women's Hospital, Harvard Medical School, Boston, chaired this group.
- The introduction provides an overview of the changes that have occurred in the Alzheimer's field since the first diagnostic criteria were published in 1984, and outlines future challenges that need to be addressed. Clifford Jack, M.D., Mayo Clinic, Rochester, Minn., is lead author of this article.

Preliminary recommendations were announced in July 2010 at the Alzheimer's Association International Conference on Alzheimer's Disease (AAICAD). These early drafts were then made available for comment on the Alzheimer's Association website, along with further presentation and discussion at a variety of medical and scientific meetings.

The three sets of recommendations differ in terms of relevance to current clinical practice.

- The clinical diagnostic criteria for Alzheimer's dementia and MCI due to Alzheimer's are intended to guide diagnosis in the current clinical setting, such as a doctor's office, including settings where no access to testing for biomarkers exists.
- The use of biomarkers in both Alzheimer's dementia and MCI due to Alzheimer's disease is intended only for research at this time. However, some biomarkers, especially those using advanced imaging techniques, could enter clinical practice in the near future, though much remains to be learned about their utility in this setting.
- The recommendations of the preclinical Alzheimer's workgroup are intended for research purposes only, and do not have any clinical utility at this time.

A fourth workgroup has been organized to examine the postmortem, pathological criteria for Alzheimer's. The results of their deliberations are expected to appear later in 2011.

To learn more, visit www.alz.org/research/diagnostic_criteria.

Alzheimer's Association
The Alzheimer's Association is the world's leading voluntary health organization in Alzheimer's care, support and research. Our mission is to eliminate Alzheimer's disease through the advancement of research; to provide and enhance care and support for all affected; and to reduce the risk of dementia through the promotion of brain health. For more information, please visit alz.org, or call 800-272-3900.

National Institute on Aging (NIA)
NIA, part of the National Institutes of Health, a component of the U.S. Department of Health and Human Services, leads the federal government effort conducting and supporting research on aging and the health and well being of older people. For information on age-related cognitive change and neurodegenerative disease, go to the NIA's Alzheimer's Disease Education and Referral (ADEAR) Center at www.nia.nih.gov/Alzheimers. For more on health and on aging generally, go to www.nih.nia.gov. Media contact is Peggy Vaughn, Office of Communications and Public Liaison, at 301-496-1752 or nianews3@mail.nih.gov.

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* McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34,939-44.

SUPPLEMENT 1

National Institute on Aging / Alzheimer's Association Workgroup Members

Alzheimer's Disease Dementia Workgroup
- Guy McKhann, MD, Johns Hopkins University School of Medicine, Baltimore (Chair)
- David Knopman, MD, Mayo Clinic, Rochester (Co-Chair)
- Howard Chertkow, MD, FRCP, McGill University, Montreal
- Bradley Hyman, MD, PhD, Massachusetts General Hospital, Harvard Medical School
- Clifford Jack, MD, Mayo Clinic, Rochester
- Claudia Kawas, MD, University of California, Irvine
- William Klunk, MD, PhD, University of Pittsburgh
- Walter Koroshetz, MD, National Institute of Neurological Disorders and Stroke
- Jennifer Manly, PhD, Columbia University, Sergievsky Center, New York
- Richard Mayeux, MD, Columbia University, Sergievsky Center, New York
- Richard Mohs, PhD, Eli Lilly and Company
- John Morris, MD, Washington University School of Medicine, St. Louis
- Professor Martin Rossor, University College London
- Philip Scheltens, MD, VU University Medical Center, Amsterdam
- Sandra Weintraub, PhD, Northwestern University Medical School, Chicago

Mild Cognitive Impairment (MCI) due to Alzheimer's Disease Workgroup
- Marilyn Albert, PhD, Johns Hopkins University School of Medicine, Baltimore (Chair)
- Steven DeKosky, MD, University of Virginia School of Medicine
- Dennis Dickson, MD, Mayo Clinic, Jacksonville
- Bruno Dubois, MD, INSERM, Hôpital de la Salpêtrière, France
- Howard Feldman, MD, Bristol Myers Squibb
- Nick Fox, MD, Dementia Research Center, Institute of Neurology, UK
- Anthony Gamst, PhD, University of California, San Diego
- David Holtzman, MD, Washington University School of Medicine, St. Louis
- William Jagust, MD, University of California, Berkeley
- Ron Petersen, PhD, MD, Mayo Clinic, Rochester
- Peter Snyder, PhD, Brown University, Rhode Island

Preclinical Alzheimer's Disease Workgroup
- Reisa Sperling, MD, Brigham and Women's Hospital, Harvard Medical School (Chair)
- Paul Aisen, MD, University of California, San Diego
- Laurel Beckett, PhD, University of California, Davis
- David Bennett, MD, Rush University Medical Center, Chicago
- Suzanne Craft, PhD, VA Puget Sound Health Care System, Seattle
- Anne Fagan, PhD, Washington University, St. Louis
- Takeshi Iwatsubo, M.D. University of Tokyo, Tokyo, Japan
- Clifford Jack, MD, Mayo Clinic, Rochester
- Jeffrey Kaye, MD, Oregon Health & Science University, Portland
- Thomas Montine, MD, PhD, Harborview Medical Center, Seattle
- Denise Park, PhD, University of Texas, Dallas
- Eric Reiman, MD, Banner Alzheimer's Institute, Phoenix
- Christopher Rowe, MD, University of Melbourne, Melbourne, Australia
- Eric Siemers, MD, Eli Lilly and Company, Indianapolis
- Yaakov Stern, PhD, Columbia University, Sergievsky Center, New York
- Kristine Yaffe, MD, University of California, San Francisco

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SUPPLEMENT 2

The newly-published articles described in this news release are from *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, May 2011. Advance online publication is scheduled for April 19, 2011.

- Clifford R. Jack Jr., et al. "Introduction to Revised Criteria for the Diagnosis of Alzheimer's Disease: National Institute on Aging and the Alzheimer's Association Workgroups."

- Guy M. McKhann and David S. Knopman, et al. "The Diagnosis of Dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association Workgroup."

- Marilyn S. Albert, et al. "The Diagnosis of Mild Cognitive Impairment due to Alzheimer's Disease: Recommendations from the National Institute on Aging and Alzheimer's Association Workgroup."

- Reisa A. Sperling, et al. "Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association Workgroup."

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SUPPLEMENT 3

Three Stages of Alzheimer's Disease

The current criteria for the diagnosis of Alzheimer's disease focus, for the most part, on reliable diagnosis when signs of problems in thinking, learning, and memory become noticeable to the person affected, family, and friends. Research, however, tells us that Alzheimer's likely begins years, perhaps even decades, before symptoms appear.

The workgroup proposals refer to three phases of disease progression over time:

Dementia due to Alzheimer's Disease – Cognitive and behavioral symptoms that impair an individual's ability to function in daily life. The workgroup:
• Emphasized the continuing need and importance to rule out other causes of cognitive decline and of documenting progressive decline over time.
• Noted that the diagnosis of Alzheimer's dementia may not always have memory impairment as its most central characteristic; a decline in other aspects of cognition (such as word-finding, vision/spatial issues, and impaired reasoning, judgment, and problem solving) may be the presenting or most prominent symptoms at first.
• Proposed that, for research purposes, diagnostic certainty may be improved by incorporation of certain biomarker measures, although the usefulness and reliability of these tests in everyday medical practice still needs to be tested.

Mild cognitive impairment (MCI) due to Alzheimer's Disease – Mild changes in memory and thinking abilities, enough to be noticed and measured, but not impairment that compromises everyday activities. The workgroup said:
• This impairment increasingly can be measured in research and is gradually being recognized in medical and specialty practice.
• More work is needed to distinguish those with MCI who will go on to develop Alzheimer's dementia from those who will not.
• Biomarkers, as they become validated, may help increase diagnostic accuracy in research settings.

Preclinical Alzheimer's Disease – Changes that may indicate the very earliest signs of disease. The workgroup recommended:
• No diagnostic criteria for this phase of the disease.
• Approaches meant for research; they propose schema for data collection, to see if a "preclinical" stage of the disease can be defined so that, eventually, people who will develop Alzheimer's dementia can be distinguished from those who will not.
• This experimental approach calls for measurement of certain proteins in blood and cerebrospinal fluid – known as "biomarkers" – as well as neuroimaging tests to characterize brain changes that may be predictive of Alzheimer's disease. They also may include new assessments to tease out the very earliest and subtle clinical signs of decline.

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SUPPLEMENT 4

<u>Two Types of Alzheimer's Biomarkers</u>

Two notable differences in the new articles from the Alzheimer's disease diagnostic criteria published in 1984 are incorporation of biomarkers of the underlying disease state and formalization of different stages of disease in the diagnostic criteria. Biomarkers of various features of preclinical Alzheimer's disease have been developed and are being validated. According to the authors, only the five most widely studied biomarkers of Alzheimer's based on the current literature are formally incorporated into the diagnostic criteria at this time.

It was decided by the authors to divide the biomarkers into two major categories:

(1) Biomarkers of beta-amyloid accumulation. These are:
- Abnormal retention of beta-amyloid identifying tracer compounds on positron emission tomography (PET) imaging.
- Low levels of beta-amyloid 1–42 in cerebrospinal fluid (CSF).

(2) Biomarkers of neuronal degeneration or injury. These are:
- Elevated levels of the protein tau (both total and phosphorylated tau) in CSF.
- Decreased fluorodeoxyglucose 18F (FDG) uptake on PET imaging in a specific pattern involving the brain's temporo-parietal cortex.
- Atrophy on structural magnetic resonance imaging (MRI), again in a specific topographic pattern involving the brain's medial, basal and lateral temporal lobes, and medial and lateral parietal cortices.

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SUPPLEMENT 5

Next Steps for the New Proposals – Incorporation of the Criteria into Research Projects

There was a broad consensus within the workgroups that much additional work needs to be done to validate the application of biomarkers to Alzheimer's disease diagnosis as they are proposed in the newly published articles. For example:

- Additional biomarker comparison studies are needed, as is more thorough validation with postmortem studies, and the use of combinations of biomarkers in studies has been limited.
- Extensive work on biomarker standardization is needed prior to widespread adoption of these recommendations at any stage of the disease.
- Currently, all potential Alzheimer's biomarkers exist as continuous measures of preclinical Alzheimer's. Therefore, biomarker standardization must also include gaining a broad consensus on how to obtain results that are interpretable as clearly normal, clearly abnormal, and perhaps intermediate.
- Moreover, obtaining standardized, reliable and reproducible diagnostic–caliber results of biomarker tests must be possible in any setting in which biomarkers are applied – research, clinical trials, or clinical care.

The authors of the article on defining the preclinical stages of Alzheimer's included extensive text regarding the various types of research needed to validate biomarkers, including:

We propose draft operational research criteria to define study cohorts at risk for developing Alzheimer's for use in 1) longitudinal natural history studies to determine whether the presence of amyloid beta, in isolation or in combination with additional markers of neurodegeneration, is predictive of cognitive decline in clinically normal older individuals, and 2) clinical trials of potential disease modifying agents to investigate effects on biomarker progression and/or the emergence of clinical symptoms.

More work is needed to clarify the optimal CSF assays, PET or MRI analytic techniques, and in particular, the specific thresholds needed to meet these criteria. There are significant challenges in implementing standardized biomarker "cut-off" values across centers, studies, and countries. Work to standardize and validate both fluid-based and imaging biomarker thresholds is ongoing in multiple academic and pharmaceutical industry laboratories, and in several multi-center initiatives.

These criteria will need to be validated in large multi-center natural history studies, or as provisional criteria for the planning of preventative clinical trials. For instance, it will be important to establish the test-retest and cross-center reliability of biomarker measurements, further characterize the sequence of biomarker changes, and the extent to which these biomarkers predict subsequent clinical decline or clinical benefit. In particular, there is an important need to evaluate methods for determining "amyloid-positivity," as it remains unclear whether there is a biologically relevant continuum of amyloid beta accumulation, or whether there is a clear threshold or "cut-off" value that could be defined on the basis of predictive value for subsequent clinical decline, as has been suggested in several CSF studies. It also remains unknown whether these thresholds should be adjusted for age or genotype. Once these thresholds are established, it may be most feasible to select research cohorts for large studies solely on the basis of "amyloid-positivity" on CSF or PET amyloid imaging, and to utilize additional biomarker and cognitive measures for post-hoc analyses to determine additional predictive value.

Although recent advances in biomarkers have revolutionized our ability to detect evidence of early AD-P, there is still a need for novel biomarker development. In particular, although the current biomarkers provide evidence of amyloid beta deposition, an in vivo marker of oligomeric forms of amyloid beta would be of great value. Imaging markers of intraneuronal pathology, including specific markers of specific forms of tau/tangles and alpha-synuclein, are also needed. In addition, more sensitive imaging biomarkers that can detect early synaptic dysfunction, functional and structural disconnection, such as functional MRI (fMRI) and diffusion tensor imaging (DTI), may one day prove useful to track early response to amyloid-lowering therapies. Finally, we may be able to use the currently available biomarkers as a new "gold standard" to re-evaluate simple blood and urine markers that were discarded on the basis of excessive overlap between clinically normal and Alzheimer's patients. The significant proportion of clinically normal individuals who are "amyloid-positive" on both CSF and PET imaging may have confounded prior studies attempting to differentiate "normal" controls from Alzheimer's.

Similarly, additional work is required to identify and validate neuropsychological and neurobehavioral measures to detect the earliest clinical manifestations of Alzheimer's. We need to develop sensitive measures in multiple cognitive and behavioral domains that will reveal evidence of early synaptic dysfunction in neural networks vulnerable to Alzheimer's pathology. We also need to develop measures of very early functional changes in other domains, including social interaction, mood, psychomotor aspects of function, and decision-making. These measures would allow us to link better the pathologic processes to the emergence of clinical symptoms, and may be particularly useful to monitor response to potential disease-modifying therapies in these very early stages.

Finally, the ethical and practical implications surrounding the issues of future implementation of making a "diagnosis" of Alzheimer's at a preclinical stage need to be studied, should the postulates put forth above prove to be correct. In particular, the poignant question of "why would anyone want to know they have Alzheimer's a decade before they might develop symptoms, if there is nothing they can do about it?" should be carefully considered well before any results from research [are] translated into clinical practice. First, there may be important reasons, including social and financial planning, that some individuals would want to know their likelihood of developing Alzheimer's dementia within the next decade, even in the absence of an available disease-modifying therapy.

It is our hope, however, that the advances in preclinical detection of [Alzheimer's] will enable earlier, more effective treatment, just as nearly all of the therapeutic gains in cancer, cardiovascular disease, osteoporosis, and diabetes involve treatment before significant clinical symptoms are present.

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