

The National Cell Repository for Alzheimer's Disease

(NCRAD) is a data and specimen collection source for families with Alzheimer disease (AD) or serious memory loss. Families having two or more living individuals with memory loss are encouraged to participate. We would like to thank the hundreds of families nationwide who are already participating in the National Cell Repository. Many family members have provided blood samples, which researchers use to study Alzheimer's disease (AD) and other related diseases. Our hope is that, through the efforts of our participants, we will one day unravel the mystery of devastating diseases, like AD. We are always eager to accept new families to help us move toward this goal.



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National Cell Repository for Alzheimer's Disease

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NCRAD Update

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Changing Concepts of Alzheimer's Disease

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Criteria for the clinical diagnosis of Alzheimer's disease (AD) were established in 1984 [1]. These criteria were very important for the field since it resulted in consistency of diagnosis for patients with AD around the world. The focus of these criteria was, however, on the diagnosis of dementia that was caused by the presence of AD pathology in the brain. Over the past 27 years it has become clear that the pathology of Alzheimer's disease begins to evolve many years before dementia becomes apparent.

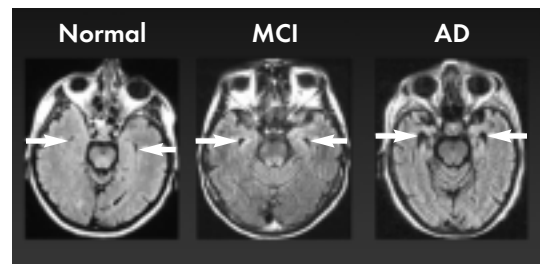


Image from Brown University and Butler Hospital.

MRI scans showing shrinkage of the brain that occurs in AD in the hippocampus, the part of the brain that is crucial to memory.

The term Mild Cognitive Impairment (MCI) began to be widely used in the late 1990's to describe those individuals who were not demented, but were experiencing a gradual decline in memory and other mental abilities. Even more recently it has become clear that some individuals who are cognitively normal have AD pathology in their brain. Thus, a consensus emerged in the field that the criteria for AD needed to reflect the fact that there is a continuum of symptoms, from very mild changes in mental ability to full blown dementia, and that this is caused by the slow accumulation of AD pathology in the brain which gradually destroys brain cells.

In recognition of these facts, the National Institute on Aging and the Alzheimer's Association established three workgroups. One workgroup was assigned the task of formulating clinical and research diagnostic criteria for the dementia phase of AD [2], a second workgroup was asked to focus on clinical and research diagnostic criteria for the symptomatic pre-dementia phase of AD, or mild cognitive impairment (MCI) [3]. The third workgroup was asked to propose a research agenda for the asymptomatic, preclinical phase of AD [4]. The reports of these groups were published in May 2011 [2-5].

The workgroups for AD dementia and MCI divided their recommendations into two sections. The first section in each document concerned the clinical diagnosis of patients. The goal was to provide clinicians working in any setting with guidelines concerning the diagnostic process (i.e., primary care physicians, specialists working in the community, academic researchers and those conducting clinical trials).

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For both AD dementia and MCI, these core clinical criteria are very similar to the approach that clinicians have been using for decades.

The second section of the criteria for AD dementia and MCI concerned research criteria that incorporated the use of biomarkers. Biomarkers are measures, usually involving a biological fluid or brain imaging, that systematically relate to the presence and progression of the underlying disease process. William Thies, PhD, Chief Medical and Scientific Officer for the Alzheimer's Association, defines a biomarker as something that can be measured in the body that indicates or reflects the presence or severity of a disease state. For example, cholesterol levels and blood pressure are considered biomarkers of heart disease. Scientists are working hard to discover, verify, and quantify biomarkers for AD. The work group reports recommended that biomarkers be used only for research, for two primary purposes: 1) To enhance the certainty that the underlying disease is AD, and 2) To estimate the likelihood of progression from one stage of disease to the next (e.g., from MCI to AD dementia). The workgroups emphasized that knowledge about biomarkers is still evolving.

There are no clinical criteria for the pre-clinical phase of the disease, since by definition any cognitive impairment experienced by these individuals is so mild that no functional impairment has developed. This phase of disease is primarily defined by changes in biomarkers, and is currently intended only for research. It should be noted that the workgroups emphasized that before biomarkers can be incorporated into clinical practice, they need to be standardized, so that measurements can be obtained in any setting and have the same meaning.

One rationale for establishing new research criteria that incorporate biomarkers is to acknowledge how much has been learned about them in the past two decades, and to accelerate their use in research settings, such as clinical trials. Thus, one of the goals of these recommendations is to hasten the development of improved treatments for patients by increasing the number of clinical trials in patients at earlier phases of disease.

The overarching goal of these recommendations was to establish a consistent framework in which to both diagnose patients and develop treatments. The general concern is that if one waits for the appearance of dementia before treating patients, it may be too late. The damage to nerve cells may be too great to restore function or delay progression. If one thinks of comparisons to other disease entities, it would be as if we waited to treat heart disease until after someone had a heart attack. It is the hope of the workgroups that these new criteria will help lead to improved treatments for patients at earlier phases of the disease and that prevention may one day be possible.

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

- **1. Preclinical Alzheimer's Disease**
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.
- **2. 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 and functioning.
- **3. Dementia due to Alzheimer's Disease**
Memory, thinking and behavioral symptoms that impair a person's ability to function in daily life.

Excerpted from a news release from the Alzheimer's Association. For more information, please visit alz.org, or call 800-272-3900.

References

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Frequently Asked Questions Regarding the National Institute on Aging/Alzheimer's Association Diagnostic Guidelines for AD

What are the main differences between the 1984 diagnostic criteria for Alzheimer's disease and the new guidelines?

The new guidelines differ from the 1984 diagnostic criteria in a few key ways:

- The new guidelines propose that Alzheimer's disease progresses on a spectrum with three stages: an early, preclinical stage with no symptoms; a middle stage of mild cognitive impairment (MCI); and a final stage of Alzheimer's dementia. The 1984 criteria recognized only one stage of disease, Alzheimer's dementia.
- The new guidelines expand the criteria for Alzheimer's dementia beyond memory loss as the initial or major symptom. They recognize that problems with other aspects of cognition, such as word-finding ability or judgment, may be the first symptom to appear. The 1984 criteria focused on memory loss as the central characteristic of Alzheimer's dementia.
- The new guidelines reflect a better understanding of the distinctions between Alzheimer's and non-Alzheimer's dementias and the possible relationship between Alzheimer's and cerebrovascular disease (which affects blood vessels that supply the brain). In 1984, these relationships were not well recognized or understood.
- The new guidelines address the use of biomarkers—measures in blood, fluid, or imaging that could indicate possible Alzheimer's disease. The use of biomarkers for Alzheimer's disease is still considered experimental and is appropriate only for use by researchers at this time. The guidelines call for validating and standardizing the use of biomarkers before they can be applied in a clinical setting, like a doctor's office. Biomarkers for Alzheimer's disease did not exist when the original criteria were developed in 1984, and have been studied intensively in recent years.

Why were the diagnostic criteria for Alzheimer's disease revised and who led the effort?

The diagnostic criteria for Alzheimer's disease were revised to reflect a better understanding of the disease. During the past 27 years, scientists have learned much about how Alzheimer's changes the brain, how these changes progress over time, and how they correspond to clinical symptoms. The new guidelines were developed by expert panels convened by the National Institute on Aging and the Alzheimer's Association.

How will doctors use the updated guidelines to better diagnose Alzheimer's disease?

Doctors in clinical practice will use the updated guidelines to better inform their diagnosis of Alzheimer's dementia and mild cognitive impairment (MCI). Other aspects of cognition, in addition to memory loss, will now be considered as a possible first symptom of the disorder.

At this time, however, the use of neuroimaging and biomarkers is not yet developed enough for clinicians to diagnose the disease in symptom-free people.

My family has a history of Alzheimer's disease. Will the new guidelines help my doctor know if I will or will not one day get the disease?

At this time, doctors cannot predict with any certainty who will or will not develop Alzheimer's dementia. Researchers are studying markers in blood and spinal fluid, as well as changes in the brain shown on brain scans, that one day may be able to tell us who is at risk for developing Alzheimer's dementia. The guidelines, as used by researchers, will help make this possible.

What is "preclinical" Alzheimer's disease?

Preclinical Alzheimer's disease is a new concept that indicates that changes in the brain, including deposition of abnormal proteins, can be detected before there are any clinical symptoms. Research will investigate the usefulness of this concept under the new guidelines. The course of Alzheimer's disease varies widely from one person to the next, but, generally, scientists have observed that changes in the brain can begin 10 or more years before clinical symptoms like memory loss appear.

What is mild cognitive impairment? How is it different from Alzheimer's dementia?

Mild cognitive impairment (MCI) is a condition characterized by memory issues or other thinking problems that are greater than normal for a person's age and education, but not serious enough to interfere with a person's ability to function independently. Many, but not all, people with MCI progress to Alzheimer's dementia. The kinds of problems associated with MCI may also be caused by certain medications, cerebrovascular disease and other factors. It is important to talk with your doctor because some of the problems brought on by these conditions can be managed or reversed.

How can doctors know when mild cognitive impairment becomes early-stage Alzheimer's dementia?

The Alzheimer's disease process progresses slowly, and it can be difficult to identify the transition from MCI to the early stages of dementia. If the symptoms of MCI continue or worsen over time and other cognitive problems become apparent, everyday functions may become compromised, and the patient will have more and more trouble functioning independently. Today—just as it was a quarter of century ago—the key factor in diagnosing Alzheimer's dementia is losing the ability to live independently. It may be, some experts suggest and the new guidelines discuss, that MCI with minor loss of independent function indicates early-stage Alzheimer's disease.

Experts can evaluate the extent of cognitive impairment by using neuropsychological tests to measure changes in memory, language, and other cognitive abilities. They also talk to the person and their caregivers and family about any changes in the person's ability to carry out everyday activities,

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ADNI - The Landmark Study

Tamie Sather, Project Coordinator - Alzheimer's Disease Cooperative Study, University of California, San Diego

The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a public-private research partnership tasked with identifying biomarkers to detect Alzheimer's disease (AD). To date, ADNI has gathered and analyzed thousands of brain scans, genetic profiles and biomarkers in blood and cerebrospinal fluid (CSF). The study was designed to enable researchers to follow AD as it progresses in an individual, from various points in the disease process.

In 2009, ADNI made a significant step forward in providing validation for a test that helps diagnose the beginning stages of AD sooner and more accurately by measuring CSF levels of two biomarkers: tau and beta-amyloid proteins. Biomarkers in CSF are revealing other changes that could identify which patients with mild cognitive impairment (MCI) may develop AD.

In 2010, funded by the federal stimulus package, the ADNI study moved into the "ADNI GO" phase. The ADNI GO research effort is the first of its kind to focus on participants who exhibit the earliest signs of memory loss and MCI - both thought to be precursors to AD.

While the ADNI GO project work continues, the overall ADNI effort is in its third phase - known as "ADNI 2". ADNI 2 will build upon the successes of earlier ADNI phases to identify the earliest signs of AD. Researchers are eager to determine when damage to the brain begins. Scientists suspect that identifiable changes to the brain take



place well before AD symptoms appear. The ADNI 2 phase of the study includes a large number of new volunteers in the earliest stages of cognitive impairment.

The study participants are followed to define any changes in brain structure and function as people transition from normal cognitive aging to MCI to AD. Like the previous phases of the study, researchers will use brain imaging techniques, genetic profiles, and biomarker measures in blood and CSF to track changes in the living brain.

ADNI Technologies and Biomarkers

Some of the leading-edge technologies used in the ADNI studies are brain-imaging techniques, such as positron emission tomography (PET), including FDG-PET (which measures glucose metabolism in the brain); PET using a radioactive compound, Florbetapir F 18, that measures brain amyloid accumulation; and structural magnetic resonance imaging (MRI). Brain scans

are showing scientists how the brain's structure and function change as AD starts and progresses. Moreover, biomarkers in CSF are revealing other changes that could identify which patients with MCI will develop AD. ADNI 2 researchers are committed to identifying who is at risk for AD and to developing measurements to accurately track the progression of the disease in an individual. Moreover, ADNI 2 researchers hope to develop tests to measure the effectiveness of potential AD treatment interventions.

Presently, there are 58 sites across the United States and Canada participating in ADNI 2. All ADNI 2 assessments are for research purposes and are supported by ADNI. Research participants may receive payment for study procedures; whether payment is offered and the amount will be determined by the individual study site.

For more information and to learn the locations of all participating research sites, contact the Alzheimer's Disease Education and Referral Center (ADEAR), a service of the National Institute on Aging, at 1-800-438-4380, or visit <http://www.nia.nih.gov/Alzheimers/ResearchInformation/ClinicalTrials/ADNI2.htm>.

ADNI 2 is actively recruiting. Are you eligible to participate?

Researchers are looking for persons between 55 and 90 years of age who:

- Are in good health
- Either have a diagnosis of early AD, MCI, or are cognitively normal
- Are fluent in English or Spanish
- Are willing and able to undergo in-clinic assessments, memory testing,

and other test procedures

- Are willing and able to participate in a longitudinal neuroimaging study
- Have a study partner - a friend or relative who can accompany the volunteer to clinic visits and has at least 10 hours of contact per week with the volunteer.

10 Signs of Alzheimer's Disease

1. Memory loss.
2. Difficulty performing familiar tasks.
3. Problems with language.
4. Disorientation to time and place.
5. Poor or decreased judgment
6. Problems with abstract thinking.
7. Misplacing things.
8. Changes in mood or behavior.
9. Changes in personality.
10. Loss of initiative.

Early diagnosis of Alzheimer's disease or other disorders causing dementia is an important step in getting appropriate treatment, care, and support services.

For more information, call the Alzheimer's Association at (800) 272-3900.

Research Opportunities

Delaying the Progression of Driving Impairment in Individuals with Mild Alzheimer's Disease

- Purpose: To determine whether the medication memantine delays the progression of driving impairment in patients with mild AD.
- Eligibility: Subjects with a clinical diagnosis of mild AD over the age of 60.
- Location: FL
- Contact: Lori Fisher, M.A., PH: 561-297-0502, e-mail: lfisher8@fau.edu

Dominantly Inherited Alzheimer Network (DIAN)

- Purpose: To study brain changes in people who carry an AD mutation in order to determine how the disease process develops before the onset of symptoms.
- Eligibility: Men and women ages 18 and older with a biological parent or sibling with AD caused by a known mutation. All participants must be able to speak and read English, and must provide contact information for someone who knows them well and would be willing to answer questions about their memory and thinking.
- Locations: USA - CA, IN, MA, MO, NY, RI; United Kingdom; Australia
- Contact: PH: 314-286-2683 or the DIAN website, <http://www.dian-info.org>

A randomized, clinical trial of Vitamin E and Memantine in Alzheimer's Disease (TEAM-AD)

- Purpose: The primary study hypothesis is that compared with placebo, alpha-tocopherol, memantine (Namenda), or the combination will significantly delay clinical progression in mild to moderately demented patients with AD.
- Eligibility: Men and women 40 years of age and older with a clinical diagnosis of AD.
- Locations: FL, IA, MA, MD, MI, MN, OH, SC, TX, WI, and Puerto Rico
- Contact: Susan Love, PH: 612-467-3342, e-mail: lovex008@tc.umn.edu, or Julie Tomaska, PH: 612-467-1563, e-mail: julie.tomaska@va.gov

The Alzheimer's Disease Neuroimaging Initiative (ADNI) Study

- Purpose: To study the rate of change of cognition, function, brain structure and function, and biomarkers in mild cognitive impairment (MCI) and AD.
- Eligibility: Individuals between the ages of 55 and 90 who are in good health, are cognitively normal or have a diagnosis of MCI or early AD, are fluent in English or Spanish, are willing and able to undergo all testing and imaging procedures, and have a study partner who can accompany them to study visits and has at least 10 hours of contact per week with the study volunteer.
- Locations: Multiple sites throughout the United States and Canada
- Contact: Alzheimer's Disease Education and Referral Center (ADEAR), PH: 800-438-4380, or <http://www.nia.nih.gov/Alzheimers/ResearchInformation/ClinicalTrials/ADNI2.htm>

Neuroimaging in Frontotemporal Dementia (NIFD)

- Purpose: To identify the best methods for imaging and analysis for tracking frontotemporal lobar degeneration (FTLD) over time.
- Eligibility: Individuals between the ages of 45 and 90 who meet the criteria for behavioral variant frontotemporal dementia (bvFTD), semantic dementia (SD), progressive nonfluent aphasia (PNFA), or healthy aging. A study partner who has frequent contact with the volunteer and can provide information about them and accompany them to study visits is also required. All volunteers must be willing and able to undergo testing procedures and agree to follow-up.
- Locations: CA, MN
- Contact: Marissa Urbano, PH: 415-476-0670, e-mail: murbano@memory.ucsf.edu

African American Genetics Study

- Purpose: To look for risk factors for memory problems and Alzheimer's disease among older African Americans.
- Eligibility: African American men and women with or without memory problems, ages 60 years and older.
- Locations: FL, NC, NY, TN
- Contact: PH: 212-305-1893

Check Out the NCRAD Website!

- The NCRAD staff has also created a new, updated version of our website, at www.ncrad.org.
- On the site we provide valuable information regarding participation in NCRAD, Alzheimer's disease and genetics,

and our autopsy program. There are also a number of helpful website links and information about other studies in which our participants may be interested. Previous copies of NCRAD newsletters are also available on the site for viewing and downloading.

Sources for Information and Support

* **Alzheimer's Association**

<http://www.alz.org>

Tel: 312-335-8700 or 800-272-3900

* **Alzheimer's Disease Education and Referral Center (ADEAR)**

<http://www.nia.nih.gov/Alzheimers>

Tel: 301-495-3311 or 800-438-4380

ADEAR lists all 29 Alzheimer's Disease Centers (ADCs) and their contact information.

Assisted Living Directory, Assisted Living Facilities Information & Senior Care

<http://www.assisted-living-directory.com/>

The Association for Frontotemporal Dementias (AFTD)

<http://www.ftd-picks.org/>

Tel: 866-507-7222

Family Caregiver Alliance

<http://www.caregiver.org>

Tel: 415-434-3388 or 800-445-8106

National Parkinson Foundation

<http://www.parkinson.org/>

Tel: 305-547-6666 or 800-327-4545

Parkinson's Disease Foundation (PDF)

www.pdf.org

Tel: 212-923-4700 or 800-457-6676

Society for Progressive Supranuclear Palsy

<http://www.psp.org>

Tel: 410-486-3330 or 800-457-4777

National Organization for Rare Disorders (NORD)

<http://www.rarediseases.org>

Tel: 203-746-6518 or 800-999-NORD (6673)

Center for Disease Control and Prevention (CDCP)

<http://www.cdc.gov>

Tel: 800-311-3435

Creutzfeldt- Jakob Foundation Inc. (CJD)

<http://cjd.foundation.org>

Tel: 954-704-0519 or 305-891-7579

National Society of Genetic Counselors

<http://www.nsgc.org/>

Tel: 312-321-6834

Research Match is a free service that pairs volunteers interested in participating in research opportunities from surveys to clinical trials with researchers. Open to all, including healthy volunteers.

<http://www.researchmatch.org>

* **ClinicalTrials.gov** is a registry of federally and privately supported clinical trials conducted in the United States and around the world. ClinicalTrials.gov gives you information about a trial's purpose, who may participate, locations, and phone numbers for more details. This information should be used in conjunction with advice from health care professionals.

<http://www.clinicaltrials.gov/>

* These are good sources for research opportunities in your area.

National Institute on Aging Guidelines

such as paying bills and preparing meals. Not everyone with MCI develops Alzheimer's. Among people with MCI, impaired ability to learn and retain new information, such as remembering a story or something that happened recently, is associated with an increased likelihood of worsening memory problems leading to Alzheimer's dementia.

Why are some of the new guidelines to be used only for research?

At this time, biomarkers are to be used only for research. Investigators are working hard to better understand how biomarkers relate to the underlying disease process and whether biomarker measures can accurately predict who will or will not develop Alzheimer's dementia. Biomarker tests also must be standardized to ensure they are measured correctly and consistently before they can be used in all clinical settings.

Can doctors use the guidelines to diagnose other kinds of dementia besides Alzheimer's?

No. The guidelines apply only to Alzheimer's disease. In specialized clinical settings and research settings, they may be used to confirm or rule out Alzheimer's as a cause of cognitive impairment and dementia. Alzheimer's disease is the most common form of dementia. Other forms include vascular dementia, which results from strokes or changes in the brain's blood supply; dementia with Lewy bodies; and the frontotemporal disorders. Researchers are still working on the best ways to diagnose these other types of dementia.

How can I learn more about the updated guidelines?

The new diagnostic criteria for Alzheimer's disease are found in the April 19, 2011, issue of Alzheimer's & Dementia: The Journal of the Alzheimer's Association, a peer-reviewed medical journal. To view the papers

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outlining the new guidelines, go to: www.alz.org/research/diagnostic_criteria

Will the new guidelines be updated as new information becomes available?

Alzheimer's disease research is ongoing. As results become available, future panels will consider emerging technologies and advances in the understanding of biomarkers and the disease process itself. Individuals with and without Alzheimer's disease can participate in this research by volunteering for clinical studies and trials. To find out more about Alzheimer's clinical trials, talk to your health care provider or contact NIA's ADEAR Center at 1-800-438-4380 or visit www.nia.nih.gov/Alzheimers. More information about clinical trials is available at: www.ClinicalTrials.gov. Also see Participating in Alzheimer's Disease Clinical Trials and Studies at: www.nia.nih.gov/Alzheimers/Publications/trials-studies.htm.