



PATHWAYS

Moving Toward a Cure

Spring/Summer 2011

MESSAGE from the Director

New Developments in Genetics

There has been much publicity recently about the discovery of several new genes associated with Alzheimer's disease (AD).

I would like to take this opportunity to put these findings into perspective within the realm of research on the genetics of AD.

There are mutations in three genes (APP, PS1, and PS2) that have been known for many years to cause a rare form of autosomal dominant familial AD with a clinical onset between the ages of 30 and 60. These mutations happen in only a few families around the world, and this form of early AD represents just 1 percent of the cases seen. More relevant to most individuals and families affected by AD is a set of genes called "susceptibility" genes. Susceptibility genes differ from the rare genetic mutations that cause familial AD. On one hand, susceptibility genes are more common than autosomal dominant mutations, but on the other hand, their presence does not always lead to AD. As their name implies, these genetic traits are associated with an increased susceptibility to AD. Several susceptibility genes have been linked with late-onset AD (age >60), but the influence of this type of genetic trait on the development of AD is not nearly as straightforward as what is seen when an autosomal dominant mutation is present.

The most important susceptibility gene associated with late-onset AD is the apolipoprotein (APOE) gene, which has three forms known as APOE ε2, APOE ε3, and APOE ε4. The last of these has been found in up to 60 percent of late-onset AD cases, leading many researchers to refer to APOE ε4 as a risk gene for AD. However, it is important to note that there are individuals carrying the APOE ε4 allele who will never develop AD. Consequently, APOE testing cannot be used for diagnostic purposes. Interestingly, although APOE ε4 is less common in Mediterranean populations



OSCAR L. LOPEZ, MD
Director

compared to Northern Europeans, the prevalence of dementia is similar across Europe. In the United States, the APOE ε4 allele is less common among Hispanics, but epidemiological studies have shown that Hispanics have an increased risk for AD compared to Caucasians. This suggests that there are other unknown genetic factors implicated in the etiology of AD.

Because there still is no clear genetic pattern that can be identified in late-onset AD, the scientific community has made significant efforts to examine this issue. Recently, there have been several genome-wide association studies (GWAS) in AD. These are highly sophisticated studies designed to examine most of the genes of different individuals, find single DNA mutations, and determine how much they vary between persons with and without AD. Last year, GWAS identified four new genes for late-onset AD called CLU, PICALM, BIN1, and CR1. In May, two publications in *Nature Genetics** described the discovery of five new genes called MS4A4, ABCA7, EPHA1, CD33, and CD2AP. Thus, in addition to the APOE gene, there are now a total of nine new genes associated with late-onset AD. Though these new genes cannot be used for diagnosis or prediction of the disease, they represent important steps toward understanding the pathways involved in the clinical expression of the disease. Genetic studies are complex and expensive, because they require hundreds of patients and the technical capabilities needed to analyze thousands of proteins in the human genome. Nevertheless, we believe that we are on the verge of important genetic discoveries that could lead us to disentangle the etiology of AD. ■

These recent discoveries would not have been made without the help of willing research participants, like those who volunteer for studies here at the Alzheimer Disease Research Center (ADRC). We are grateful for the continued support and loyalty of our participants, some of whom have been with us for as long as 20 years. Our research will continue, and we hope that an interest in helping with the fight against AD will continue to be a high priority for our faithful research participants.

*ADRC investigators coauthored these publications; Oscar Lopez, MD, coauthored both studies, and M. Ilyas Kambh, PhD, coauthored one of them.

What's HAPPENING to My Memory?

By JUDITH SAXTON, PhD, director, ADRC Clinical Core



Why did I just call my grandson Matt when I know his name is Noah? Matt is my son's name.

Continued on page 2

This article is the first in a series of five about memory. The other four will appear in future issues of *PATHWAYS*.

How Does My Memory WORK?

Why can't I remember that famous actor's name? I know I'll remember it at 2 tomorrow morning.

Why did I tell my daughter we'd have lunch on Monday when I meant to say Sunday? I was thinking about another appointment I have on Monday.

How come I can remember my grandmother's kitchen so clearly when I haven't thought about her in years?

Why can't I remember where I put my keys, parked my car, or left my purse?



Memory is not a black box into which events are dropped haphazardly. Memory is a complex, highly structured ability that takes years to develop and declines in predictable ways.

At the simplest level, memory is divided into short-term memory (STM) and long-term memory (LTM). STM is a temporary storage area with limited capacity; it's what you use when you look up a phone number and remember it long enough to dial but can't recall it the next day. The act of acquiring a new memory that you are able to retrieve at a later time involves the conversion of the labile STM into the permanent, more stable LTM. LTM is memory that has been consolidated and is more permanent. We also accumulate a store of bits of knowledge and skills over our lifetime that are called semantic or implicit memories—things that we would usually say we know rather than remember, like how to ride a bicycle, the route to work, or that $2 \times 2 = 4$, even though we may not actually remember the first time we rode a bicycle, drove to work, or learned the multiplication tables. There is evidence that this kind of implicit knowledge is very stable (you never forget how to ride a bicycle) and often is preserved in people with otherwise impaired memory, probably because it is processed differently in the brain.

In general, memory involves three stages: acquisition of information into STM, consolidation into LTM, and subsequent retrieval. If any one of these processes goes awry, memory is impaired. Retrieval is the ability to access the learned and stored material and is what we usually think of as the act of remembering. This is where most of the trouble lies in normal aging, although older individuals also have difficulty learning new material.

When everything is working well, to-be-remembered information about the environment is perceived through the senses and processed by the brain. During this acquisition phase, while the information is in STM, we are consciously aware of the information: It is in the "mind's eye" or the "mind's ear" but has not yet been encoded into

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a permanent memory store, so it is vulnerable to loss. This is why football players who sustain a concussion are often unable to recall the play in which they were injured or even the game in which it happened, because that memory did not have time to be consolidated into LTM. Transfer into long-term storage is accomplished through a brain region known as the hippocampus. Over the course of a few days, the to-be-remembered information is consolidated into LTM by a process known as long-term potentiation, which strengthens cortical connections.

Consolidation is a slow, dynamic process that can take weeks to decades to complete, and memories that have not been consolidated are still vulnerable to loss. In particular, when a lot of similar information comes in rapid succession, the bits of information can interfere with each other such that they all can't be consolidated. This is one reason why learning is more efficient when learning trials are spaced out over time. Once consolidated, memories are less vulnerable although still dependent upon an individual's ability to access and retrieve the material as needed. This is probably one of the reasons why very old memories, like one's grandmother's kitchen, are so resistant to loss.

Memories associated with strong emotions also are less likely to be forgotten, suggesting that emotional content aids in the consolidation or retrieval process. This applies to both positive feelings and negative emotions like embarrassment and fear, which can make events difficult to forget even if we would prefer not to remember them. ■

Mild Cognitive Impairment, Alzheimer's Disease, and the New Diagnostic Criteria

By WILLIAM E. KLUNK,
MD, PhD, codirector,
University of Pittsburgh
Alzheimer Disease
Research Center

Like most chronic diseases, Alzheimer's disease (AD) does not begin overnight. The beginnings are very gradual, and the initial differentiation from the changes in memory that are universal in older people is challenging for memory specialists, families, and even the patients themselves. Nevertheless, it is widely accepted that identification of any disease in its earliest stages increases the chance of discovering effective treatments and of applying those treatments at a time when they will do the most good. Therefore, much effort has been directed at the early diagnosis of AD. This is apparent in the recent publication of new diagnostic criteria not only for AD but for earlier stages of this disease, including the stage called mild cognitive impairment or MCI (see www.alz.org/research/diagnostic_criteria).

AD is defined by impairments in at least two areas of brain function that result in a loss of normal functioning for an individual. Memory is the most common area of brain function to be impaired; the four other areas are the ability to think through complex situations, use good judgment, organize, and plan; the ability to maintain one's personal vocabulary and use language to communicate effectively; the ability to recognize familiar people and things from those that are unfamiliar; and the ability to understand spatial relationships, particularly in three-dimensional space. Not surprisingly, in people who eventually develop AD, one of these five cognitive areas (often memory) becomes impaired before any of the others. Very often, these first signs and symptoms become noticeable when the individual can still maintain essentially normal functioning. Sometimes, two or more areas can be impaired, but the deficits are still mild enough to not really affect the individual's normal functioning. However, despite the fact that a person can function pretty much normally, either the person or a family member begins to suspect that something is wrong.

When someone presents to an expert center such as the University of Pittsburgh Alzheimer Disease Research Center (ADRC) with symptoms that are of the type and severity necessary for a diagnosis of AD, the diagnosis can be made with great certainty. At the ADRC, as at most AD research centers, diagnostic accuracy rates (confirmed through autopsy) are more than 90 percent. It is not surprising that as fewer and fewer symptoms are present, the diagnosis becomes more and more difficult to make. The process of diagnosis is much like the old TV show *Name That Tune*: When contestants were given many notes, they could almost always name the tune, but when they were given just one or two notes, it became very difficult. The notes are like symptoms for medical diagnoses. AD patients who

present clinicians with many symptoms are often accurately diagnosed. Some patients present with just one or two symptoms, making an accurate diagnosis more difficult. In these situations, when patients may have just one mild symptom (often, but not always, memory loss) that has minimal impact on their functioning, memory specialists often give the diagnosis of MCI.

The assumption that often is made is that MCI is an early form of AD, but this is not always true. We cannot predict a progression from MCI to AD with anywhere near the 90 percent accuracy of the diagnosis of AD using purely clinical assessments. The clinical diagnosis of MCI means



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exactly what the name says: There is detectable cognitive impairment present, but it is too mild to be called AD (or dementia of any type). It is true that MCI often represents an early stage of AD, but the accuracy of predicting AD from a diagnosis of MCI varies with the diagnostic setting, just as it does for AD. In research centers like ADRC, approximately two-thirds of patients with a diagnosis of MCI progress to a diagnosis of AD over a period of three to five years. In other settings, such as large population screening studies, the fraction may be only one-half. So, there are two important subtypes of MCI: those who have MCI because they are in an early stage of AD and those who have MCI due to some other reason.

Continued on page 4

There are many other reasons in addition to AD why a person could have MCI. Some of these reasons include early forms of other brain diseases such as frontotemporal dementia, Lewy body dementia, and other dementias. These forms may progress to the type of dementia that caused the mild impairment. However, not all forms of MCI progress to a dementia of any type. Some patients with MCI do not progress and have a chronic mild impairment. This may be because the mild impairment was caused by a stroke and the patient avoids further strokes. There are other conditions that can affect a specific brain area that is critical for memory called the hippocampus. These MCI subjects may develop progressively worse memory function, but they do not develop the broader pattern of dementia typical of AD.

A smaller subset of MCI patients find that their symptoms simply disappear over a year or two. To understand this fully, it is necessary to have a basic appreciation of how MCI is diagnosed. The first requirement for a diagnosis of MCI is a concern by the patient, or by someone who knows the patient well, that there has been a change in the patient's cognitive function despite the fact that the patient can generally maintain his or her independence and perform daily tasks with minimal aid or assistance. The person may have difficulty doing common tasks (for example, perform them more slowly or make more mistakes), but he or she is still independent. The line between impaired but independent and functionally impaired (as is required for a diagnosis of AD) is a blurry one and presents challenges for even the most experienced clinicians.

Therefore, we employ a second requirement for the diagnosis of MCI. This is a less subjective sort of measurement in which the patient completes a series of memory and thinking tests (called neuropsychological tests). These can be done using pencil and paper, verbally, or on a computer. All of these tests have been extensively studied in a variety of populations, and normal values are established for particular ranges of age, education, etc. Thus, even the first time a person is evaluated, the test scores are compared to a normal population. Because there is a range of scores even within any normal population, cutoffs are defined and scores below this are called abnormal. The problem is that a certain, small number of people in a normal population will score below these cutoffs even though they have no problem. We try to distinguish this group from those who have a significant problem by using the first requirement—a report that the patient has shown a change from his or her normal level. Even with a combination

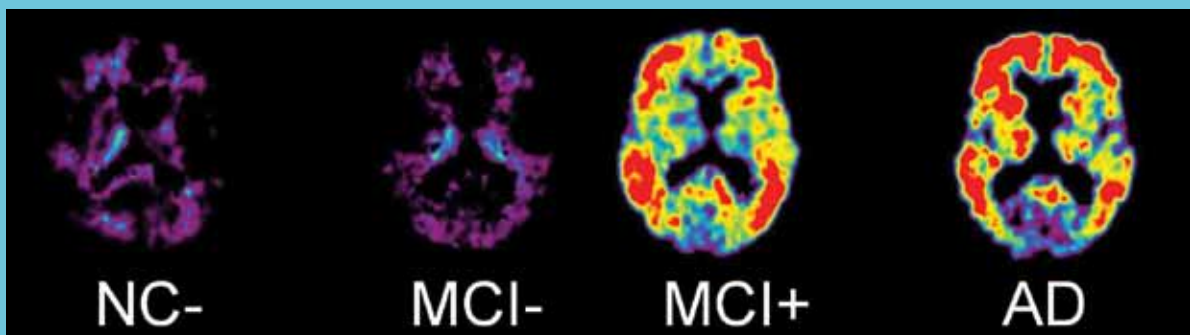
of the first requirement (subjective concern) and the second requirement (objective problem on testing), clinicians, families, and patients can be fooled.

For example, we all know that our mental sharpness varies from day to day and even across the span of a day. We don't function at our best if we have the flu, if we didn't sleep well the night before, if we are distracted by stress in our lives, and for many other reasons. It is possible that a patient who normally functions just above the cutoff for the normal range will test below the normal range on one of these off days. If the reason for not being at one's best is somewhat chronic, such as having clinical depression or a chronic illness, then the person may have a concern about his or her functioning and show abnormal scores on his or her testing at a given time. If the person is tested again a year later and the overriding problem is now gone (for example, the depression was successfully treated), then the person may again score normally, may no longer have concerns about his or her functioning, and would no longer have a diagnosis of MCI.

It becomes very important, then, to distinguish between MCI that is an early stage of AD from MCI that is not likely due to AD. The new guidelines for the diagnosis of AD and MCI attempt to do this by employing knowledge about the biology of AD gained over the past two decades. Over this time, we have learned that the changes in the brain of an AD patient that are detected after death through autopsy often can be detected in those destined to develop AD years—perhaps even a decade—prior to the development of the full clinical syndrome of AD. These changes are called biomarkers in living patients. These biomarkers consist of evidence of the presence of the amyloid plaques and neurofibrillary tangles that are found after death in AD as well as evidence of specific patterns of brain shrinkage on MRI brain scans or evidence of abnormal brain metabolism on another type of brain scan called an FDG PET scan.

At present, evidence of neurofibrillary tangles can be found only with a spinal tap (lumbar puncture). Evidence for amyloid plaques also can be found with a spinal tap, but since the development of a new type of brain scan here at the University of Pittsburgh ADRC in 2002, amyloid plaques now can be seen with an amyloid PET scan. The first type of amyloid PET scan was done with a PET tracer called Pittsburgh Compound B, or PiB for short. PiB PET scans can clearly differentiate MCI subjects who have amyloid plaques like AD patients from those who do not (see figure below).

PiB amyloid PET scans showing the brain of a patient with MCI due to AD (MCI+) and the brain of a patient with MCI not likely due to AD (MCI-) along with the PiB amyloid PET scans of an AD patient (AD) and a cognitively normal control subject (NC-)



Many of our ADRC participants have been involved in amyloid PET scans using PiB in research studies, but these studies do not allow the participant to know whether or not there is evidence of amyloid plaques in his or her brain. Soon, the U.S. Food and Drug Administration is likely to approve other PET tracers similar to PiB, and then amyloid PET scans can be performed for clinical purposes and feedback can be given to patients and used by doctors in decisions regarding treatment.

The new criteria will help us to distinguish MCI due to AD (sometimes called prodromal AD) from MCI not likely due to AD. This has immediate significance in personal planning decisions but also will have long-term effects on the success of drug trials aimed at finding more effective treatments.

As previously stated, it is widely accepted that identification of any disease in its earliest stages increases the chances of discovering effective treatments and in applying those treatments at a time when they will do the most good. If we no longer have to set up drug trials with an unknown mixture of MCI patients who will eventually develop AD (and thus possibly can be helped by anti-AD treatments) and MCI patients who will never develop AD (and thus have no possibility of being helped by an anti-AD treatment), we will have a better chance of discovering effective new treatments for AD. In addition, if we can identify patients who will develop AD while they are still in the MCI stage, we will have a better chance of successfully treating them and of preserving their nearly normal functioning.

Thus, it is a critically important time for people who suspect that they may have MCI to become involved in research that will further develop imaging and biomarker capabilities and for researchers to employ this knowledge in drug trials aimed at finding effective new treatments that can arrest AD at an early stage and, perhaps, prevent those with MCI from progressing to AD. ■

Get involved!

We are actively recruiting participants for several research studies of this type and invite anyone with interest to call the ADRC at 412-692-2721 or e-mail oakleym@upmc.edu.

ADRC Receives Generous Donation from Alzheimer's Assistance & Referral Network

By BETH SARLES, MPH, neuropsychology program coordinator

On November 4, 2010, MaryAnn Oakley, MA, education and information core coordinator, and Beth Sarles, MPH, neuropsychology program coordinator, spoke at a meeting of the Alzheimer's Assistance & Referral Network (AARN) in Boardman, Ohio. Oakley and Sarles presented information about Alzheimer's disease and the research being conducted at the ADRC. Following the presentation, Dorothy Barto, director of AARN, presented a check in the amount of \$4,500 to the University of Pittsburgh Alzheimer Disease Research Center (ADRC). AARN is a referral service for those living in the eastern Ohio and Western Pennsylvania areas. It is a resource for support groups and educational sessions and offers a toll-free information line.

The faculty and staff of the ADRC would like to take this opportunity to once again thank Barto and AARN for their generous contribution. Thanks also to everyone who attended the presentation and to AARN for its kind support. For more information about AARN, visit www.alz-ohio.web.officelive.com or call 1-866-822-2102. ■



The Andy Warhol Museum, Exterior Photo by Ric Evans

Andy Warhol Museum Partners with ADRC on New Program

The Andy Warhol Museum is partnering with the Alzheimer Disease Research Center (ADRC) at the University of Pittsburgh

to offer a new program for individuals who are experiencing memory loss or other cognitive impairment. This innovative program promotes creative expression and socialization by using a combination of guided tours, small group discussions, and art making inspired by the Warhol tradition.

Individuals with mild to moderate cognitive or memory impairment and a friend or relative are invited to take part in the program. Groups of four to eight people will be meeting at the Warhol on Tuesday, June 28, 2011, from 10:30 a.m. to 12:30 p.m. for the activity.

If you are interested in taking part in this program, please call MaryAnn Oakley at the ADRC at 412-692-2721 or e-mail her at oakleym@upmc.edu. ■

In Memoriam

The University of Pittsburgh Alzheimer Disease Research Center thanks the following individuals and companies for their generous donations received October 1, 2010–April 13, 2011.

In Memory of Phoebe Bernstein

Richard and Ellyn Gottlieb

In Memory of Olga Bomba

Thomas M. Calkusic

In Memory of John Booth

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In Memory of W. Ann Buvinger-Robinson

Rhonda M. Pearman

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In Memory of Florence Dudley

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In Memory of Audrey M. Elder

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In Memory of George Elk

Ross and Barbara
Hemmendinger

In Memory of James Hassen Jr.

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In Memory of Stella Ivanovic

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Dennis and Mary Thompson
Harry Trush
Dorothy Warnock

In Memory of Robert Krantzler

R.B. and B.L. Margolis

In Memory of Robert Kwalwasser

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Francis and Linda McLaughlin

In Memory of Charles Miller

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In Memory of Gloria Miller

Raymond and Mary Jo Smith

In Memory of Ann Murano

R.B. and B.L. Margolis

In Memory of Edward Ortipin

John and Mary Tancer

In Memory of Brahm Papke

Hugh and Doris Papke

In Memory of James Pletcher

Jean Pletcher

In Memory of Lillian Purcell

Ralph and Suzanne Altieri
Robert Boscia
Joseph and Edna Dipaolo Jr.

Thank you!

Your contributions are greatly appreciated and help to support research and education in the area of Alzheimer's disease. You can remember or honor a loved one by using the envelope enclosed in this newsletter to send in your donation.

In Memory of Inez Ressler

Paul Ressler

In Memory of John A. Schietroma

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Richard and Marian Sackett
Cindy Janesky and Jack
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***The Thompson High School
Volleyball Team Block Alzheimer's
Out Of Our Lives Fundraiser***

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Wythe and Ellen Weathers



ADRC and Afro-American Music Institute Form New Partnership

Judith A. Saxton, PhD, neuropsychologist and Alzheimer Disease Research Center (ADRC) clinical core director, presented “What to Expect as Your Brain Ages” at the Afro-American Music Institute in the Homewood neighborhood of Pittsburgh on April 9, 2011. This event marked the beginning of a new partnership between the ADRC and the music institute through which the ADRC will continue to provide educational programming about the aging brain, memory, and Alzheimer’s disease to the institute.

Attendees listened to Saxton’s explanation of what happens to memory as we age and then had the opportunity to sit in on short musical performances by some of the institute’s students. Students range in age from 4 to 90 years of age.

For more information about the Afro-American Music Institute, visit afroamericanmusic.org. ■



Thompson High School Fundraiser a Big Success

The Thompson High School volleyball team in Thompson, N.D., held a fundraising event in fall 2010 to benefit the University of Pittsburgh Alzheimer Disease Research Center (ADRC). Block Alzheimer’s Out of Our Lives was the name of the event coordinated by coaches Deb DeMoe and Lisa Strand. The fundraiser included a volleyball game, a serving contest, and a cookie and bracelet sale and raised \$1,540. DeMoe’s daughter, McKenna, is a member of the team.

The DeMoe family of North Dakota has participated in AD research at ADRC for a number of years because many of its family members have been afflicted with familial AD. The DeMoes’ contributions to research, both in fundraising endeavors and in giving of their precious time, along with the contributions of other families in the ADRC’s familial AD research programs, have led to increased knowledge in the field of AD. We are grateful for all of their efforts. Many thanks to the Thompson High School volleyball team. Go Tommies! ■

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Visit Our Web Site

For up-to-date information about the Alzheimer Disease Research Center, the autopsy program, clinical trials, and community presentations, please visit www.adrc.pitt.edu.



Welcome Back!

Alzheimer Outreach Center. She has a Bachelor of Science degree in psychology from the University of Pittsburgh and currently is working toward a master's degree in public health with a concentration in behavioral and community health.

Previously, Garrett worked with the ADRC on its Pennsylvania grant project from August 2006 through June 2010. During that time, she was responsible for the recruitment and interviewing of African American urban-dwelling seniors for the Memory and Aging in Urban and Rural Communities Study. In addition, she coordinated group presentations and participated in health fairs to raise awareness about Alzheimer's disease and other dementias. Her exuberant personality, empathy, and strong commitment to providing information and education to community members greatly enhanced the success of the project.

In her new position, Garrett is responsible for organizing the meetings of the ADRC's Community Advisory Council (CAC), which is composed of social service and health care providers, older adults, and community leaders from the local African American community. The Walter Allen Lecture Series, a semiannual community outreach effort named for a prominent local African American photographer affected by dementia, will continue under her coordination. Other outreach initiatives will include events at senior centers, churches, and other venues identified by CAC and other community agencies. ■



Marita Garrett has recently returned to work as an outreach coordinator, focusing on urban communities, for the Alzheimer Disease Research Center (ADRC) and

Staff Spotlight

ADRC DATA MANAGER

SHELLEY FERSON

Shelley Ferson feels very fortunate to work at the Alzheimer Disease Research Center (ADRC) at the University of Pittsburgh.

"Not only are the clinicians, doctors, and administrators at this center enjoyable to work with, but they also are so good at what they do that I have no doubts that my job supports people who are making a difference in the lives of Alzheimer's disease patients and their families," she says.

Ferson is one of several data managers at the ADRC who handle all of the collection forms that are done for the ADRC registry, the National Alzheimer's Coordinating Center's Uniform Data Set, and some additional ancillary research studies. Ferson spends time on data quality control, reviewing both new and existing data that go all the way back to the beginning of the center in 1985. She also designs and builds databases that contain research, clinical, and ancillary study data. Currently, her main project is to redesign and rebuild the ADRC's multiple databases into one new consolidated and updated system.

For the past five years, Ferson worked for the Epidemiology Data Center in Pitt's Graduate School of Public Health. While there, she spent the majority of her time working on a project for the ADRC.

Prior to that, Ferson graduated from the University of Michigan and worked at the National Archive of Criminal Justice Data for a few years. The archive focused on preserving, enhancing, and sharing data that already had been collected by organizations

"Not only are the clinicians, doctors, and administrators at this center enjoyable to work with, but they also are good at what they do."

-Shelley Ferson



like the National Institute of Justice and the Federal Bureau of Investigation, among others. Working with data that already had been collected brought on a desire to work with data earlier in the process—as they were being collected. She wanted to try to make sure that data were well put together from the start.

When asked what the most rewarding part of her job is, Ferson replies, "It's creating databases and programs that both support the collection of high-quality data and make the clinicians' jobs easier."

In her spare time, Ferson and her husband, Seth, try to motivate themselves to work on their fixer-upper home. What she's discovered, unfortunately, is that they are not particularly enthusiastic fixers! In addition, Ferson spends time reading, watching television, and doing puzzles, usually with at least one of her two cats flopped down next to her. ■

Groundbreaking NIH-Supported Study Expands, Seeks New Volunteers

The National Institutes of Health (NIH) are expanding the Alzheimer's Disease Neuroimaging Initiative (ADNI), a groundbreaking research study that will recruit hundreds of new volunteers to help define the subtle changes that may take place in the brains of older people many years before overt symptoms of Alzheimer's disease (AD) appear.

Researchers are seeking new volunteers to join those already participating in the study as it enters a second phase called ADNI2. Over the next five years, approximately 1,000 people ages 55–90 will be enrolled at approximately 55 sites in the United States and Canada. They will be followed to define any changes in brain structure and function as people transition from normal cognitive aging to mild cognitive impairment (MCI), often a precursor to Alzheimer's dementia. The study will use imaging techniques and biomarker measures in blood and cerebrospinal fluid specially developed to track changes in the living brain. Researchers hope to identify who is at risk for AD, track progression of the disease, and devise tests to measure the effectiveness of potential interventions.

"ADNI2 will build upon the successes of this ongoing effort to identify the earliest signs of Alzheimer's disease, when damage to the brain may begin well before symptoms appear," said National Institute on Aging (NIA) Director Richard J. Hodes, MD. "This phase of the study, which includes greater numbers of volunteers in the earliest stages of cognitive impairment, should give us new insights into the onset and progression of Alzheimer's disease."

Michael Weiner, MD, of the San Francisco, Calif., VA Medical Center and the University of California, San Francisco, is principal investigator for the study. "By determining how brain scans, biomarker measures, and cognitive testing results relate to each other and to the symptoms a person is having, we are getting a much clearer picture about the onset and progression of this devastating neurodegenerative disorder," Weiner said.

ADNI2 will recruit 550 new volunteers. The study also will continue to follow participants recruited during two earlier phases: ADNI1, started in 2004, and ADNI-GO (Grand Opportunity), begun in 2010.

This effort will continue to track changes in the brain with clinical and cognitive testing and brain scans measuring glucose metabolism and the amount of beta-amyloid protein—a hallmark of AD—deposited in the brain. Researchers also are collecting serum and plasma for biomarker measures and blood samples for genetic analysis. All new participants in ADNI2 will receive lumbar punctures to measure cerebrospinal fluid biomarkers and will have blood drawn for plasma biomarkers.

One important aspect of the study is the sharing of data soon after they are obtained. Study data are posted to a publicly accessible database available to qualified researchers worldwide. To date, more than 1,700 researchers have signed up for ADNI database access.

To volunteer or learn more about ADNI2, contact MaryAnn Oakley at the University of Pittsburgh Alzheimer Disease Research Center at 412-692-2721 or oakleym@upmc.edu.

ADNI is the largest public-private partnership to date in Alzheimer's disease research. It is led by the National Institute on Aging at NIH through a grant to the nonprofit Northern California Institute for Research and Education (NCIRE), with private sector support provided through the Foundation for the National Institutes of Health.



ADNI is stimulating the development of worldwide collaboration among academic, government, and industry researchers and has resulted in more than 170 published papers. The ongoing study has resulted in new findings about how changes in the structure of the hippocampus, a brain area important to learning and memory, may help to detect disease progression and effectiveness of potential treatments. It also has established biomarker and imaging measures that predict risk for cognitive decline and conversion to dementia in this clinical cohort.

Neil Buckholtz, PhD, who has led the study for NIA's Division of Neuroscience, stressed the importance of public participation in the study, particularly as recruitment turns attention to people with the very earliest signs of possible disease. Researchers hope to add 100 more participants with early MCI to the 200 already being followed to achieve a primary goal: identifying the onset of the disease before symptoms appear. ■

"We are grateful to all the volunteers who have participated in ADNI thus far and who may join the study. Their efforts so far have told us a great deal about Alzheimer's disease, and the next phase should provide even greater insights."

-Neil Buckholtz

Volunteers Needed for Research Studies

Lifestyles and Behavior on Cognitive Function

DESCRIPTION

This study will look at the effect of various life factors, such as physical activity, on brain health in late adulthood. Participants will be asked to wear an armband that measures activity for a one-week period.

STUDY LENGTH

One week

STUDY REQUIREMENTS

Participant who is 65–90 years of age and is coming to the ADRC for an initial or annual evaluation

CONTACT

MaryAnn Oakley at
412-692-2721 or
oakleym@upmc.edu

3M Study: Maximizing Medication Management

DESCRIPTION

This study will examine the effect of a new program for teaching family caregivers about managing and administering medications to persons with cognitive impairment.

STUDY LENGTH

Approximately six months

STUDY REQUIREMENTS

- Family or informal caregiver who is caring for a friend or family member who needs help with managing his or her medications or
- A participant who has difficulty remembering, needs help with managing medications, and has at least one health condition that requires medication

Alzheimer's Disease Neuroimaging Study 2 (ADNI2)

DESCRIPTION

The purpose of this study is to determine whether imaging of the brain (through MRI, PET, and amyloid imaging scans) can help to predict the onset and monitor the progression of cognitive change. The study will test blood and cerebrospinal fluid (from lumbar punctures) to determine whether biomarkers can predict and monitor the disease.

STUDY LENGTH

54 months

STUDY REQUIREMENTS

- Between 55 and 90 years of age
- A study partner who is able to attend all clinic visits with the participant
- Participant who has a diagnosis of either early Alzheimer's disease or mild cognitive impairment or is cognitively normal

A major focus of the ADRC is to match participants with opportunities for involvement in additional studies being conducted by ADRC-affiliated researchers. Individuals enrolled at the ADRC are routinely invited to participate in additional studies, depending on eligibility requirements and interest in volunteering. If you have questions about whether a particular study is a good match for you, please contact us.

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Ask the Medical Professional

By ROBERT R. KAUFMAN, PharmD

Q: My mother has Alzheimer's disease and I am considering switching her medication from a brand-name drug to a generic drug. Will the generic drug be just as effective?

A: With several drug companies making generics for Aricept, I first need to explain that there are different distinctions for generics.

There are "branded generics" (sometimes referred to as "approved generics"), for which the generic company usually negotiates with the original manufacturer for the rights to market a generic form of the drug under its original new drug application (NDA), for which the brand drug originally received U.S. Food and Drug Administration (FDA) approval. These branded generics use the same formula and are identical to the original brand drug in contents. In the case of Aricept, Greenstone LLC has obtained the rights to market the branded generic drug, and its 5 mg and 10 mg tablets are the same shape, size, and color as the original Aricept (the 23 mg tablets are not yet available in generic). These branded generics gain their approval from FDA under the original NDA that the innovating company submitted.

"Nonbranded generics" have different inactive ingredients, like fillers and dyes, to which some patients may have different responses. A patient may have an allergic response or find that he or she has an intolerance to one of the inactive ingredients, and the patient may have to use the brand or branded generic drug to avoid the response. The intolerance also could cause anything from increased side effects to changes in absorption and drug availability in the bloodstream. Aside from such variables, these generic drugs should be equally as effective

as the brand-name Aricept. These generic drugs also must receive approval from FDA, but they do not go through the original NDA of the originating drug company. The challenge with change of drug therapy in Alzheimer's disease patients is in evaluating the effectiveness of drug therapy versus disease progression. Good documentation and assessments are essential and very helpful for being able to identify not only the allergic responses or intolerances mentioned earlier but also the effectiveness of therapy versus disease progression.

All of the currently marketed generics of Aricept carry an AB rating, which means that they have been considered equivalent to the brand-name drug within acceptable margins. This allows for them to be substituted for the brand Aricept. Several others are being marketed now, and more are due to hit the market in June 2011. When making any change in drug therapy, always be alert to possible allergic reactions and/or intolerances and changes in patient responses. A helpful hint: If you plan to make a change to a generic or if cost forces you to switch to a generic, you can help to limit the variables if you stick to the same generic company. As generics make it to the market, they are very competitive in price, and different pharmacies will carry different generics. ■

Kaufman is an assistant professor at the University of Pittsburgh School of Nursing. He also is the pharmacist consultant for Maximizing Medication Management (3M), a research study designed to help family caregivers to better manage their loved ones' medication administration regimens. For information about participating in 3M, call 1-800-653-9234.