Brain Vulnerability and Protection from Alzheimer’s Disease

Alzheimer’s disease (AD) is the most frequent form of dementia in elderly individuals, and its prevalence becomes more common with advanced age. It is probably no surprise to you that age is the most important risk factor for AD. Indeed, studies conducted by our group have shown that chronological age is associated with shrinkage, or atrophy, of the brain. In addition to advanced age, AD has been linked to genetic factors (like the apolipoprotein E 4 allele), a family history of the disease, and having fewer years of education. Certain medical conditions further increase the brain’s vulnerability for AD. Examples of medical conditions that have been associated with AD include high blood pressure, diabetes, heart disease, and cerebrovascular disease (meaning disease of the blood vessels that supply the brain). While identifying factors that increase the brain’s vulnerability to AD has been a major focus of research, so has the identification of factors that can protect the brain from AD. Research has shown that there are lifestyle factors that can reduce the effects of genetic and demographic AD risk factors. These lifestyle factors are considered to be protective against AD and include physical and cognitive activity and diet. Our research has consistently shown that complex interactions among these risk and protective factors, along with the biological cascade of AD, determine the likelihood that a person will show signs and symptoms of AD once the disease is under way at the cellular level.

Studies conducted by our group and others have suggested that vascular (blood vessel) disease in particular creates vulnerability to AD pathology and affects the timing and severity of AD symptoms that a person experiences. Therefore, we are now conducting studies to examine whether vascular disease speeds up the transition from normal to abnormal cognition in late life. In addition, we are examining the relationship between vascular disease and amyloid deposition using Pittsburgh Compound B. The phrase “amyloid deposition” refers to the buildup of proteins that form the so-called plaques of AD. This study will allow us to determine how vascular and lifestyle factors can influence the buildup of amyloid in the brains of older persons before symptoms of AD begin. Understanding this process will both give us new information about when and how the cerebral vascular disease should be treated and provide critical information about how to implement future prevention therapies for AD.
Why Does Memory Get Worse with Age?

As a person gets older, changes occur in all parts of the body, including the brain:

- **Certain parts of the brain shrink.** The hippocampus and the prefrontal cortex (an area at the front of the brain) are areas that are important for learning, memory, planning, and complex mental activities.

- **Changes in neurons and neurotransmitters affect communication between neurons.** Communication between brain cells can be reduced because the physical connections between these cells is degraded or lost.

- **Changes in the brain’s blood vessels occur.** Blood flow can be reduced because arteries narrow and less growth of new capillaries occurs.

- **Damage by free radicals** (molecules that react easily with other molecules) slowly accumulates over decades.

- **Inflammation increases** (inflammation is the complex process that occurs when the body responds to an injury or disease).

Major declines in mental abilities are not inevitable as people age.

Older people notice declines in their ability to learn new things and retrieve information; however, if given enough time to perform a task, the scores of healthy people in their 70s and 80s on tests of learning and memory often are similar to those of young adults. In fact, as they age, adults often improve in other cognitive areas, such as vocabulary and other forms of verbal knowledge.

It also seems that additional brain regions can be activated in older adults during cognitive tasks. We’re not sure why this happens, but one thought is that the brain compensates for difficulties other regions may be experiencing. These findings have led many scientists to believe that major declines in mental abilities are not inevitable as people age. Growing evidence of the adaptive or “plastic” capabilities of the older brain provides hope that people may be able to do things to sustain good brain function as they age.

ADRC Patients and Family Members Invited to Warhol Tour and Artistic Expression Activity

The University of Pittsburgh Alzheimer Disease Research Center and the Andy Warhol Museum have partnered to offer a new and innovative program for patients and family members affected by memory loss and other cognitive changes.

Patients and their family members are invited to participate in a tour and artistic expression activity offered at the Andy Warhol Museum on Pittsburgh’s North Side. The program will be held on Thursday, August 23, 2012, from 10:30 a.m. to 12:30 p.m.

Please contact MaryAnn Oakley at 412-692-2721 or oakleym@upmc.edu for more information or to register for this event.
One in eight baby boomers will get AD after they turn 65, and by 2050, the number of Americans with AD will likely reach 13.5 million—and could go as high as 16 million. Elderly African Americans are twice as likely to develop the disease than any other demographic, but we don’t know why.

In addition, many members of the African American community are often misdiagnosed, and many others go untreated.

“It is critical for the well-being of the African American community that we know more about AD and how it affects all populations, including people of color,” says Karen Bell, MD, clinical professor of neurology at Columbia University and former director of minority recruitment efforts for the National Institute on Aging-funded Alzheimer’s Disease Cooperative Study. “We must think about our children and grandchildren and learn enough now about Alzheimer’s to develop treatments or a cure that can make their future brighter than our own.”

For more than 10 years, the Alzheimer’s Disease Neuroimaging Initiative (ADNI)—the largest clinical trial on Alzheimer’s in the nation—has been seeking answers about AD. ADNI is helping to identify the earliest signs of the disease, when brain damage begins, and when treatments offer the greatest promise for slowing down its progression. ADNI is not testing experimental drugs but rather using scans like MRIs to follow normal individuals, people with mild cognitive impairment, and those diagnosed with AD to monitor changes in their brains that can lead to clues about how AD works. Perhaps no other study has contributed as much to the field of Alzheimer’s research as ADNI, but more African Americans need to be represented in this research to reflect the real burden of the disease.

Low rates of clinical trial participation are a serious impediment to new discoveries in the field. According to the Alzheimer’s research community, the greatest barrier it faces is not the disease itself but finding enough volunteers for studies to progress at the pace needed to develop new treatments as well as a cure.

“If things don’t change soon, baby boomers are going to be living with devastating rates of Alzheimer’s,” says Michael Weiner, MD, primary investigator for ADNI; a volunteer participant in the study; and caregiver to his mother, who has Alzheimer’s. “But the good news is that they have the numbers and the power to drive that change by getting involved in research.”

ADNI is currently seeking volunteers to participate in its groundbreaking AD research studies. Anyone between the ages of 55 and 90 who is healthy, has been diagnosed with mild cognitive impairment, or has Alzheimer’s disease is encouraged to apply. African Americans are urgently needed to participate at any of the 54 research sites across the country that are engaged in ADNI work.

With 5.4 million Americans living with AD, chances are that you or someone you know is affected. Perhaps you are one of the 15.2 million caregivers who provide loving, unpaid care to those suffering from the disease. Or maybe you have watched a friend trying to juggle her job; her kids; and taking care of her mom, who is getting ever more forgetful. You can help to make a difference.

“If we all work together and donate our time to studying this disease, we can find the answers we need to potentially change the world as we know it,” says Bell. “I believe it is possible to stop Alzheimer’s in its tracks, but it will take our community coming together, and our nation coming together, to succeed.”

To volunteer or to learn more about ADNI, contact MaryAnn Oakley at the University of Pittsburgh Alzheimer Disease Research Center at 412-692-2721 or oakleym@upmc.edu.
ADRC Bids a Fond Farewell to Judith Saxton

JUDITH SAXTON, PhD, director of the University of Pittsburgh Alzheimer Disease Research Center Clinical Core, will retire effective July 1, 2012, after an illustrious career with Pitt and the ADRC. She has been involved with the center since its inception in 1985, serving initially in staff positions performing neuropsychological assessments and as the coordinator of the Education and Information Core. In 1990, she earned her PhD in psychology at the University of Reading in England and subsequently moved up the faculty ranks from assistant to associate to full professor of neurology and psychiatry. She has made several major contributions to the dementia field, including her development of the Severe Impairment Battery (SIB) and her work in developing novel computer-based screening tests suitable for detecting mild cognitive impairment (MCI) and early Alzheimer’s disease (AD) in the community.

Early in her academic career, she was awarded an ADRC pilot grant leading to the development of SIB, which measures progressive cognitive impairment in the later stages of AD. The test has been adopted by the U.S. Food and Drug Administration as a standard outcome measure in trials of drugs for moderate to severe AD. It has become widely accepted and has been translated into more than 20 languages. Saxton is known nationally and internationally for the development of this neuropsychological test and is a recognized expert in the field.

She also has served as principal investigator on federally funded studies of age-associated memory impairment and alcohol dementia as well as a recently completed study of MCI in underserved communities funded by the Commonwealth of Pennsylvania. She also was the director of the clinical core in the In Vivo PIB PET Amyloid Imaging Study led by William Klunk, MD, PhD, ADRC codirector.

Her most recent National Institute on Aging grant, Cognitive Assessment of Elderly Primary Care Patients, focused on MCI, which is considered to be a precursor to AD, and on factors that predict outcomes of MCI, such as progression to dementia, reversion to normal cognitive status, and stable MCI in primary care patients. The study investigated the usefulness of “memory screening” in primary care and the impact on the clinical and cognitive outcomes of providing cognitive reports to physicians. It used a brief, portable computer assessment of memory and thinking, the Computer Assessment of Mild Cognitive Impairment (CAMCI), which was developed by Saxton and her colleagues. The test was designed for elderly patients with little or no computer experience and is a prime example of assessment tools that will likely become useful in the near future to detect patients who may benefit from treatments designed to stop the progression of or reverse early AD.

In addition to her research initiatives, Saxton has played a key role in the mentorship of ADRC staff, graduate students, postdoctoral fellows, psychiatry residents, and junior faculty members. Several of her mentees have gone on to successfully apply for National Institutes of Health funding and have secured independent faculty positions. She has lectured for a variety of graduate school, medical school, and resident educational courses. In addition, she has been a beloved speaker at ADRC outreach seminars and has demonstrated her ability to translate complicated research advances into easy-to-understand language.

Saxton has made several major contributions to the dementia field, making her known nationally and internationally as a recognized expert in the field.

The ADRC faculty and staff wish Dr. Saxton the very best in her retirement and her plans for travel, spending time with her numerous grandchildren, and new adventures. She will maintain an adjunct faculty appointment at the University and will continue to provide mentorship and consultation to our young faculty members. We consider ourselves very fortunate to have had the benefit of her expertise and wonderful personality. We will miss the sound of her English accent at our consensus conference, her thoughtful approaches to research challenges, and her resourceful problem solving.
When I came to the United States in January 1983, I had never heard of Alzheimer’s disease (AD). My husband and I were recent immigrants from England, and we liked Pittsburgh and wanted to stay, so I needed to find a job. François Boller had just received funding from the National Institute on Aging to conduct one of the first longitudinal studies of AD. As part of the study, patients with AD were to complete detailed annual assessments, and I would be part of the team that would administer those evaluations. The goal was to understand the natural history of AD; no one had done that before, and we were breaking new ground.

I had grown up in a multigenerational home and knew that I got on well with “old people,” so I expected to enjoy the study and thought it would be interesting. It was, and I stayed almost 30 years building a successful career. During that time, I have worked with some of the smartest people in the world, and over the next few weeks before my retirement, I will thank each of them for the part they have played in my career. Right now, though, I want to thank you.

Research into clinical disorders by necessity requires large numbers of individuals willing to give their time, and sometimes literally their blood, with no thought of personal benefit. Since I started to work at the University of Pittsburgh Alzheimer Disease Research Center, more than 4,000 such individuals have come through its doors, and many of you still come each year. The past 30 years have seen significant strides in our understanding of AD, none of which would have been possible without your participation.

If there is one small regret I have, it is that I won’t celebrate with you on the day our researchers finally unravel the key to this devastating disorder, but be assured that I will be cheering just as loudly from my deck chair overlooking the beautiful blue sea while I watch my grandchildren play in the sand.

Reflections from Judith Saxton

“The past 30 years have seen significant strides in our understanding of AD, none of which would have been possible without your participation.”

-Judith Saxton, PhD
ADRC Clinical Core Codirector

Robert Sweet, MD, Named New ADRC Clinical Core Director

The University of Pittsburgh Alzheimer Disease Research Center (ADRC) welcomes ROBERT SWEET, MD, as the new director of its Clinical Core. Sweet will be taking over for Judith A. Saxton, PhD, who has held this position since 2008. The Clinical Core is one of six that make up the organizational structure of the ADRC.

Sweet received a bachelor’s degree from Rensselaer Polytechnic Institute and a medical degree from the University of Maryland School of Medicine. He completed his residency in psychiatry at Albany Medical College. After serving as an assistant professor of psychiatry at Albany Medical College, he joined the psychiatry faculty at the University of Pittsburgh School of Medicine. Sweet currently is professor of psychiatry and neurology and vice chair of the Institutional Review Board at the University of Pittsburgh. Sweet also is the director of a National Institute of Mental Health-funded postdoctoral training program emphasizing translational neuroscience research, Training for Transformative Discovery in Psychiatry.

Sweet is coassociate director for research at the Mental Illness Research, Education and Clinical Center, VA Pittsburgh Healthcare System, and codirector of its Advanced Fellowship in Mental Illness Research and Treatment. Sweet is board certified in psychiatry with added qualifications in geriatrics and is an active member of several professional organizations, including the American College of Neuropsychopharmacology, International College of Geriatric Psychoneuropharmacology, Society for Neuroscience, Society of Biological Psychiatry, and American Association for Geriatric Psychiatry.

Sweet’s research interests have focused on the causes of psychosis. His lab conducts studies to refine the definition of psychotic phenotypes and outcomes in Alzheimer’s disease (AD) and relates these to underlying genetic variation. Sweet’s research has been reported in numerous scientific journals, and he frequently presents his findings at national and international meetings. Sweet’s genetic studies of psychosis in AD at the ADRC started as an ADRC program project grant titled Molecular Pharmacology of Psychosis Risk and was funded from 2000 to 2005. His success with this study subsequently led him to receive a National Institute on Aging grant titled Prediction of Psychosis in Alzheimer’s Disease, which was funded from 2007 to 2012. The ADRC recently received news that this work will continue to be funded through 2017.

In addition to the studies at the ADRC, Sweet has been involved as an investigator on a national initiative to discover genes associated with AD (the National Institute on Aging Genetics Initiative for Late-Onset Alzheimer’s Disease). He is the lead investigator for the collection and interpretation of behavioral data, including psychosis data, as part of the study.

It is with great pleasure that we congratulate Dr. Sweet on his new position at the ADRC.
In Memoriam

The University of Pittsburgh Alzheimer Disease Research Center thanks the following individuals, companies, and groups for their generous donations received October 11, 2011–May 9, 2012.

In Memory of Alice Bernardi
David and Mona Matalik

In Memory of Henry John Borish
David and Catherine Demor
William and Judith Flynn

In Memory of Richard “Dick” Caringola
Patricia Caringola
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In Memory of Charles Hennessey
Sharon Antrim

In Memory of Abraham Honig
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Matthew Pipich

In Memory of John Pritulsky
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Richard and Rosemarie Becker

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In Honor of Sarah Jane Gleeson
Robert Marie Churilla

In Honor of MaryAnn Oakley
Vincent and Filomena Varvaro

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Cory Erickson, Sub-Zero Productions
Mary Jo Grover
Peter and Stacy Schumacher
Steven and Catherine Spicer
Thompson Public School District No. 61

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.
The October 2011 edition of IDEA Fitness Journal noted that more evidence is coming to the forefront indicating that cardiovascular exercise contributes to long-term brain health. In a study presented at the American College of Sports Medicine’s 58th Annual Meeting in June 2011, older adults who had exercised regularly were found to have better motor control and memory than inactive adults of the same age.

**Try these brain-challenging physical exercises***:

- Walk forward and backward. Walking backward may feel kind of awkward because you normally don’t do it every day and your brain isn’t used to it. Suddenly, you have to think about it!
- Shuffle sideways in one direction then the other. Moving side to side can really elevate your heart rate quickly because your body is not used to it.
- Balance on one leg at a time, then close your eyes and see how long you can do it. It’s amazing how much your brain relies on your vision to help with your balance, but you can improve your balance with practice.
- Try doing hopscotch forward, then move backward. It’s not as easy as it looks!
- Catch a ball using your dominant hand 10 times in a row, then switch and try to do it with your nondominant hand. Do you notice a difference? If so, you will notice improvement over time if you keep trying it. See how fast you can do it before switching to the other hand.

*Always check with your physician to be sure you are healthy enough to begin an exercise program.

Jackie Frederick is a fitness professional certified through the American Council on Exercise and the fitness and wellness director at Oxford Athletic Club in Wexford, Pa.

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**ADRC University of Virginia Satellite**

As many of you will recall, Steven T. DeKosky, MD, was the director of the University of Pittsburgh Alzheimer Disease Research Center (ADRC) from 1994 to 2008. In 2008, he moved to the University of Virginia (UVa) to become dean of its School of Medicine. Following his move, we immediately began talks to establish a satellite clinic of ADRC at UVa. The clinic became a reality in 2010 with DeKosky as the director and Carol Manning, PhD, as codirector.

The ADRC satellite at the University of Virginia focuses on increasing the representation of rural African Americans in research as well as providing evaluation and follow-up to patients and control subjects followed in the Memory and Aging Care Clinic at UVa and enrolled in the ADRC registry. Major goals include working collaboratively with rural community partners to bring awareness of Alzheimer’s disease to this population as well as offering clinical trials to a population often underrepresented in dementia research. Key personnel include Erin Foff, MD, PhD, and DeKosky, neurologists; Ishan Williams, PhD, recruitment/enrollment coordinator; Manning, neuropsychologist and director of the Memory and Aging Care Clinic; Colleen Webber, clinical trials coordinator; Lisa Opie, neuropsychometrician; and several neuropsychology fellows.

Going forward, we will include a UVa satellite clinic section in each newsletter to keep you abreast of its activities.

**Welcome, UVa! We look forward to a successful collaboration.**
Visit Our Web Site

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

Klung Named to Alzheimer’s Association Medical and Scientific Advisory Council

In July 2011, William E. Klunk, MD, PhD, codirector of the University of Pittsburgh Alzheimer Disease Research Center, was named vice chair of the Medical and Scientific Advisory Council for the Alzheimer’s Association. The council comprises leading scientists and clinicians in the field of dementia research and treatment. Its members advise the Alzheimer’s Association on research funding, programs, and policy.

Garrett Named 2012 Fab 40 Honoree

Marita Garrett, outreach coordinator at the University of Pittsburgh Alzheimer Disease Research Center, was honored as one of the New Pittsburgh Courier’s Fab 40 for 2012, a select group of Pittsburgh’s top young African American men and women recognized for their outstanding community contributions. The New Pittsburgh Courier notes, “These movers and shakers represent an era in which more doors are opening to African Americans than ever before.” A reception was held at the Fairmont Pittsburgh hotel downtown on February 24, 2012, to celebrate the accomplishments of the 40 honorees.

ADRC PATHWAYS SPRING/SUMMER 2012
Volunteers Needed for Research Studies

Get involved! We are in constant need of participants for several research studies and invite anyone with interest to call the ADRC at 412-692-2721 or e-mail oakleym@upmc.edu.

Cueing Kitchen for People with Cognitive Impairments

DESCRIPTION
The purpose of this research study is to evaluate different types of reminders that have been designed to help people who have difficulty completing kitchen tasks due to problems of memory, attention, and planning as a result of a medical condition such as dementia.

STUDY LENGTH
One visit (approximately 2–2½ hours)

STUDY REQUIREMENTS
Individuals who have a diagnosis of Alzheimer’s disease (AD) in the moderate range, live in their own homes, and have a study partner who will accompany them to the study visit.

Perceptual Memory Study

DESCRIPTION
The goal of this study is to learn more about the neural bases of perceptual decision making and, in doing so, to better understand how memory is affected in aging. Using functional magnetic resonance imaging (fMRI), this study will examine changes in brain function while participants perform cognitive tests. The fMRI scan and test results will help researchers to gain insight into which parts of the nervous system are involved in different aspects of the tests.

STUDY LENGTH
One visit (3–4 hours)

STUDY REQUIREMENTS
Individuals between 65 and 85 years of age who are currently experiencing progressive cognitive deficits (i.e., mild cognitive impairment) or who are cognitively healthy.
The Learning and Memory Study

**DESCRIPTION**
The purpose of this study is to help researchers find out more about how people learn and store information in their memory. The data gathered through this project is expected to add to the knowledge of learning and memory.

**STUDY LENGTH**
One visit (2–3 hours)

**STUDY REQUIREMENTS**
- 45 years of age or older
- Cognitively healthy individuals or individuals who have a diagnosis of early AD

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3M Study: Maximizing Medication Management

**DESCRIPTION**
This study will examine the effects 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 management

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Alzheimer’s Disease Neuroimaging Study 2 (ADNI2)

**DESCRIPTION**
The goal 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 if 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 accompany the participant to all clinical visits
- Participant who has a diagnosis of early Alzheimer’s disease or mild cognitive impairment

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

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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.
In April 2012, the U.S. Food and Drug Administration (FDA) approved florbetapir (Amyvid), which is a radioactive dye for use with positron-emission tomography (PET) for visualization of amyloid plaque buildup in the brain. Currently, several groups, including the Alzheimer’s Association, are actively involved in coming up with recommendations for how best to use this new brain imaging tool. In the meantime, here is some guidance given by the Alzheimer’s Association that we at the University of Pittsburgh ADRC endorse.

William E. Klunk, MD, PhD, codirector of Pitt’s ADRC and a coinventor of flutemetamol, shares the answers to questions he helped the Alzheimer’s Association to formulate:

Q: What will this test tell me?
A: The test will tell you if you have amyloid plaques in your brain.

Q: Who should have this test?
A: People with a questionable dementia diagnosis or a difficult dementia diagnosis should have this test.

Q: Will this test tell me if I have or don’t have Alzheimer’s disease (AD)?
A: No. When used in conjunction with cognitive testing for AD dementia, it could increase the certainty of a diagnosis of Alzheimer’s dementia or could be used to rule out AD as a possible cause. This could be especially useful in cases where it is difficult to determine which of the dementia disorders is the cause of the problem.

Q: Will this test tell me if I will get or won’t get AD in the future?
A: For people who don’t have current memory problems, no. There is not yet enough information about amyloid imaging in normal people to know what this test means for them. For people who have memory problems or mild cognitive impairment, this test may indicate an increased likelihood of developing AD dementia over the next few years, but this research is ongoing. Brain amyloid is one factor in the development of AD, but it is not likely to be sufficient by itself. We’re not yet certain if everyone with amyloid in their brain will go on to get AD dementia.

Q: How is the test administered?
A: A radioactive chemical, known as Amyvid, is injected into a vein in your arm. You then lie in a PET scanner for 20–30 minutes.

Q: How much does the test cost?
A: This is not yet clear, but other PET scans can cost between $1,000 and $3,000.

Q: Will this test be covered by my insurance?
A: Insurers often lag behind FDA approval, so it is unlikely that insurance will cover the test immediately. It is not clear when or if this test will be covered by insurance. If it is eventually covered, insurers may put conditions on payment. For example, people may need to have a full clinical examination before getting this scan.

It should be noted that a second radioactive dye, called flutemetamol, was developed here in Pittsburgh, and FDA approval of flutemetamol is expected later this year or early next year.