

Research Highlights:

Discoveries underscore the predictive value of biomarkers and the potential influence of modifiable risk factors

Each year, researchers around the globe explore a diversity of topics in Alzheimer science. These topics are impressive in their breadth and depth. In 2009 topics ranged from the role of heat-shock proteins in the development of the tau tangles that characterize Alzheimer's disease to the influence of emotional closeness between an individual with Alzheimer's and his or her caregiver on the individual's rate of cognitive and functional decline.

But perhaps most visible in 2009 were discoveries supporting the potential role of biomarkers in early detection and diagnosis of Alzheimer's disease and the influence of lifestyle factors such as exercise and diet in modifying one's risk of developing Alzheimer's.

A biomarker is a substance or characteristic that can be objectively measured and evaluated as an indicator of normal body processes, disease processes or the body's response(s) to therapy. For example, blood pressure is a biomarker that indicates risk of cardiovascular disease.

During the Alzheimer's Association International Conference on Alzheimer's Disease (AAICAD) 2009, Ronald Petersen, Ph.D., M.D., chair of the Association's Medical and Scientific Advisory Council, provided the context for why Alzheimer biomarkers are needed. "With the continued aging of the population and the growing epidemic of Alzheimer's, early detection of the disease is crucial for risk assessment, testing new therapies and eventual early intervention with better drugs, once they are developed," he said.

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“It is widely believed that Alzheimer’s disease brain changes, including amyloid plaques and neurofibrillary tangles, begin many years before we see symptoms. It is critical to identify affected individuals while they are still relatively cognitively healthy so that future therapies can preserve healthy memory and thinking function. And, in order to develop those new therapies, we need to identify ‘at risk’ individuals now to steer them to clinical trials,” Dr. Petersen added.

Discoveries about biomarkers were matched by a wealth of findings suggesting that diet, exercise and other lifestyle choices can impact one’s risk of Alzheimer’s. Age and family history are known to be the top risk factors for Alzheimer’s disease.

“We can’t do anything about aging or family history, but research continues to show us that there are lifestyle decisions we all can make to keep

our brains healthier and that also may lower our risk of memory decline as we age,” said William Thies, Ph.D., Chief Medical and Scientific Officer at the Alzheimer’s Association, at AAICAD.



Biomarkers

Alzheimer’s disease biomarkers were one of the highest profile areas of research discovery in 2009. The Alzheimer science community believes that disease-modifying drugs will likely be most effective when given in the very early stages of the disease and that biomarkers will play an important role in determining which individuals should receive these drugs.

Biomarkers identified through imaging techniques and analysis of cerebrospinal fluid (CSF) gained particular attention in 2009, but were joined by coverage of other biomarkers as well.

To facilitate the identification of Alzheimer biomarkers, UC-San Diego researchers developed a rapid, automated method for measuring the volume of very specific sub-regions of the brain. The method, used in combination with magnetic resonance imaging (MRI), showed that the volume of the entorhinal cortex was especially susceptible to change in the early stages of the disease and that it may be a better biomarker of Alzheimer’s than

overall brain atrophy. The study involved data from 600 individuals participating in the Alzheimer’s Disease Neuroimaging Initiative (ADNI).

ADNI volunteers have also been instrumental in understanding whether levels of beta-amyloid and tau in CSF are biomarkers of Alzheimer’s disease. University of Pennsylvania researchers tested CSF from 410 ADNI volunteers and found that those with MCI and Alzheimer’s had higher concentrations of tau and lower concentrations of beta-amyloid as the disease progressed. Levels of beta-amyloid in CSF were 96 percent accurate in detecting Alzheimer’s among those whose Alzheimer’s was

confirmed on autopsy. CSF levels accurately predicted conversion from MCI to Alzheimer's in 82 percent of cases.

European researchers studying CSF samples from 168 volunteers from seven countries found that those with low beta-amyloid and high tau levels in CSF had 27 times the risk of cognitive deterioration



as those without this CSF pattern. The pattern was present in all individuals with MCI who went on to develop Alzheimer's.

A study conducted in the United States and Europe backed up the potential effectiveness of CSF as a biomarker for Alzheimer's. The study involved 750 people with MCI, 529 with Alzheimer's, and 304 without these conditions. During follow-up, 271 individuals with MCI developed Alzheimer's and demonstrated an "Alzheimer's pattern" of CSF levels at baseline: low levels of beta-amyloid and high levels of phosphorylated tau and total tau.

At AAICAD, U.S. researchers presented data from a study of 85 ADNI participants with MCI that examined the potential role of a variety of biomarkers in predicting progression from MCI to Alzheimer's. Of all potential biomarkers tested, glucose metabolism in the brain as measured by positron emission tomography (PET) scans and performance on a memory recall test called the Auditory-Verbal Learning Test most accurately predicted progression from MCI to Alzheimer's. Individuals with low glucose metabolism in the brain and poor performance on the memory test had a 15-fold increased risk of developing Alzheimer's in two years.

Using data from the Nurses' Health Study, investigators at Brigham and Women's Hospital, Boston, examined whether the ratio of beta-amyloid 1-40 to beta-amyloid 1-42 in plasma influenced the risk of developing Alzheimer's. They determined the ratio in mid-life (mean age, 63) and 10 years later for the 481 study participants. A high ratio in mid-life was associated with worse late-life cognitive decline, and a greater increase in the ratio over time was associated with faster cognitive decline.

PET combined with the tracer element Pittsburgh Compound B (PIB) provided some of the earliest evidence of potential biomarkers for Alzheimer's, and the imaging method continues to be influential. In two studies from Washington University, St. Louis, researchers found that high levels of beta-amyloid in the brains of healthy individuals are associated with a greater risk for developing Alzheimer's, loss of brain volume and declines in cognitive function.

Non-Biomarker Techniques for Early Detection

Advances were also made in non-biomarker techniques for early detection of Alzheimer's and other dementias.

Researchers examining data from 3,375 people aged 65 and older in the Cardiovascular Health Study found that after six years 480 had developed dementia. When the study began, researchers gathered data on the participants. Based on these data and which individuals went on to develop

Investigators following 444 individuals for an average of six years found that those who developed Alzheimer's experienced a decline in visuospatial skill three years before diagnosis.

dementia, the researchers created a 15-point scale to determine risk of developing dementia. People who scored eight points or more on the scale were at high risk of developing dementia. In addition to known risk factors such as older age and having the APOE-e4 gene, individuals who were underweight, did not drink alcohol, had undergone coronary bypass surgery and were slow at physical tasks such as buttoning a shirt were more likely to develop dementia. The scale was 88 percent accurate in identifying those who developed dementia.

Scientists in Britain developed a cognitive test that accurately detected 93 percent of people with Alzheimer's in a study of 540 healthy individuals and 139 with Alzheimer's or MCI. The test measured performance on 10 tasks, including ability to copy a

sentence and perform calculations and tasks that tested verbal fluency and recall ability. Healthy individuals had an average score of 47 out of 50, while those with Alzheimer's had an average score of 33.

While memory loss is often one of the first symptoms of Alzheimer's, investigators following 444 individuals for an average of six years found that those who developed Alzheimer's experienced a decline in visuospatial skill three years before diagnosis. Overall cognitive ability declined two years before diagnosis. Verbal and working memory declined just one year before diagnosis, suggesting that visuospatial skills may be an earlier indicator of cognitive decline than memory loss.

Modifiable Risk Factors

In addition to making significant contributions to the body of knowledge regarding early detection, researchers in 2009 shared study results reinforcing the association between lifestyle factors and the risk of developing dementia.

While some Alzheimer risk factors, such as genetic make-up, cannot be changed, lifestyle factors can be modified, and these modifications could lead to more years of healthy brain function.

Physical Activity

In a high-profile study commissioned by the National Football League, University of Michigan scientists found that former football players had rates of dementia, Alzheimer's and other memory-related diseases that were up to 19 times higher than national norms. Scientists conducted telephone surveys of 1,063 retired players who had played for at least three seasons. Among players age 50 or older, 6.1 percent reporting receiving a dementia-related diagnosis, five times higher than the national average. Among players ages 30 through 49, 1.2 percent reported receiving such a diagnosis, 19 times the national average. These data contribute to research linking serious head injury with an increased risk of dementia.

While physical activity in general is known to benefit both the heart and the brain, little research

has focused on the association between brain health and muscle strength in particular. To shed light on this, researchers measured the arm, leg, and abdominal strength of 970 people ages 54 to 100. Those who ranked in the top 10 percent for muscle strength were 61 percent less likely to develop Alzheimer's than those who ranked in the lowest 10 percent. The mental abilities of stronger individuals also declined at a slower rate over time.

The *Journal of the American Medical Association* reported that exercise, combined with a healthy

Researchers found that residents who were very physically active had a 33 percent lower risk of developing Alzheimer's than sedentary residents.

diet, was especially effective in lowering one's risk of developing Alzheimer's. The report was based on a study of 1,880 elderly New York City residents followed for five years. Researchers found that residents who were very physically active (1.3 hours a week of vigorous activity such as jogging or 4 hours a week of light exercise such as walking) had a 33 percent lower risk of developing Alzheimer's than sedentary residents. Residents who most often adhered to a Mediterranean diet rich in fruits, vegetables, cereal and fish but low in meat and dairy foods had a 40 percent lower risk than individuals who less frequently followed such a diet. The overall risk of developing Alzheimer's was 9 percent for those who were very active and followed a healthy diet, compared with 21 percent for those who were least active and less diet-conscious.



Diet

Another type of healthy diet called DASH (Dietary Approaches to Stop Hypertension) is similar to the Mediterranean diet and was associated with better cognitive function in a study of more than 3,800 people age 65 or older. Over the 11 years of the study, study participants' diets were scored at four different times. Scores were based on their consumption of fruits, vegetables, whole grains, low-fat dairy foods and fish (all recommended), as well as sodium, sweets and non-fish meat (recommended in limited amounts). The higher the DASH diet score, the more closely participants adhered to the diet. Investigators found that the higher the DASH score, the higher the participants' scores for cognitive function at the start of the study and over time. Four of the food groups—vegetables, whole grains, low-fat dairy food, and nuts/legumes—were independently associated with higher scores on the Modified Mini-Mental State Examination.

Drinking any amount of alcohol, be it small or large, was associated with faster cognitive decline in people with MCI.

DHA, an omega-3 fatty acid found in fish and other foods, has been the subject of much research over the years for its potential effect on Alzheimer's. In two studies reported at AAICAD 2009, researchers said that DHA did not slow memory decline over 18 months in 402 people with mild to moderate Alzheimer's, but that among 485 people with mild memory complaints, those who took a DHA supplement performed better on a computer memory test

after six months than those receiving a placebo. However, more data are needed before taking a DHA supplement can be recommended.

Like DHA supplementation, alcohol consumption is a topic of wide interest in terms of its potential impact on Alzheimer's. In a six-year study of more than 3,000 people aged 75 and older, researchers found that drinking one or two alcoholic beverages daily was associated with a 37 percent lower risk of developing dementia, but that individuals consuming more than 14 alcoholic beverages per week were twice as likely to develop dementia. Drinking any amount of alcohol, be it small or large, was associated with faster cognitive decline in people with MCI.

Co-existing Health Conditions

Diet is often a contributor to health conditions that previous studies have shown increase the risk of developing Alzheimer's. Results of large-scale studies published in 2009 add to the growing evidence of diabetes, high cholesterol and high blood pressure as risk factors for Alzheimer's. For example, a study supported in part by a grant from the **Alzheimer's Association** found that among 13,000 twins, those who developed diabetes before age 65 had a 125 percent increased risk of Alzheimer's disease. Twin studies are valuable in that they enable researchers to eliminate genetic differences that might cause disease.

Data from nearly 20,000 participants in the Reasons for Geographic and Racial Differences in Stroke study served as the basis for an evaluation of the role of blood pressure on brain function. In these participants, all age 45 or older, the higher one's blood pressure, the greater one's chances of having

cognitive impairment. In fact, with each 10-point increase in diastolic blood pressure, the chance of cognitive impairment increased 7 percent. Diastolic blood pressure measures the force on arteries



when the heart is at rest. When diastolic blood pressure rises, it can cause thickening of the arterial walls in the brain, decreasing blood flow. Systolic blood pressure, the force on arteries when the heart contracts, wasn't associated with impaired brain function.

In a remarkably long four-decade study of nearly 10,000 individuals who were followed beginning in their 40s, researchers found that high cholesterol (240 mg/dL or higher) in midlife is correlated with a 66 percent increased risk of Alzheimer's disease

People with metabolic syndrome, a condition that is characterized by several heart disease risk factors including high blood pressure and low levels of good cholesterol, are at higher risk of developing Alzheimer's.

later in life. Borderline high cholesterol (200 to 239 mg/dL) was correlated with a 52 percent increased risk. The results are another reminder that midlife health can foreshadow health in one's later years and that taking action on modifiable risk factors such as high cholesterol may have significant rewards in decades to come.

Likewise, people with metabolic syndrome, a condition that is characterized by several heart disease risk factors including high blood pressure and low levels of good cholesterol, are at higher risk of developing Alzheimer's, according to researchers. In a four-year study of nearly 5,000 women with an average age of 66, 36 percent of women with metabolic syndrome developed cognitive impairment, compared with just 4 percent of women without metabolic syndrome.

Post-traumatic stress disorder (PTSD) is a health condition that has gained increased attention over the years, and researchers in 2009 showed that PTSD is associated with a higher risk of dementia. They studied more than 180,000 veterans aged 55 and older over seven years and found that the rate of new cases of dementia was 10.6 percent in those with PTSD compared with 6.6 percent in those without. Results were similar when those with histories of traumatic brain injury, substance abuse and depression were excluded. Researchers note that much more research is needed to understand the link between dementia and PTSD but that evidence such as this underscores the importance of physicians paying particular attention to early signs of dementia in patients with PTSD.

Other Risk Factors

Smoking is a known risk factor for Alzheimer's disease, but is second-hand smoke a risk factor too? To find out, investigators tested saliva samples from 4,800 nonsmokers age 50 and older for levels of cotinine, a product of nicotine that stays in the

saliva for about a day after exposure to smoke. Investigators found that people with the highest levels of cotinine had a 44 percent higher risk of cognitive impairment than people with the lowest scores and that impaired cognitive function increased with the amount of exposure to second-hand smoke. The findings underscore the importance of limiting one's exposure to smoke in maintaining brain health.

Numerous studies have suggested that completing more years of formal education produces a "cognitive reserve" that delays the onset of Alzheimer symptoms. But does this cognitive reserve affect the rate at which one's cognitive abilities decline once symptoms are present? Different studies have had varying answers to that question. Research conducted in 2009 involving 6,500 individuals age

72 and older suggests that it does not. Study participants' education levels ranged from eight or fewer years of schooling to 16 or more. Their memory and thinking skills were measured every

Researchers in 2009 showed that post-traumatic stress disorder is associated with a higher risk of dementia.

three years. While those with more years of education performed better on tests at the beginning of the study, once they started having memory problems their rate of cognitive decline was no slower than that of individuals with fewer years of education.

Genetic Risk Factors

Researchers believe that people develop Alzheimer's disease as the result of a combination of different factors, including genetic, lifestyle and environmental factors.

Mutations in three genes guarantee that individuals will develop Alzheimer's, but only a very small percentage of individuals with Alzheimer's (1–5 percent) carry these genes. The e4 form of the gene apolipoprotein E (APOE-e4) is carried by about 25 percent of individuals and increases the risk of developing Alzheimer's, but does not guarantee that individuals will develop the disease. Aware that genetics plays a role in Alzheimer's, researchers continue to study genetic variations and their association with Alzheimer's to better understand the disease and to identify factors that might aid in early detection.

Mayo Clinic researchers reported in the journal *Nature Genetics* the discovery of the first sex-specific gene that increases one's risk of Alzheimer's disease. Located on the X chromosome, PCDH11X

is a common gene that exerts its influence most strongly when a woman inherits it from both parents. Examining genetic data from 2,400 people with Alzheimer's and 3,800 without, they found that women with Alzheimer's disease were twice as likely to have two copies of the gene as women in the control group. Inheriting just one copy of the gene also increased one's risk, but to a smaller extent than having two. Researchers noted that the discovery does not necessarily mean women are at higher risk than men, as yet-undiscovered male-specific genetic risk factors may exist.

Pooling DNA data for 16,000 people across Europe and the United States, scientists identified three potential new genetic risk factors for late-onset Alzheimer's: variants of the genes PICALM, CLU and CR1. This was the largest genome-wide association

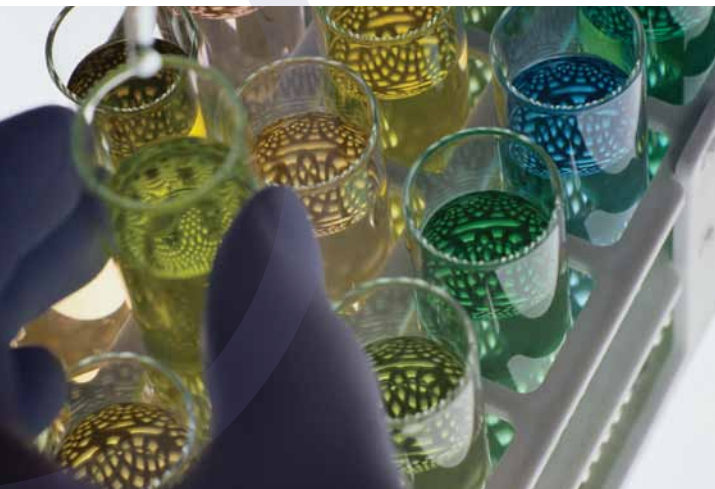
study reported to date for Alzheimer's. Genome-wide association studies aim to identify genetic associations with a disease by studying the DNA on all of the chromosomes in a specific population. PICALM is located on chromosome 11, CLU on chromosome 8 and CR1 on chromosome 1. These

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genes normally have helpful functions in the brain. CLU is thought to suppress the deposition of beta-amyloid, PICALM is believed to help keep synapses healthy, and CR1 may help remove beta-amyloid from the brain. However, the newly reported variants of these genes appear to have negative effects on the brain, with further research needed to understand how they might act to increase Alzheimer risk.

In a family carrying the mutant gene A673V, Italian researchers found that those carrying two copies of the gene were destined to develop Alzheimer's

while those with one copy or no copies of the gene did not develop the disease. The gene is the first recessive genetic trait found for Alzheimer's, meaning that two copies of the gene must be inherited for the disease to develop. Scientists studied cells from family members with zero, one or two copies of A673V, with fascinating results. While cells with two copies of the mutation produced more beta-amyloid, and the beta-amyloid was more likely to clump together, cells with one copy of A673V produced less beta-amyloid clumps than cells with no copies of A673V.



Drug Pipeline

Each year brings a remarkable growth in knowledge of Alzheimer's disease, and clinical trials of new drugs are essential to expanding that knowledge and identifying improved treatments.

Randy Nixon, Ph.D., professor of psychiatry and cell biology at New York University and vice chair of the Association's Medical and Scientific Advisory Council, remarked at AAICAD 2009, "There are currently dozens of drugs in Phase II and III clinical trials for Alzheimer's. This, combined with advancements in diagnostic tools, has the potential to change the landscape of Alzheimer's in our lifetime." Results of numerous Phase II and Phase III studies made headlines in 2009.

Docosahexaenoic acid (DHA), the most abundant omega-three fatty acid in the brain, has been of interest as a treatment for Alzheimer's for some time. Results of two studies presented at AAICAD 2009 showed that DHA did not slow cognitive decline in people with mild or moderate Alzheimer's but was associated with improved performance on a memory test in volunteers with mild memory complaints. "These two studies—and other recent Alzheimer's therapy trials—raise the possibility that treatments for Alzheimer's must be given very early in the disease for them to be truly effective," said William Thies, PhD., chief medical and scientific officer at the Alzheimer's Association.

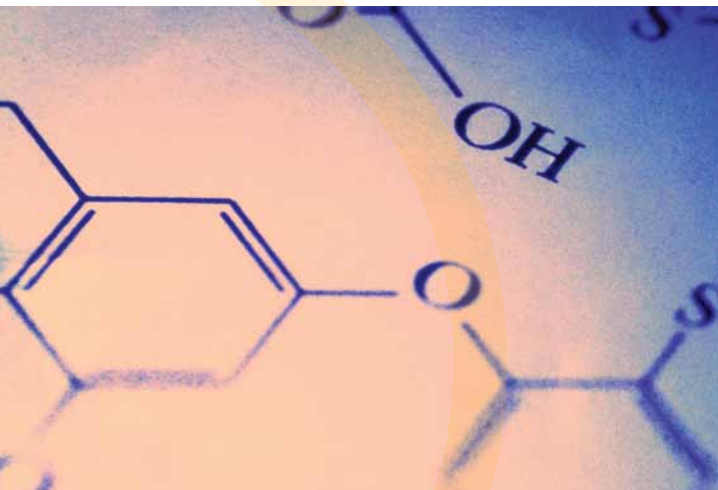
The larger of the two trials, funded by the National Institute on Aging, lasted 18 months and involved 402 people with Alzheimer's at 51 sites across the United States who received either a placebo or 2 grams of DHA daily. While DHA levels in the brain increased in the treatment group, it did not slow the rate of change on tests of mental function, dementia severity, activities of daily living or behavioral symptoms. Interestingly, it did slow the rate of decline on a mental function test in those with the APOE-e4 gene. "One of the issues raised by this study—and other recent Alzheimer's and mild cognitive impairment therapy trials—concerns a

possible interaction between certain therapies and genetic status. This issue needs to be explored more completely in future trials," Dr. Thies added.

The smaller of the two studies lasted six months and involved 485 older people who received either placebo or 900 milligrams of DHA daily. Volunteers' performance on a visuospatial memory test was measured at the beginning and end of the study. Those who received DHA made significantly fewer errors on the test at the end of the study than those who did not.

Beta-amyloid is a protein that is the main constituent of amyloid plaques found in the brains of people with Alzheimer's disease.

While Phase III clinical trials of dimebolin (Dimebon®) were under way in 2009, researchers shared results of a study aimed at shedding light on how the drug appeared to stabilize function in people with mild or moderate Alzheimer's who participated in earlier studies. Researchers conducted experiments in cells and in mouse models of Alzheimer's to assess the effects of dimebolin on beta-amyloid and other brain proteins known to be related to Alzheimer's disease. Beta-amyloid is a protein that is the main constituent of amyloid plaques found in the brains of people with Alzheimer's disease. It is widely considered a key player in the development and progression of Alzheimer's. The goal of anti-amyloid drugs in clinical trials is to reduce beta-amyloid levels in the brain. In a surprising result, researchers found that treatment with dimebolin caused an acute increase



in brain beta-amyloid levels in mice. “This result is highly unexpected in what may prove to be a clinically beneficial Alzheimer’s drug,” said one of the researchers. “We need more research to further clarify how dimebolin affects beta-amyloid levels in the brain.”

The makers of bapineuzumab, an Alzheimer vaccine designed to reduce levels of beta-amyloid in the brain, announced that the highest dose of the drug would be dropped from two Phase III clinical trials due to increased risk of vasogenic edema, a type of brain swelling caused by accumulation of water in brain tissue. The 0.5 mg/kg and 1.0 mg/kg doses in these two trials will continue as planned. The trials involve people with mild or moderate Alzheimer’s who do not have the APOE-e4 gene. The decision had no impact on two other ongoing studies testing a single 0.5 mg/kg dose of bapineuzumab in APOE-e4 carriers. The Phase III program for

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The two highest doses of ELND005, an Alzheimer drug from the makers of bapineuzumab, were dropped from a Phase II trial due to serious adverse events including an increased number of deaths in those receiving the highest doses. Nine deaths were reported in the groups receiving 1,000 mg or 2,000 mg twice daily. The Phase II trial enrolled approximately 353 patients with mild to moderate AD, who were divided into three treatment groups and one placebo group. ELND005 is designed to reduce deposits of beta-amyloid in the brain by preventing the formation of beta-amyloid oligomers, which recent research has shown may be the most toxic form of beta-amyloid.

Care for People with Dementia

Until new therapies to slow or stop the progression of Alzheimer’s disease are developed, more than 5 million Americans with Alzheimer’s will continue to require assistance from family or other caregivers to cope with the symptoms and declining function brought on by the disease.

The challenges experienced by people with the disease and their caregivers and physicians is an area of expanding investigation by the scientific community.

A study conducted in Australia involving 289 people with dementia aged 60 and older found that those whose care was person-centered and based on dementia-care mapping had less agitation when the study ended and four months after the study. Person-centered care makes the person with dementia a central part of care-planning and focuses on their individual needs. Dementia-care mapping is a tool to improve person-centered care that scores factors related to the individual’s well-being, such as enjoyment of eating, touching and interacting. While training in dementia-care mapping is expensive and labor-intensive, training in person-centered care is quickly taught and one-fourth the cost of dementia-care mapping. The authors suggest that patient-centered approaches to care be standard practice in residential care homes.

Death rates for individuals with Alzheimer’s who receive antipsychotic medication are significantly higher than for individuals who do not take this medication, reinforcing the guideline that the medication only be used as a last resort and for as short a period as possible. In a three-year study, 128 people with Alzheimer’s were assigned to either continue to receive one of several antipsychotic medications or to be switched to a placebo. At the end of the study, the risk of death was 42 percent lower among those on the placebo. After two years’ follow-up, 46 percent of those taking antipsychotics were alive, compared with 71 percent of those taking a placebo. After three years, 30 percent of

people receiving antipsychotics were alive, compared with 59 percent of those on placebo.

Half of family caregivers admitted to abusive behavior while caring for an individual with dementia, according to an article in the *British Medical Journal*. Of 220 caregivers surveyed, 52 percent reported occasionally screaming or yelling at the individual, 33 percent reported “significant” abuse such as frequently insulting or swearing at the individual, and 1 percent (3 caregivers) reported physically abusing a family member. As dementia progresses, individuals can become aggressive, and in some cases caregivers were reacting to being the subject of aggressive behavior. Some caregivers wished that physicians had asked them how they were coping with being a caregiver and said this might help prevent abusive behaviors.

Dementia-care mapping is a tool to improve person-centered care that scores factors related to the individual’s well-being, such as enjoyment of eating, touching and interacting.

While the study highlights the fact that it’s not paid caregivers alone who abuse vulnerable individuals, it also highlights the need for increased support services for caregivers.

Up to one-third of individuals with severe dementia receive nutrition via a feeding tube, yet a review of seven studies involving 409 such individuals found

that there was not significant evidence that feeding tube use increased survival or improved quality of life. Because individuals at this stage of dementia are unable to give informed consent, they often continue to receive tube feeding. The researchers highlighted the importance of individuals with dementia having advance directives to prevent what may be unwanted use of a feeding tube at this stage of their illness.

While cholinesterase inhibitors can temporarily help improve the memories of those with Alzheimer's disease, they do come with risks, one of them being an increased risk of fainting caused by slowed heart rates. Researchers used healthcare databases in Ontario, Canada, to identify nearly 20,000 people with dementia who were receiving cholinesterase inhibitors and 61,000 who were not and found that those taking the medications were almost twice as likely to be hospitalized for fainting. They were also 49 percent more likely to have a pacemaker implanted and 18 percent more likely to suffer hip fracture. The researchers said the study served as reminder that the benefits of cholinesterase inhibitors should be carefully weighed against their risks before being prescribed.



Individuals with Alzheimer's who are hospitalized may experience delirium as a result of a change in environment and daily routines, and according to scientists, the delirium may have unexpectedly serious consequences. The scientists studied 400 people with Alzheimer's over 15 years and found

that the rate of cognitive decline in those with an episode of delirium during hospitalization was three times that of those who had not experienced delirium. They noted that up to 40 percent of delirium episodes can be prevented by measures such as telling individuals that they are in the

Higher rates of emotional closeness were associated with significantly slower cognitive and functional decline.

hospital so they are better oriented to their surroundings, allowing as much uninterrupted sleep as possible and avoiding unnecessary medications.

To better understand the effect of emotional closeness between caregivers and individuals with Alzheimer's disease, researchers studied 167 people with Alzheimer's and their caregivers every six months for up to four years. Those with Alzheimer's underwent physical, cognitive and functional tests, while caregivers were interviewed and completed a survey in which they were asked to rate their degree of emotional closeness to the individual with Alzheimer's. Researchers found that higher rates of emotional closeness were associated with significantly slower cognitive and functional decline and that the effect was similar to that of some of the cholinesterase inhibitors used to treat Alzheimer symptoms. More research is needed to understand the "closeness effect," but one of the investigators said it was possible that feelings of closeness result in caregivers being more attentive to the individual's needs and more likely to encourage them to participate in cognitively and socially stimulating activities that promote cognitive and functional health.

Basic Science Discoveries

Basic science discoveries form the foundation of advances in medicine. Advances in Alzheimer’s disease are no exception. Our understanding of the roles of beta-amyloid, tau and the amyloid precursor protein (APP) in the development of Alzheimer’s has evolved from science discoveries made in the lab. Likewise, science discoveries made in the lab hold the key to developing new treatments for Alzheimer’s disease and other dementias.

The plaques that characterize Alzheimer’s begin as individual fragments of APP called beta-amyloid 1-42 that clump together and go on to impede the functioning of synapses in the brain. In 2009, U.S. researchers studying why some nerve cells self-destruct during normal embryonic development discovered that a second APP fragment, N-APP, was a key part of the programmed cell death that occurs. They believe that the mechanism that causes excess nerves to be destroyed as the brain and spinal cord develop, a process that is supposed to stop early in life, may be turned on in Alzheimer’s, killing healthy brain cells. The researchers were able to block nerve destruction in human embryonic cells. The next step is to find out if the process can be stopped in adult brain cells. If successful, the method used to stop cell destruction could be tested as a potential new treatment for Alzheimer’s.

In a surprising discovery, investigators reported in the journal *Nature Neuroscience* that nerve cells in the brain make a form of collagen called collagen VI and that collagen VI attempts to protect nerve cells from the toxic effects of beta-amyloid. This may help explain why levels of collagen VI are increased in the brains of people with Alzheimer’s. Looking more closely, they found that small clusters of beta-amyloid called oligomers (which are much smaller than beta-amyloid plaques and are believed by many to be more toxic than plaques) bind to vulnerable neurons in the brain, but that collagen VI interrupts that binding and may help move the oligomers away from the neurons. If the role of collagen VI in cell models of Alzheimer’s is borne

out in more advanced models, collagen VI could prove to be a new weapon against Alzheimer’s disease.

Astrocytes, star-shaped nervous system cells that make up about half the volume of the brain, typically support normal brain function. However, researchers at the MassGeneral Institute for Neurodegenerative Disease in Boston found that



the beta-amyloid plaques of Alzheimer’s activate the astrocyte network in the brain and may cause the harmful effects of beta-amyloid to be spread cell by cell in waves to distant parts of the brain. Researchers are now trying to determine whether increased astrocyte signaling harms brain cells or may actually be an effort by the body to protect brain cells.

Researchers have known for some time that clusters of beta-amyloid contribute to the nerve cell damage that leads to Alzheimer’s. However, they haven’t always understood which clusters were most harmful: the large clusters called plaques, the small clusters called oligomers, or clusters somewhere between.



Recent studies have suggested that oligomers are most toxic, and in 2009 researchers at UCLA narrowed in on exactly how toxic they are. The researchers created beta-amyloid clusters in the lab that exactly matched those that form in the brains of people with Alzheimer's. They found that toxicity increases dramatically as the clusters grow from two to three or four beta-amyloid molecules. Clusters consisting of two molecules are three times as toxic as one-molecule clusters, and three- and four-molecule clusters are more than 10 times as toxic as one-molecule clusters. Detailed study of the atomic structure of these clusters will make development of anti-toxicity drugs much easier and likely more successful, said researchers.

The **Alzheimer's Association** played a key role in funding research showing that inhibiting a protein called heat-shock protein 70 (Hsp70) reduces levels of hyperphosphorylated tau in the brain. Hyperphosphorylated tau disrupts the movement of nutrients in brain nerve cells and threatens the very structure of nerve cells. Hsp70 is a "chaperone" protein that guides the activity of tau inside cells. The researchers originally thought that activating Hsp70 would cause the protein to remove hyperphosphorylated tau. However, instead of attaching to tau and removing it, Hsp70 attached to tau and continued to hold on to it, allowing it to accumulate

inside cells. Researchers are now working to identify a compound to effectively inhibit Hsp70 that could be tested as a treatment for Alzheimer's.

Research on the role of brain-derived neurotrophic factor (BDNF) was a focus of attention in 2009. In February, **Alzheimer's Association**-funded researchers reported in *Nature Medicine* that injecting the BDNF gene or protein slowed and even stopped the progression of Alzheimer's disease in animal models. BDNF is produced in the entorhinal cortex, which is involved in memory. Alzheimer's disease affects the entorhinal cortex and is associated with decreased production of BDNF. In September, a second group of researchers found that injection of neural stem cells into the brain in animal models of the disease resulted in improved performance in memory tests. The stem cells secreted BDNF,

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which caused existing tissue to sprout new neurites, strengthening and increasing the number of connections between neurons. The discovery gives researchers hope that stem cells or a derivative of them, such as BDNF, may one day be used to treat Alzheimer's.