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ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE

ADNIExclusive

A Special Newsletter for Participants in the Alzheimer's Disease Neuroimaging Initiative

Summer 2013

Dear Friends and Fellow Trialists:

Michael Weiner, M.D.
Fellow Participant & ADNI Principal Investigator

There is a lot happening in AD research – and specifically in relation to ADNI – however I'd like to address first things first: I am pleased to report to you that ADNI 2 is fully enrolled as of July 2013.

Many thanks to all of you who suggested a friend or family member consider enrolling in ADNI. As you may know, we keep track of how participants get to ADNI. It was interesting to learn recently that a significant number of new ADNI enrollees found their way to the study via a current ADNI participant.

As a participant, you made this study milestone happen by enrolling in ADNI 2. I hope my letters to you give you some idea of the invaluable contribution you are making to the advancement of AD research through participation in ADNI. Along those lines, I'd like to report and to discuss some of the AD research discoveries and news that is a direct result of, or directly related to, our work in ADNI.

ADNI WGS Available to Scientists Worldwide

Last year I wrote about the ADNI whole genome sequencing (WGS) project. You may recall that WGS' represents all six billion letters in an individual's DNA in one comprehensive analysis. In July, at the annual Alzheimer's

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For more information email us at
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ADNI Results: Duke Team Finds Silent AD Pathology Occurs Earlier and More Often in First Degree Relatives

Earlier this year, Murali Doraiswamy, MD and colleagues at Duke University Medical Center reported that people who have close family diagnosed with late-onset AD are much more likely to develop silent buildup of brain plaques associated with the disease.

Using ADNI data, the study confirms earlier findings on a known genetic variation that increases one's risk for Alzheimer's, and raises new questions about other genetic factors involved in the disease that have yet to be identified.

Family history is a known risk factor and predictor of late-onset Alzheimer's disease, and studies suggest a two- to four-fold greater risk for Alzheimer's in individuals with a mother, father, brother or sister who develop the disease. These first-degree relatives share roughly 50 percent of their genes with another member of their family. Common genetic variations, including changes to the APOE gene, account for around 50 percent of the heritability of Alzheimer's, but the disease's other genetic roots are still unexplained.

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Michael W. Weiner, MD (continued from page 1)

Disease International Conference (AAIC), we announced availability of the massive ADNI WGS dataset to researchers worldwide.

ADNI WGS represents the first "Big Data" project for Alzheimer's disease. The addition of the ADNI WGS is expected to advance existing research strategies and to result in the development of new approaches in AD therapeutics. With the ongoing support of our federal, academic, and private partners, ADNI will continue to be a leader in open data sharing for qualified scientists around the world.

...'subjective cognitive decline' will likely play an important role in identifying patients before reaching the MCI stage of the disease and ADNI will provide the roadmap.

Mining the Historic ADNI Genetic Data

Prior to ADNI WGS, we were already looking at a "snippet" of ADNI participant genetic information. The ADNI "snippets" of genetic data have been available to researchers for a couple of years and provide a window into AD genetics.

You may recall that people who are carriers of the APOE4 gene are at higher risk for Alzheimer's disease. In a paper published in the journal Nature in July 2013, researchers report key molecular pathways inside neurons that are altered by the presence of APOE4. The researchers applied big data mining techniques to snippets of genetic data from ADNI to look for patterns in changes in gene activity in 100 ADNI people without cognitive impairment who carried APOE4 genes and 100 ADNI people without impairment who did not carry the APOE4 gene.

The research team reported changes in the expression of 215 genes between carriers and non-carriers of APOE4. Out of those, they identified 20 that appeared to be "master regulators" of key reactions inside neurons. Two of those genes, SV2A and RNF219, appear to change how they function depending on the person's APOE4 status.

Apolipoprotein E, or APOE, is a molecule that transports cholesterol out of the brain. There are three major forms of this cholesterol carrier – APOE2, APOE3 and APOE4. People who make APOE4 are at increased risk for Alzheimer's disease, people who make APOE3 have a neutral or intermediate risk, and people who make APOE2 appear to be at lower risk for developing the disease.

One implication of this work is that different genetic forms or subtypes of Alzheimer's disease may have specific underlying mechanisms, and therefore respond differently to medications. More research is needed to confirm these results, but this paper represents a major step in applying genetic research and data mining techniques on existing datasets.

I hope to be able to start reporting WGS ADNI findings by this time next year.

Subjective Memory Issues

There is a lot of talk in the AD research world about "subjective memory concerns" or "subjective memory decline" or "subjective memory impairment" and you may be aware of ADNI's new subjective memory concern (SMC) cohort which opened to enrollment earlier this year. There is mounting evidence that healthy people who self-report that their memory is declining, sometimes referred to as 'senior moments,' even when cognitively normal on testing, may already have Alzheimer's-related changes in their brains. These individuals have also been found to more likely to be diagnosed with cognitive impairment down the road.

The ADNI SMC is designed to determine what is happening with AD biomarkers in older individuals who report memory impairment too subtle to be measured by current cognitive

tests used in the majority of AD clinical trials. The key aspect is that there is a sense that one's memory is declining, rather than an occasional forgotten name or misplaced item.

Over the last several months, various AD researchers reported data showing early memory complaints may be the initial signs of an eventual progressive cognitive decline. Researchers from the University of Kentucky reported results from a study of 531 people, average age 73. Those who reported a change in memory function since their last doctor visit were nearly twice as likely to be diagnosed with dementia or mild cognitive impairment about six to nine years later.

In another study of 3,861 nurses who were at least 70 years old, subjects were asked about memory symptoms and periodically tested for them later. About 900 of the subjects carried the ApoE4 gene. Among the ApoE4 carriers, concern about a single memory symptom predicted future memory decline on tests over the next six years. In the others without the gene, concern about three or more memory symptoms was linked to memory decline on tests.

And, in a study out of Harvard Medical School, researchers found that complaints about memory decline correlated with the amount of beta-amyloid seen on brain scans of 189 ADNI participants 65 and older. This confirmed an earlier study of 131 subjects that also correlated memory complaints to amyloid plaque burden.

Finally, a study of 2,230 mentally healthy Germans found that those who complained of memory problems at age 80 were much more likely to have such problems at age 88 than those without the complaints.

So, cognitively normal people with some types of memory concerns were more likely to have Alzheimer's pathology in their brains. As we try to move earlier and earlier in diagnosing AD in its development, 'subjective cognitive decline' will likely play an important role in identifying patients before reaching the MCI stage of the disease and ADNI will provide the roadmap.

In this Newsletter

In this newsletter we have included a summary of the work of the National Alzheimer's Project Act panel chaired by ADNI Protocol Principal Investigator Ron Petersen, MD from the Mayo Clinic. The NAPA panel is responsible for mapping the AD research agenda and AD-related policy initiatives over the next decade. I think you will be surprised by the scope of issues that need to be addressed if we are to effectively improve AD treatment and care.

There is a also a summary of recent work by Duke ADNI PI P. Murali Doraiswamy, MD and colleagues. Dr. Doraiswamy and his team take a look at family history of AD and its relationship to plaque buildup in the brain.

Finally, Neelum Aggarwahl, MD from the Rush Alzheimer's Disease Research Center provides an analysis of the long-term cognitive impact of estrogen therapy on women. As always, "Dr. A", as her patients call her, provides a straight forward explanation of the important study findings.

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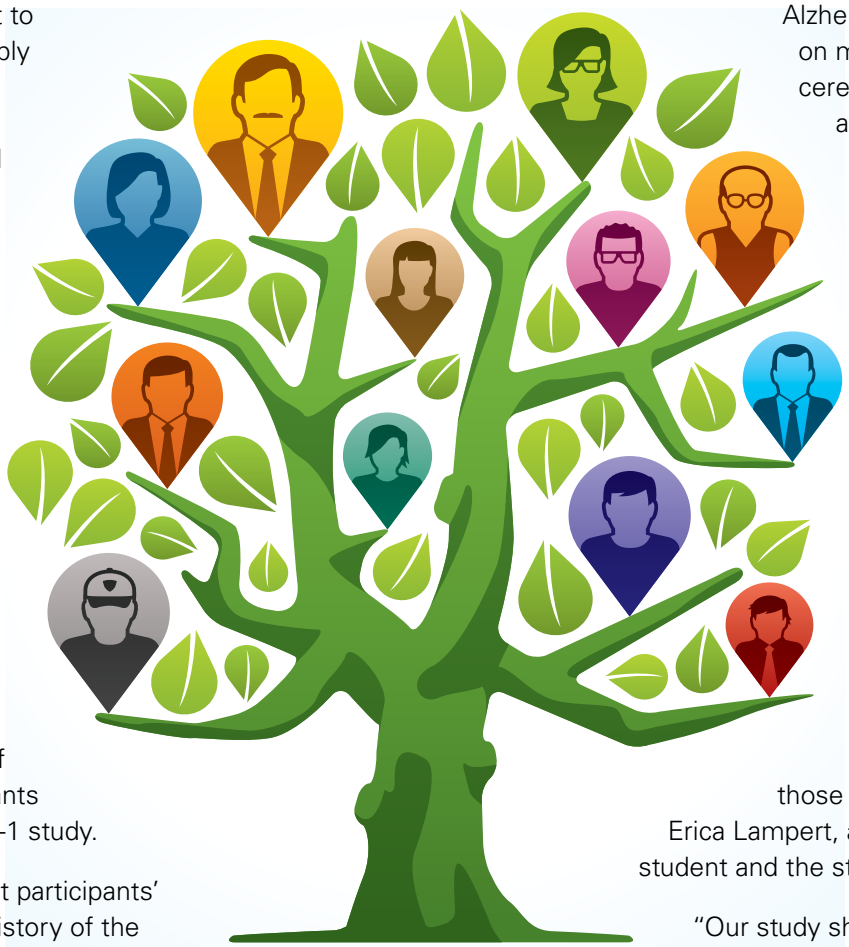
"In this study, we sought to understand whether simply having a positive family history, in otherwise normal or mildly forgetful people, was enough to trigger silent buildup of Alzheimer's plaques and shrinkage of memory centers," said senior author P. Murali Doraiswamy, professor of psychiatry and medicine at Duke.



Duke neuroscience researchers analyzed baseline data from 257 ADNI participants, both cognitively healthy and with varying levels of impairment. The participants were all part of the ADNI-1 study.

The researchers looked at participants' age, gender and family history of the disease, with a positive family history defined as having a parent or sibling with Alzheimer's. This information was compared with cognitive assessments and other biological tests, including APOE genotyping, MRI scans measuring hippocampal volume, and studies of three different pathologic markers (Aß42, t-tau, and t-tau/Aß42 ratio) found in cerebrospinal fluid.

As expected, the researchers found that a variation in the APOE gene associated with a greater risk and earlier onset of Alzheimer's was overrepresented in participants with a family history of the disease. However, other biological differences were also seen in those with a family history, suggesting that unidentified genetic factors may influence the disease's development before the onset of dementia.

Nearly half of all healthy people with a positive family history would have met the criteria for preclinical Alzheimer's disease based on measurements of their cerebrospinal fluid, but only about 20 percent of those without a family history would have met such criteria.

"We already knew that family history increases one's risk for developing Alzheimer's, but we now are showing that people with a positive family history may also have higher levels of Alzheimer's pathology earlier, which could be a reason why they experience a faster cognitive decline than those without a family history," Erica Lampert, a Duke neuroscience student and the study's first author said.

"Our study shows the power of a simple one-minute questionnaire about family history to predict silent brain changes," Doraiswamy said. "In the absence of full understanding of all genetic risks for late-onset Alzheimer's, family history information can serve as a risk stratification tool for prevention research and personalizing care." He encouraged those with a known positive family history to seek out clinical trials specific to preventing the disease.

Lampert EJ et al. Prevalence of Alzheimer Pathologic Endophenotypes in First Degree Relatives. PLoS ONE 2013 Apr 17;8(4):e60747.

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More from the Duke University AD Experts: Keeping the Mind Sharp as We Age

Although there is no sure-fire way to prevent dementia, the ADNI PI and memory expert Murali Doraiswamy, MD, from Duke University, says there are many things you can do to keep your mind sharp as you age: Fertilize it like you would a garden: Studies have shown that mental activities such as working crossword puzzles or playing chess can not only maintain your brain, they can improve its function. Mental activities seem to boost production of nerve growth factors -- sort of a fertilizer for the brain, says Doraiswamy. This keeps your nerve cells more connected, and the more connections one has the more reserve capacity one has to stave off diseases like Alzheimer's.

Cross-train it like an athlete: Beyond your usual sudoku or bridge, look for new activities to cross-train your brain. Your brain will benefit from the workout -- like using muscles that rarely get worked. Learn a new skill or attend a lecture on an unfamiliar topic. Try something you've never done before – learn something new or perform a routine activity in a different way.

Treat it like a teenager: let it hang out with friends -- and sleep in. Be a social butterfly and avoid being isolated. Your brain likes being around people. It also uses sleep as valuable time for turning experiences into memories, so don't skimp on shut-eye. In fact, chronic sleep deprivation can cause Alzheimer's-like symptoms.

Indulge its cravings: The brain's favorite foods are the same as the heart's favorite foods: richly colored fruits and vegetables and omega-3 fatty acids. The best bets in terms of nutritional supplements are B vitamins, folic acid, and fish oil. Your brain also craves a good aerobic workout, which stimulates blood flow, enhances levels of brain-healthy chemicals, and improves stress, depression, and sleep -- a triple treat for the brain.

Know its limits: Don't stress it. While excess cholesterol is probably as bad for your head as it is for your heart, stress is the ultimate enemy of brain function. In addition to aerobic exercise, yoga, meditation, and mindfulness can help you worry less and be happy more. "The brain likes optimism," says Doraiswamy.

Dr. Doraiswamy teamed with Lisa P. Gwyther, MSW, founder and director of the Alzheimer's Family Support Program at the Duke University Center for Aging, to co-author the book The Alzheimer's Action Plan. The tips contained in the text are adapted from the book and this summary is printed with permission from Duke Medicine News and Communications.

Estrogen Therapy Has No Long-term Effect on Cognition in Women

NEELUM T. AGGARWAL, MD
Steering Committee Member, ADCS
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A high-profile article in the JAMA this summer examined whether estrogen hormone therapy in post-menopausal women, aged 50-55 years, had long term effects on cognitive function. The study included post-menopausal women from the Women's Health Initiative study, who had begun treatment in the two randomized, placebo-controlled, clinical trials of hormone therapy when they were aged 50-55 years.

A total of 1,326 women, enrolled in the study, had a mean range follow up of seven years (3.9-10 years). Cognitive function was measured by the telephone-administered Telephone Interview for Cognitive Status – modified (TICS-m). The TICS-m assessed a variety of cognitive functions, namely, immediate and delayed verbal memory, attention and executive function, verbal fluency and working memory.

no overall long term benefit or long term harm was found for women who underwent CEE therapy

Overall, there was no difference in the mean scores on cognitive tests between women who had been assigned to the active or placebo groups and were consistent between the groups who received conjugated estrogen (CEE) and medroxyprogesterone acetate (MPA). Assignment to the CEE group, demonstrated slightly lower scores on verbal fluency, with CEE + MPA showing slightly better scores. Adherence to medication and overall exposure to medication were weakly correlated with higher executive function but did not have any relation to the size of the treatment effect for any measure of cognitive function.

The findings from this study, suggest that for cognitive function, no overall long term benefit or long term harm was found for women who underwent CEE therapy. These findings add to the literature on women that has found a variety of findings across the spectrum: with verbal fluency improved, harmed or unchanged by hormone therapy. Higher levels of endogenous estrogens have also been associated with greater declines in verbal fluency in older women.

So what does this mean? Results from this study suggest no adverse long term effect on cognitive function of prescribing CEE-based medications to younger, post menopausal women.

The National Alzheimer's Plan Update

ADNI Protocol Principal Investigator Ron Petersen, MD, PhD from the Mayo Clinic is the chairman of the federal advisory panel for the National Alzheimer's Project Act (NAPA). Dr. Petersen is the Director of the Mayo Alzheimer's Disease Research Center and the Mayo Clinic Study of Aging.

The NAPA advisory panel meets quarterly to evaluate programs targeting the needs of individuals and caregivers coping with the consequences of Alzheimer's disease and related disorders. Below is an outline of the NAPA panel activity as reported this summer (July 2013).

NAPA Highlights 2013

- Funded new research projects, including two new clinical trials
- Launched http://www.alzheimers.gov to increase public awareness and connect people with a diagnosis and their caregivers with important resources
- Identified tools for physicians to assess cognitive impairment.
- Administration on Aging/NIA Webinars on clinical trial enrollment
- NIH meeting on AD for people with Down syndrome (April 2013)
- NIH research summit on other dementias (May 2013)
- Next AD Research Summit in January 2015
- Guidance about drugs for early Alzheimer's disease
- Draft guidance released in February 2013

NAPA Goals Update
Enhancing Care Quality and Efficiency

- Develop a unified curriculum for primary care practitioners about AD
- Ensure aging network has research-based up-to-date info on AD
- Engage public health workforce on brain health
- CDC release of "The Healthy Brain Initiative: The Public Health Road Map for State and National Partnerships, 2013-2018" July 2013
- Identify and review measures of high-quality dementia care
- Convene an expert panel on advanced dementia
- New models of care for AD
- Share results and lessons about new models
- Patient-centered alternatives to institutional care
- Ensure that people with AD experience safe and effective transitions between care settings and health care systems
- Determine avoidable hospitalizations and ER use among people with AD
- Identify and disseminate info on intervention to reduce preventable hospitalizations
- CDC review of interventions

Expanding Supports for People with AD and Their Families

- Caregivers health and well-being
- Assist families in planning for care needs
- Maintain the dignity, safety, and rights of people with AD
- Enhance and disseminate information on abuse of people with dementia
- Promote dementia-capable legal service systems
- Educate fiduciaries about managing the finances of people

BRAIN TEASERS

Commonyms – What do these words have in common?

1. Home – Diner – License
2. Jackie – Dolly – Eleanor
3. Corn – Baby – Olive
4. America – Kangaroo – Crunch
5. Sharp – Cream – Cottage
6. Santa's Sleigh – Churches – Schools

Commonym answers: 1. They are plates; 2. They are first ladies; 3. They are oils; 4. They are captains; 5. It is cheese; 6. They have bells.

Mad Gabs (Hint: sound out the sentence)

1. Able Owe Knees Hand Which
2. Ace Date Tough Gay Hoss
3. Ace Heal Ink Van
4. Ace Heck Hunch Ants
5. Ace Height Force or Rise

Mad Gab Answers: 1. A Bologna Sandwich, 2. A State of Chaos, 3. A Ceiling Fan, 4. A Second Chance 5. A Sight for Sore Eyes