Biomarkers and Further Progress on a Blood Test for Alzheimer’s

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A commonly used analogy when discussing biomarkers for Alzheimer’s disease is that of cancer. An individual may have a biomarker that indicates increased risk for breast cancer: positive BRCA1 gene mutation. Years later, that individual might have an abnormal mammogram showing a small tumor (disease state), and if left untreated she might develop metastatic disease with tumors in the lungs as seen by PET scan (disease progression).

In Alzheimer’s dementia, a genetic mutation, such as PSEN1 is a biomarker that indicates increased risk for developing AD. A positive amyloid PET scan can indicate presence of amyloid plaques (indicating increased risk and disease state). Finally, an MRI demonstrating brain atrophy, or shrinkage, can indicate neurodegeneration (which shows disease progression). A major effort in the field has been to find an accurate, reliable, practical and inexpensive biomarker for AD. The discovery of a blood test for AD would truly represent a watershed moment in the field, and likely be second in importance only to the discovery of a disease modifying drug.

In the most recent development, a paper recently published in the journal Alzheimer’s and Dementia, described a panel of 10 proteins in the blood. The researchers looked at blood samples from 1,148 subjects: 476 with AD dementia, 220 with MCI, and 452 elderly controls with no dementia. The researchers have identified a panel of plasma biomarkers that correlate closely with other biomarkers of AD, specifically, neuroimaging measures of disease and cognitive measures of memory functioning. Moreover, the 10 protein biomarkers can accurately predict disease conversion from MCI to AD dementia within a year of blood sampling. At the July 2014 AAIC meeting in Copenhagen we heard about a retinal measure of amyloid as a potential biomarker, as well as a simple smell test, which also seems to correlate with AD pathology in the brain.

As with other biomarker studies, we need to better understand if this protein panel, retinal scan and smell test will serve as an indicators of disease risk, disease state and disease progression. However, with this recent work, we are getting much closer to that possibility.
Smell and Eye Tests Show Potential to Detect Alzheimer’s Early

New Alzheimer's biomarker results reported at Alzheimer's Association International Conference 2014

A decreased ability to identify odors might indicate the development of cognitive impairment and Alzheimer's disease, while examinations of the eye could indicate the build-up of beta-amyloid, a protein associated with Alzheimer's, in the brain, according to the results of four research trials reported at the Alzheimer's Association International Conference® 2014 (AAIC® 2014) in Copenhagen.

In two of the studies, the decreased ability to identify odors was significantly associated with loss of brain cell function and progression to Alzheimer's disease. In two other studies, the level of beta-amyloid detected in the eye (a) was significantly correlated with the burden of beta-amyloid in the brain and (b) allowed researchers to accurately identify the people with Alzheimer's in the studies. Beta-amyloid protein is the primary material found in the sticky brain “plaques” characteristic of Alzheimer's disease. It is known to build up in the brain many years before typical Alzheimer's symptoms of memory loss and other cognitive problems.

“In the face of the growing worldwide Alzheimer's disease epidemic, there is a pressing need for simple, less invasive diagnostic tests that will identify the risk of Alzheimer's much earlier in the disease process,” said Heather Snyder, Ph.D., Alzheimer's Association director of Medical and Scientific Operations. “This is especially true as Alzheimer's researchers move treatment and prevention trials earlier in the course of the disease.”

“More research is needed in the very promising area of Alzheimer's biomarkers because early detection is essential for early intervention and prevention, when new treatments become available. For now, these four studies reported at AAIC point to possible methods of early detection in a research setting to choose study populations for clinical trials of Alzheimer's treatments and preventions,” Snyder said.

Clinically, at this time it is only possible to detect Alzheimer's late in its development, when significant brain damage has already occurred. Biological markers of Alzheimer's disease may be able to detect it at an earlier stage. For example, using brain PET imaging in conjunction with a specialized chemical that binds to beta-amyloid protein, the buildup of the protein as plaques in the brain can be revealed years before symptoms appear. These scans can be expensive and are not available everywhere. Amyloid can also be detected in cerebrospinal fluid through a lumbar puncture where a needle is inserted between two bones (vertebrae) in your lower back to remove a sample of the fluid that surrounds your brain and spinal cord.

Greater Neurodegeneration Associated with Worse Olfactory Function in Cognitively Normal Elderly

There is growing evidence that the decreased ability to correctly identify odors is a predictor of cognitive impairment and an early clinical feature of Alzheimer's. As the disease begins to kill brain cells, this often includes cells that are important to the sense of smell.

Matthew E. Growdon, B.A., M.D./M.P.H. candidate at Harvard Medical School and Harvard School of Public Health, and colleagues investigated the associations between sense of smell, memory performance, biomarkers of loss of brain cell function, and amyloid deposition in 215 clinically normal elderly individuals enrolled in the Harvard Aging Brain Study at the Massachusetts General Hospital. The researchers administered the 40-item University of Pennsylvania Smell Identification Test (UPSIT) and a comprehensive battery of cognitive tests. They also measured the size of two brain structures deep in the temporal lobes – the entorhinal cortex and the hippocampus (which are important for memory) – and amyloid deposits in the brain.

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Smell and Eye Tests cont’d…..

At AAIC 2014, Growdon reported that, in this study population, a smaller hippocampus and a thinner entorhinal cortex were associated with worse smell identification and worse memory. The scientists also found that, in a subgroup of study participants with elevated levels of amyloid in their brain, greater brain cell death, as indicated by a thinner entorhinal cortex, was significantly associated with worse olfactory function – after adjusting for variables including age, gender, and an estimate of cognitive reserve.

“Our research suggests that there may be a role for smell identification testing in clinically normal, older individuals who are at risk for Alzheimer's disease,” said Growdon. “For example, it may prove useful to identify proper candidates for more expensive or invasive tests. Our findings are promising but must be interpreted with caution. These results reflect a snapshot in time; research conducted over time will give us a better idea of the utility of olfactory testing for early detection of Alzheimer's.”

The Harvard Aging Brain Study is funded by the National Institute on Aging and the Alzheimer's Association.

Odor Identification Deficits Linked with Transition from Mild Cognitive Impairment to AD

Davangere Devanand, M.B.B.S., M.D., Professor of Psychiatry (in Neurology and in the Sergievsky Center) at Columbia University Medical Center and colleagues investigated a multi-ethnic (34% White, 30% African-American, 36% Hispanic) sample of 1037 non-demented elderly people in New York City, with an average age of 80.7, and assessed them in a variety of ways at three time periods – from 2004-2006, 2006-2008, and 2008-2010. UPSIT was administered in English and Spanish between 2004 and 2006. During follow-up 109 people transitioned to dementia (101=Alzheimer's); there were 270 deaths.

At AAIC 2014, Devanand reported that, in 757 subjects who were followed, lower odor identification scores on UPSIT were significantly associated with the transition to dementia and Alzheimer's disease, after controlling for demographic, cognitive, and functional measures, language of administration, and apolipoprotein E genotype. For each point lower that a person scored on the UPSIT, the risk of Alzheimer's increased by about 10%. Further, lower baseline UPSIT scores, but not measures of verbal memory, were significantly associated with cognitive decline in participants without baseline cognitive impairment.

“Odor identification deficits were associated with the transition to dementia and Alzheimer's disease, and with cognitive decline in cognitively intact participants, in our community sample. The test was effective in both English and Spanish,” said Devanand. “If further large-scale studies reproduce these results, a relatively inexpensive test such as odor identification may be able to identify subjects at increased risk of dementia and Alzheimer's disease at a very early stage, and may be useful in identifying people at increased risk of cognitive decline more broadly.”

Eye Exam for Beta-Amyloid Correlates with Levels in the Brain and Detects People with Alzheimer's

Recent studies have identified beta-amyloid plaques in the retinas of people with Alzheimer's – similar to those found in the brain – suggesting the possibility of simple, non-invasive methods of early detection.

At AAIC 2014, Shaun Frost of the CSIRO (Commonwealth Scientific and Industrial Research Organization, Australia) and colleagues reported preliminary results of a study of volunteers who took a proprietary supplement containing curcumin, which binds to beta-amyloid with high affinity and has fluorescent properties that allow amyloid plaques to be detected in the eye using a novel system from NeuroVision Imaging, LLC, and a technique called retinal amyloid imaging (RAI). Volunteers also underwent brain amyloid PET imaging to correlate the retina and brain amyloid accumulation.

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An abstract prepared by the scientists for AAIC 2014 gives the results for 40 participants out of 200 total in the study. The full study is expected to be completed later this year.

Preliminary results suggest that amyloid levels detected in the retina were significantly correlated with brain amyloid levels as shown by PET imaging. The retinal amyloid test also differentiated between Alzheimer's and non-Alzheimer's subjects with 100 percent sensitivity and 80.6 percent specificity.

Furthermore, longitudinal studies on an initial cohort demonstrated an average of 3.5% increase in retinal amyloid over a 3.5-month period of time demonstrating promise of the technique as a means for monitoring response to therapy.

“We envision this technology potentially as an initial screen that could complement what is currently used: brain PET imaging, MRI imaging, and clinical tests,” Frost said. “If further research shows that our initial findings are correct, it could potentially be delivered as part of an individual's regular eye check-up. The high resolution level of our images could also allow accurate monitoring of individual retinal plaques as a possible method to follow progression and response to therapy.”

The trial is a collaboration between CSIRO, Edith Cowan University, McCusker Alzheimer's Research Foundation and California-based NeuroVision Imaging. The project is part of the Australian Imaging and Biomarkers Lifestyle Study of Aging (AIBL).

**Amyloid Detected in the Lens of the Eye Strongly Correlates to Amyloid Levels Detected in the Brain**

At AAIC 2014, Paul D. Hartung, M.S, President and CEO of Cognoptix, Inc. and colleagues reported the results of a study of a novel fluorescent ligand eye scanning (FLES) system that detects beta-amyloid in the lens of the eye using a topically-applied ointment that binds to amyloid and a laser scanner.

The researchers studied 20 people with probable Alzheimer's disease, including mild cases, and 20 age-matched healthy volunteers; all participants' Alzheimer's status was masked from the observers. The ointment was applied to the inside of participants' lower eyelids the day before measurement. Laser scanning detected beta-amyloid in the eye by the presence of a specific fluorescent signature. Brain amyloid positron emission tomography (PET) scanning was performed on all participants to estimate amyloid plaque density in the brain.

Using results from the fluorescent imaging, researchers were able to differentiate people with Alzheimer's from healthy controls with high sensitivity (85 percent) and specificity (95 percent). In addition, amyloid levels based on the eye lens test correlated significantly with results obtained through PET brain imaging. No serious adverse events were reported, according to the scientists.

“There is a critical need for a fast, dependable, low-cost and readily available test for the early diagnosis and management of Alzheimer's disease,” said Pierre N. Tariot, M.D., Director of the Banner Alzheimer's Institute in Phoenix, and a principal investigator in the study.

“The results of this small Phase 2 feasibility study validate our previously reported results and demonstrate the ability of the FLES system to reproduce the findings of clinical diagnosis of Alzheimer's with high sensitivity and specificity,” said Hartung. “This system shows promise as a technique for early detection and monitoring of the disease.”
Can Lifestyle Changes Affect Cognition?

Two-Year Clinical Trial of Multifaceted Lifestyle-Based Intervention Provides Cognitive Benefits for Older Adults at Risk of Dementia

Positive results presented at the Alzheimer's Association International Conference® 2014 (AAIC® 2014) in Copenhagen include data from a two-year clinical trial in Finland of a multi-component lifestyle intervention, known as the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER Study).

The study with 1,260 older adults at risk for cognitive impairment and Alzheimer's showed that physical activity, nutritional guidance, cognitive training, social activities and management of heart health risk factors improved cognitive performance, both overall and in separate measures of executive function, such as planning abilities, and the relationship between cognitive functions and physical movement.

"AAIC is the premiere Alzheimer's and dementia research conference, and this year's topics are exciting both in their scope and findings,” said Keith Fargo, Ph.D., Alzheimer's Association director of Scientific Programs & Outreach. “Regarding the FINGER Study, researchers have previously observed a number of modifiable factors associated with increased risk of late-life cognitive impairment and Alzheimer's, but short-term studies focusing on single, isolated risk factors have had modest results, at best. Longer, larger, better controlled trials looking at modifying multiple risk factors - like the FINGER Study - have been needed. This new data is very encouraging, and we look forward to further studies to confirm and extend these findings.”

Lifestyle Changes Improve Memory and Thinking in At-Risk Older Adults in Two-Year Clinical Trial.

At AAIC 2014, Miia Kivipelto, M.D., Ph.D., Professor at the Karolinska Institutet, Sweden and the National Institute for Health and Welfare, Helsinki, Finland, and colleagues reported on the results of the FINGER Study, a two-year randomized controlled trial of 1,260 participants age 60 to 77 with modifiable risk factors for cognitive impairment and Alzheimer's.

Participants were divided into two groups; one received an intervention that included nutritional guidance, physical exercise, cognitive training, social activities, and management of heart health risk factors, while the control group received regular health advice. After two years, the intervention group performed significantly better on a comprehensive cognitive examination. In addition to performing better overall, the intervention group did significantly better on specific tests of memory, executive function (complex aspects of thought such as planning, judgment, and problem-solving), and speed of cognitive processing.

“This is the first randomized control trial showing that it is possible to prevent cognitive decline using a multi-domain intervention among older at-risk individuals. These results highlight the value of addressing multiple risk factors in improving performance in several cognitive domains,” said Kivipelto. “Participants told us their experience was very positive, and dropout rate only 11 percent after two years.”

The researchers say an extended, 7-year follow up study is planned, and will include measures of dementia/Alzheimer's incidence and biomarkers including brain imaging with MRI and PET.
Researchers Identify Additional Abnormal Protein, TDP-43, in Brains of People with Alzheimer’s

Abnormal build-up of beta-amyloid and tau proteins are considered the primary indicators of Alzheimer's disease in the brain. Amyloid “plaques” and tau “tangles” form and increase for years in the brains of people with the disease, usually well before symptoms such as memory loss become apparent.

Little is known about the role in memory loss and dementia of another protein, TAR DNA binding protein of 43kDa (TDP-43), which is seen in ALS. Keith Josephs, M.D. of the Mayo Clinic and colleagues conducted a study to determine whether TDP-43 has an effect, independent of amyloid and tau, on the course and symptoms of Alzheimer's. The results were reported at AAIC 2014.

The researchers conducted post-mortem examinations on the brains of 342 people who were determined to have Alzheimer's disease based on the extent of tau tangles in the cortex. The subjects' brains were screened for the presence, amount, and distribution of TDP-43, and these findings were correlated with the results of tests of memory and cognition taken when the subjects were alive. The researchers also used MRI to assess atrophy in several brain regions.

After controlling for other factors including age at death, amyloid deposition, genetic risk for Alzheimer's, and vascular disease, the scientists concluded that the 195 study subjects with TDP-43 were 10 times more likely to have been cognitively impaired at death than subjects without TDP-43. They found that the “third protein” had strong correlations with cognition, memory loss, and shrinkage of the hippocampus, an area of the brain that is important to memory and is especially damaged in Alzheimer's.

The scientists speculate that absence of TDP-43 may help explain why some people have plaques and tangles in their brain, but do not experience dementia.

“These findings show that TDP-43 amplifies memory loss and hippocampal atrophy in Alzheimer's disease, and also appears to overpower what has been termed ‘resilient cognition' in Alzheimer’s, where subjects remain cognitively normal in spite of high levels of Alzheimer's brain changes,” said Josephs. “This suggests that TDP-43 is a key player in the Alzheimer's neurodegenerative process, and should be considered a potential therapeutic target for treatment of the disease.”
The presence of tangles of abnormal tau protein in the brain is one of the defining characteristics of Alzheimer's disease. The detection of brain tau deposits in living people has only recently become possible through advances in positron emission tomography (PET), an imaging technology that uses a radioactive imaging agent to highlight areas of interest inside the body.

In previous research, levels of tau in the brain have been found to be more closely associated with cognitive decline in Alzheimer's than levels of the other characteristic Alzheimer's protein, known as beta amyloid. Identifying the early buildup of these proteins in the brain, even before memory and thinking symptoms are present, is considered a strong candidate for early detection and diagnosis of Alzheimer's and for identifying volunteers for prevention studies.

In the largest study of its type to be reported, Keith Johnson, M.D. of Massachusetts General Hospital and colleagues conducted a study to determine if tau found in the brains of normal adults through PET imaging was associated with changes in memory. Johnson reported the results at AAIC 2014.

Using an imaging agent (F18 T807, Lilly) that binds with tau in the brain, the researchers conducted PET scans of 56 cognitively normal individuals with a median age of 72 who had undergone annual memory testing over the previous three years. They found that higher levels of tau in areas of the brain important to memory (entorhinal cortex and temporal neocortex) were associated with worsening on the memory test.

“These preliminary data suggest that tau in these brain areas is related to memory decline in normal older individuals,” said Johnson. “This study demonstrates the potential for PET technology to be used for early detection, and to help pick participants for prevention trials and treatment trials that target tau.”
Phase 2 clinical trial results for crenezumab (Genentech) were presented July 16 at the Alzheimer's Association International Conference (AAIC 2014) in Copenhagen. The test drug did not meet its primary endpoints for cognition and activities of daily living (function).

There was, however, a positive finding in a subgroup of the study population with mild Alzheimer's disease who received the drug by intravenous (IV) infusion. The Alzheimer's Association notes a key learning from the trial, and others with similar results, is that treating Alzheimer's earlier in the disease process shows potential for effective treatment and prevention.

These results are an indication that Alzheimer's disease prevention trials testing therapies in people who have Alzheimer's-related brain changes but do not yet have symptoms of dementia have the potential to be more successful than those conducted on people who already are experiencing dementia symptoms.

Crenezumab is currently being tested in one of the Alzheimer's prevention trials being led by Banner Alzheimer's Institute (BAI), the Alzheimer's Prevention Initiative Autosomal Dominant Alzheimer's Disease Treatment Trial (API-ADAT). The study population is the extended family group impacted by young onset, genetic Alzheimer's near Medellin, Colombia.

These results also reinforce the need for more research into early causes and biological markers for Alzheimer's in order to make early intervention possible.

Current investigations into Alzheimer's disease suggest there may be more than one “pathway” for the development and progression of the disease, specifically one instigated by amyloid as well as non-amyloid pathways. While much is being done to understand the onset and progression of Alzheimer's disease, the Alzheimer's Association stresses there is a critical need for new ideas in Alzheimer's treatment and prevention. For example, these emerging non-amyloid pathways present a great opportunity for innovation.

In March 2014, the Alzheimer's Association awarded its largest-ever research grant – $8 million over four years – to support the Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN) study as a companion to the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) Study, a pioneering Alzheimer's prevention trial.

A first of its kind study, one objective of LEARN is to follow a group of amyloid negative individuals to determine causes of cognitive decline besides buildup of amyloid beta in the brain. The Alzheimer's Association's goal with the LEARN grant, a goal shared with the A4 effort, is to jump-start the development of new detection methods, treatments, and prevention strategies for Alzheimer's disease and other dementias.
At AAIC 2014, Claudia L. Satizabal, Ph.D. of Boston University School of Medicine and colleagues reported on the results of a study of dementia trends among participants in the Framingham Heart Study, an ongoing, long-term (since 1948), multi-generational cardiovascular health study of residents of Framingham, Massachusetts, to which dementia tracking has been added since 1975.

Framingham Study participants undergo comprehensive assessments for cardiovascular risk factors every two to four years, and remain under intensive surveillance for dementia and stroke. Study researchers defined four non-overlapping five-year time windows (epochs) across the past three decades, each beginning with a baseline examination, and studied new cases of dementia among all dementia-free participants age 60 and older.

After adjusting for age at entry and gender, the researchers found that compared with the first epoch, the second epoch had a 22 percent reduction in new cases of dementia, the third had a 38 percent reduction, and the fourth had a 44 percent reduction. The reduction was strongest in participants between age 60 and 69.

The researchers found the decrease in dementia incidence was greatest in women across all epochs, while men showed a more gradual decrease over time. The decreasing trend in dementia incidence was true for individuals with a higher educational level, defined as having a high school diploma, whereas individuals without a high school diploma did not appear to benefit from this reduction.

During that 30-year time period, the researchers observed among the participants a substantial improvement in educational achievement, better management of blood pressure, higher levels of HDL cholesterol, and a considerable decline in smoking, heart disease and stroke across the same epochs. However, an increasing trend in obesity and diabetes was seen in this population.

“These reductions in age-specific rates of new cases of dementia in the Framingham Study participants might be partly explained by the beneficial trends we observed in educational attainment and heart health risk factors,” said Satizabal. “This leads us to cautious optimism that some cases of dementia may be preventable. However, one of the limitations of this work is that the Framingham sample is largely of European descent. Additional studies are needed in populations of different racial and ethnic backgrounds.”
ADCS Clinical Trials Enrolling...

For information on the following studies please visit:

http://www.adcs.org/Studies/clinalResearchStudy.aspx

A4 – Anti Amyloid in Asymptomatic Alzheimer’s Disease

SNIFF – the Study of Nasal Insulin to Fight Forgetfulness

NOBLE
A New Study for People with Mild to Moderate Alzheimer’s Disease
The Dominantly Inherited Alzheimer Network (DIAN). DIAN is an international research partnership of leading scientists determined to understand a rare form of Alzheimer’s disease that is caused by a gene mutation. Understanding of this form of Alzheimer's disease may provide clues to decoding other dementias and developing dementia treatments.

Funded by a multiple-year research grant from the National Institute on Aging, DIAN currently involves thirteen outstanding research institutions in the United States, United Kingdom, Germany and Australia. John C. Morris, M.D., Friedman Distinguished Professor of Neurology at Washington University School of Medicine in St. Louis, is the project’s principal investigator.

DIAN is currently enrolling study participants who are biological adult children of a parent with a mutated gene known to cause dominantly inherited Alzheimer’s disease. Such individuals may or may not carry the gene themselves and may or may not have disease symptoms (click here for information about genetic testing).

To register for DIAN drug trials or DIAN, visit www.DIANExpandedRegistry.org.

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