Initiative Could Transform Alzheimer's Research

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A $60 million, 6-year study is being launched to find and validate biologic and imaging markers that could be used as objective measures of therapeutic response in Alzheimer's disease.

The results of the Alzheimer's Disease Neuroimaging Initiative (ADNI) could dramatically shorten clinical trials of potential therapies by sidestepping the years of cognitive testing now necessary to determine a drug effects, according to experts interviewed for this article.

The time is ripe for an objective biologic marker of disease progression. Several potentially disease-modifying drugs are in phase II trials, with cognitive measures the only validated treatment outcomes. Relying solely on cognition to determine treatment effect is problematic in many ways, said Dr. Michael W. Weiner, ADNI's principal investigator and the director of the Veterans Administration's Center for Imaging of Neurodegenerative Disease, San Francisco.

Everyone with AD declines, but they don't do so in a linear fashion, Dr. Weiner said "There is a lot of variability in these kinds of measures. One day, a patient might do well, and the next, do poorly depending on his general health, emotional status, or a number of other factors. This variability really affects the ability to determine a true treatment effect."

Nor, using cognitive outcomes alone, is it possible to distinguish between a drug's effects on disease progression and any memory-enhancing effects it also might exhibit, he said.

A validated biomarker, on the other hand, could show a drug's true effect, with profound influence on drug development, said Dr. John Q. Trojanowski, director of the Alzheimer's Disease Center at the University of Pennsylvania, Philadelphia, and leader of ADNI's biomarker core. "The pace of drug discovery would quicken incredibly, and the costs come down incredibly, if we had a chemical or imaging marker that reflected reversing or blocking disease progression."

Funded by a mix of federal and private sources, ADNI will search for such markers in 800 patients aged 55-90 years: 200 with AD, 400 with mild cognitive impairment (MCI), and 200 healthy controls. Examining three imaging techniques and four biomarkers, the study aims to find predictors of progression in AD patients, and predictors of transformation from normal to MCI and from MCI to AD.

Since the study's main goal is to improve the climate for clinical trials, pharmaceutical companies have an enormous stake in its outcome. Faced with a cost of up to $1 billion to bring just one drug to market, it's not surprising that 13 of the world's largest drug makers have agreed to fund about a third of ADNI's cost. The National Institutes of Health is footing the rest of the bill.

"For an investment of a few million dollars, [pharmaceutical companies are] hoping for biomarkers that would enable them to bring the cost of their clinical trials down by millions of dollars," said Dr. Trojanowski. "Chances are that this is a reasonable expectation."

Patient enrollment wrapped up last year, and now the work is beginning at 57 centers across the United States and Canada. In addition to the baseline visit, AD patients will have three follow-ups (6, 12, and 24 months). Normal controls will have four follow-ups, including an additional visit at 36 months. MCI patients will be seen a total of six times: at baseline and at 6, 12, 18, 24, and 36 months.

Each cohort will have apolipoprotein E genotyping at baseline and undergo standard magnetic resonance imaging at all time points. Half also will receive fluorodeoxyglucose PET scanning at each time point, and another 25% will undergo the more sensitive 3-Tesla MRI, which allows metabolic and physiologic imaging.

A group of 120 patients also will be enrolled in a substudy of Pittsburgh compound B PET scanning. Because the compound binds to amyloid plaques in the brain, it offers a reliable way by which to trace disease progression and may be able to detect early pathologic changes before cognitive changes develop.

At all follow-up visits, patients will donate blood and urine for evaluation for these potential markers; 55% will undergo at least two lumbar punctures for the collection of cerebrospinal fluid. ADNI will focus on four of the most promising biomarkers:

- Homocysteine, while not diagnostically significant, may reflect disease progression.
- Isoprostanes, indicators of oxidative damage, have been shown to be increased in the hippocampi and CSF of AD patients.
- Phosphorylated tau and amyloid-β are the neuropathologic hallmarks of AD tangles and plaques, respectively.

Most research indicates that patients with low levels of amyloid-β and high levels of tau in CSF are more likely to have AD, although some recent studies have challenged this idea.

In fact, none of the biomarkers or imaging modalities included in the ADNI study has been validated in large numbers of patients. Without validation, none can be used as a primary outcome in drug trials, leaving researchers to fall back on imprecise cognitive measures for their main assessment of efficacy, Dr. Trojanowski said.

"If, instead, we could show that biomarkers were changing during a drug trial, in the same way that we can show changes in cholesterol or blood sugar in response to drugs, then we could have a very, very powerful new tool," Dr. Trojanowski said.

ADNI is an important study in a worldwide effort to discover clinical markers of AD, the investigators agreed. Australia, Japan, and some European countries are undertaking similar projects. Termed "World Wide ADNI," this informal network will facilitate the performance of international treatment trials and, ultimately, the approval of disease-modifying treatments worldwide. Researchers from these studies are working to harmonize the methodologies, increasing the statistical power of their combined results, Dr. Trojanowski said.

Dr. Weiner noted before ADNI has evaluated even a single patient, it has already changed the way scientists are attacking AD research. Most AD biomarker and imaging research now consists of small studies, each with a unique methodology. Researchers hold their information close to the vest until publication, with months and sometimes years elapsing between the study's conclusion and the sharing of its results.

Not only will all 57 ADNI study centers follow consistent protocols for all the imaging studies and biomarker collection, but also those protocols will be available to any researcher pursuing an independent study. The sharing of methodology and, eventually, of results, is another of ADNI's unique characteristics, Dr. Weiner said. All data will be sent to centralized storage hubs, which will be freely available to anyone—researcher, physician, patient, or family member—who applies for access. The information won't be subject to embargo; scans and biomarker measurements will be available online as soon as they're processed.

"We are going to share everything we get in an unprecedented way. Allowing other researchers to have immediate access to the data is going to maximize this study's effect."

For more information, including filing a request for access to eventual data, physicians should go to www.adni-info.org. ■

Availability of Markers Bound to Raise Thorny Questions

The first benefits of biologic or imaging markers would be felt in research, where they could hasten the development of disease-modifying drugs. But once those drugs are available, such markers also will be used to identify people most likely to benefit from them and could become part of screening to identify those at risk of developing Alzheimer's disease years before symptoms emerge.

"If and when these therapies become available, who will get them?" asked Dr. Ronald Petersen, director of the Mayo Clinical Alzheimer's Disease Research Center, Rochester, Minn. "Are we going to give them to people with memory impairment first? Or ultimately to those who are asymptomatic but who are at risk? And how will we know who these people are?"

Dr. Petersen hopes eventual findings from his own study help answer some of these questions. He is the lead investigator for the Mayo Clinic Study of Aging, a longitudinal study of 2,000 people aged 70-89 years. The National Institute on Aging provides the study's $1.5 million annual funding package.

In addition to characterizing what brain aging looks like, the study will examine the influence of genetics, family history, and medical comorbidities on the risk of developing Alzheimer's. It will combine this information with cognitive testing, biomarkers, and different imaging modalities in an effort to construct a multivariate model that could predict which apparently healthy people will develop mild cognitive impairment and who might then progress to Alzheimer's.

The Clinical Study of Aging is not related to Alzheimer's Disease Neuroimaging Initiative (ADNI), but both aim to identify the most informative biomarkers and imaging techniques for AD. Eventually, Dr. Petersen predicted, data from both studies might be used to construct a layered screening technique that could identify those who would benefit from early disease prevention or disease-modifying therapy.

Such a model probably would progress from least- to most-invasive testing depending on individual risk, he said. Patients flagged as moderate or high risk might then receive a functional brain scan and a lumbar puncture for cerebrospinal fluid marker sampling. Amyloid imaging with Pittsburgh compound B might also be part of the work-up.

In stratifying patients for treatment, "Earlier may be better than later," said Dr. John Morris, director of the Alzheimer's Disease Research Center at Washington University, St. Louis. "We know that by the time people start experiencing memory problems, the neuropathological lesions of AD [plaques and tangles] already are present in the brain and, in brain regions vulnerable to AD, nerve cells and their synapses have been lost. Even if truly effective drugs are developed, giving them to people with symptomatic AD—even to those with mild cognitive impairment—may be too late because, by the time symptoms appear, the brain already has been damaged."

ADNI does not include what could be the critical population in this theory—younger normal controls. "While the study does include nondemented patients (200 normal individuals and 400 with MCI), these people are all older than 55. It is still speculative to consider when the AD process begins in the brain, but it may be in midlife or even earlier."

To be truly effective in combating the disease, he suggested, it will be important to study younger groups to detect the beginnings of AD with imaging or biological markers before symptoms appear so that eventually therapies hopefully can be given to prevent the occurrence of dementia.

"It's similar to treating atherosclerosis," he said. "It's a lot easier to treat cholesterol levels to prevent vascular damage than to wait until a heart attack occurs and try to fix things from that point."