NEWS

Alzheimer's Biomarker Initiative Hits Its Stride

An effort to develop biomarkers for Alzheimer's disease is churning out new data and making plans to expand

Into the scanner. Researchers hope to use MRI brain scans to track the progression of Alzheimer's disease.

IMAGINE YOU'RE AN EXECUTIVE AT A PHARMACEUTICAL company and your scientists have just briefed you on a promising new drug for Alzheimer's disease. Dollar signs are no doubt swirling before your eyes. Alzheimer's afflicts 4 million people in the United States alone, and burgeoning elderly populations in countries like India and China portend skyrocketing demand for decades to come. But hold on. First, you have to run clinical trials. Because the cognitive tests and clinical measures used to gauge the efficacy of Alzheimer's treatments are notoriously variable, you may need to enroll 1000 people or more in the hope of seeing a statistically significant benefit. And given that Alzheimer's can be diagnosed definitively only by examining the brain after death, you can expect that at least 10% of the subjects won't have Alzheimer's but some other type of dementia that won't respond to your drug. Even those who do have Alzheimer's may be too far gone to benefit. Suddenly, those dollar signs begin fading from view.

Such concerns are what motivated pharmaceutical companies to band together and join the National Institutes of Health to form an innovative partnership, the Alzheimer's Disease Neuroimaging Initiative (ADNI). Launched in October 2004 with $64 million to fund its first 5 years, its raison d'être is to develop methods for improving Alzheimer's disease clinical trials. ADNI has enrolled more than 800 volunteers between the ages of 55 and 90—roughly a quarter of them healthy, another quarter clinically diagnosed with probable Alzheimer's, and the rest diagnosed with mild cognitive impairment (MCI), a condition that often presages Alzheimer's. They undergo testing every 6 to 12 months with a variety of methods, including magnetic resonance imaging (MRI), positron emission tomography (PET) brain scans, and lumbar punctures to collect cerebrospinal fluid (CSF). The hope is to find biomarkers—signs of brain atrophy in an MRI scan, for example—that track the progression of Alzheimer's more faithfully than do the cognitive and clinical measures now used in treatment trials.

Five years in, a trickle of data is becoming a torrent. ADNI researchers are now poring over brain scans and other biomarker data to document changes as people who started out with a clean slate of cognitive health have developed MCI, and as those with MCI have progressed to Alzheimer's. ADNI's organizers caution that it's too early to draw definitive conclusions, but some potentially useful lessons are emerging, including hints about which biomarkers best track different stages of the disease. Pharmaceutical companies are already incorporating some of the ADNI measures into clinical trials, and researchers in Europe, Asia, and Australia are developing similar initiatives (see box, p. 388).

"As far as I can see, it's just been a phenomenal success," says neurologist Michael Weiner of the University of California (UC), San Francisco, and the Veterans Administration Medical Center. Weiner, who is ADNI principal investigator, and the other project leaders found out last month that they'd won a $24 million Grand Opportunities grant from the National Institute on Aging that will enable them to expand the study to include people with even earlier stages of MCI. And Weiner says a proposal for ADNI2, a continuation of ADNI that would enroll hundreds more volunteers and expand the genetic testing arm of the study, will be sent off by the end of this month.

Tracking a killer

Although several drugs provide modest improvements in the memory impairments and other cognitive problems caused by Alzheimer's, so far no treatment has been proven to slow the underlying neurodegeneration (*Science*, 29 July 2005, p. 731). A handful of promising candidates have flopped in recent clinical trials, sparking much discussion about whether the field's longstanding leading hypothesis—that the accumulation of the β-amyloid peptide and formation of amyloid plaques is the core mechanism of Alzheimer's disease—is in need of revision, or worse.

Yet many researchers contend that the recent trials are less a death knell for the amyloid hypothesis than an illustration of the need for better biomarkers. For one thing, they point out, the trials all enrolled people who already had a clinical diagnosis of Alzheimer's disease. For these patients, who presumably have significant neurodegeneration, clearing β-amyloid from the brain may simply be too little too late. The real test for the amyloid hypothesis will come from identifying people earlier in the course of the disease and giving them anti-amyloid treatments to see if it delays or prevents dementia. "It's now quietly recognized that Alzheimer's disease pathology is probably present 10 or 20 years before someone becomes demented," says Weiner.

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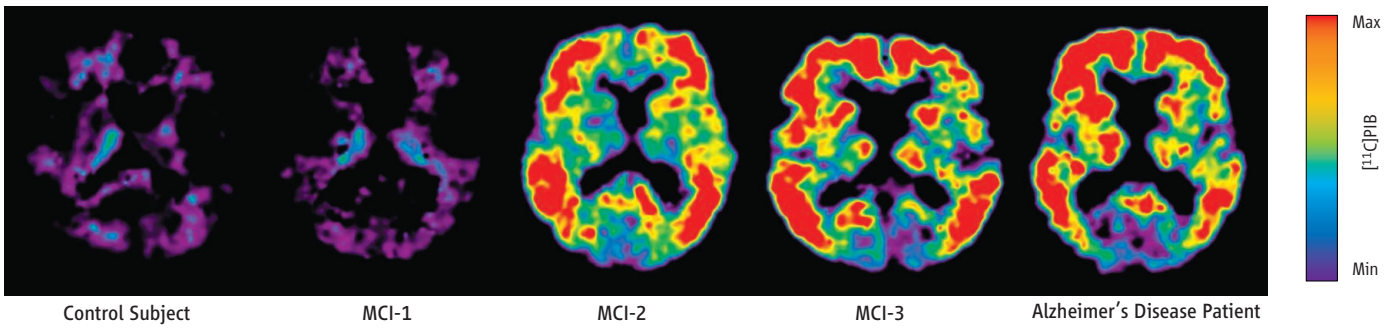
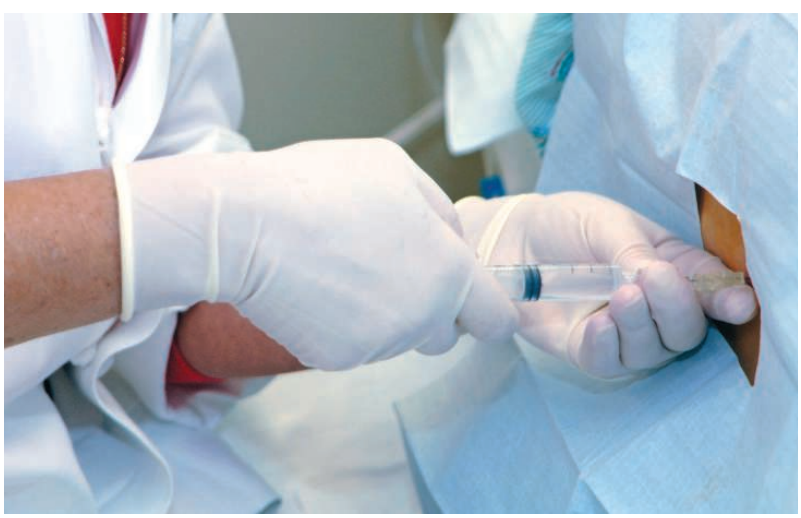
PIB SCANS



Not a pretty picture. Amyloid deposits make for a colorful PIB scan of an Alzheimer's patient's brain (*far right*). People with MCI show diverse results.

Although the original goal of ADNI was to streamline clinical trials by developing biomarkers that track the progression of the disease more reliably than conventional clinical and neuropsychological measures do, Weiner says it's becoming apparent that some of the biomarkers under investigation may be valuable for diagnosing or even predicting Alzheimer's in patients suffering from only mild memory loss.

The three types of biomarker measurements included in the original plans for ADNI—anatomical MRI scans, PET scans to measure metabolic activity, and CSF samples—were chosen because they'd already shown promise in mostly smaller, single-center studies. ADNI researchers developed extensive protocols so that data collected at the 59 centers could be combined and compared. Standardizing complex procedures such as MRI and PET scanning across multiple centers with different equipment wasn't easy, says neurologist William Jagust of UC Berkeley, who heads ADNI's PET core. "If you'd told me 10 years ago I'd be heading a multicenter imaging study, I'd have thought you were crazy," he says. "The technology is just so complicated."



This is spinal tap. Cerebrospinal fluid may contain clues about one's risk for Alzheimer's disease.

For the neuroimaging community, ADNI is also an unusual experiment in open-access science. All of the brain scans and other data procured so far are freely available to the scientific community at the ADNI Web site (www.loni.ucla.edu/ADNI/), typically within about a week of being collected, Weiner says. "Hundreds of scientists all over the world have made many tens of thousands of downloads," he says. A significant number of the several dozen papers published so far on ADNI data have been authored by researchers not directly funded by the project, he notes. The open-access policy has given ADNI researchers an incentive to analyze and publish their data quickly, Weiner says. "It's really made me realize the power of releasing all the data."

A late addition

Just as ADNI was getting under way in 2004, researchers at the University of Pittsburgh published the first report on a new method for detecting β-amyloid in the living human brain with a PET scan. The method uses a radioactive compound, called the Pittsburgh Compound-B (PIB), that binds to amyloid plaques. Researchers scrambled to secure funding to add on a PIB component to the original ADNI grant and test it in about 100 ADNI volunteers. In what came as a surprise to some researchers, nine of the 19 volunteers from the healthy control group tested "PIB+," indicating significant β-amyloid deposits in the brain.

Several larger studies that got under way before ADNI have found that about 30% to 35% of healthy people in their 70s and 80s are PIB+, says Chet Mathis, who was part of the team that developed PIB and now heads the β-amyloid imaging core of ADNI. (Mathis has a financial interest in PIB via a licensing agreement with GE Healthcare.) To some researchers, the PIB findings, along with earlier postmortem studies that reported amyloid plaques in the brains of elderly people who died without suffering dementia, are another strike against the amyloid hypothesis, Mathis says. But it's also possible that the healthy PIB+ individuals will eventually develop the disease, Mathis notes. He and others say following those individuals—in ADNI and other longitudinal studies—will be an important test of the amyloid hypothesis.

Indeed, three non-ADNI studies published since 2008 suggest that PIB may be useful for identifying which MCI patients are most likely to progress to Alzheimer's, Mathis says. Pooled together, those three studies found that nearly 60% of PIB+ MCI patients advanced to Alzheimer's disease within a year or two, compared with less than 5% of the PIB-MCI patients. The ADNI data show a similar but less pronounced trend, Mathis says. All in all, he says, the findings so far suggest that PIB is "among the earliest biomarkers" for picking up signs of Alzheimer's.

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Compounds in spinal fluid may also indicate early signs of trouble, says Leslie Shaw of the University of Pennsylvania, who co-directs ADNI's CSF biomarker core. Previous studies found that the CSF of Alzheimer's patients contains low levels of β-amyloid (possibly because circulating levels of the peptide decrease as it becomes bound up in plaques) and high levels of tau, the protein that makes up the fibrillary tangles that are another pathological hallmark of the disease. In an April paper in the *Annals of Neurology*, Shaw and colleagues reported that the same pattern—low β-amyloid, high tau—was present in roughly 90% of CSF samples from ADNI volunteers who entered the study with MCI and progressed to Alzheimer's within the 1st year.

A major theme emerging from the ADNI data is that different biomarkers may prove more useful for evaluating people at different points on the continuum from normal aging to mild cognitive impairment to Alzheimer's. Although CSF and PIB may be useful for predicting who is most likely to progress from MCI to Alzheimer's, other biomarkers may be more sensitive to changes at later states of the disease, says Clifford Jack Jr. of the Mayo Clinic in Rochester, Minnesota, who heads ADNI's MRI core. In a recent analysis, Jack and colleagues found that an MRI measurement of brain atrophy correlated well with cognitive changes over the course of a year. PIB measurements, on the other hand, changed little during this time span, the team reported in the May issue of *Brain*. In that study, Jack and colleagues used a "boundary shift integral" technique developed by Nick Fox of University College London to track changes in the fluid-filled ventricles in the brain, which expand as brain tissue degenerates. This algorithm is just one of many ways to quantify changes in MRI scans, and Jack notes that other ADNI researchers have demonstrated similarly promising results with other methods (see MRI image, p. 389).

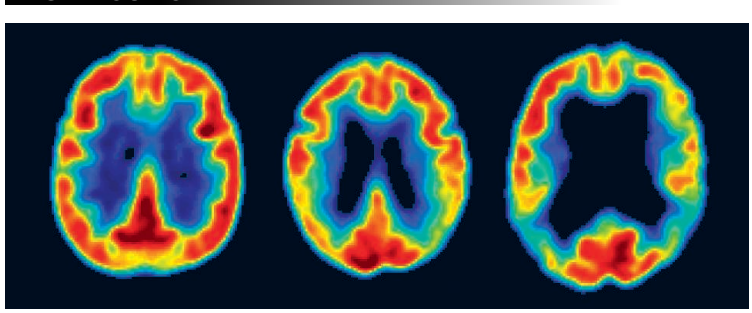
The other major neuroimaging component of ADNI, fluorodeoxyglucose (FDG) PET scanning, also tracks cognitive changes, says Jagust. Unlike MRI, which produces images of brain anatomy, FDG-PET uses radioactively tagged glucose to measure brain metabolism. In people with Alzheimer's, FDG-PET reveals reduced metabolism in the brain, particularly in regions of the parietal and temporal lobes, Jagust says. "FDG-PET is probably going to turn out to be a pretty good predictor in the early-to-middle stages of the disease," he says. One popular hypothesis is that the method will fill in the gap between β-amyloid biomarkers and MRI, picking up changes in brain metabolism that occur when β-amyloid deposition is under way but not yet advanced enough to cause structural damage that shows up on an MRI scan.

Methods on trial

But will ADNI pay off for the pharma companies paying roughly a third of its budget? Their road to regulatory approval for Alzheimer's disease treatments is difficult because the only measures now accepted by the Food and Drug Administration (FDA) for evaluating treatments are cognitive and clinical scales. But these measurements have their downsides, says Laurel Beckett of UC Davis, who leads ADNI's biostatistics core. "The cognitive measures are just so noisy," Beckett says. "They go up and down for who knows what reasons because people just have good days and bad days." That variability, coupled with the slow progression of the disease and the relatively modest effects of most candidate treatments, is why Alzheimer's trials have had to enroll so many patients in hopes of demonstrating a statistically significant effect.

Some researchers hope it will one day be possible to use surrogate markers in clinical trials for Alzheimer's therapies, much as measurements of blood pressure and cholesterol levels have been used to approve drugs for heart disease. Several analyses of the ADNI data have suggested that some biomarkers, such as changes in brain volume measured by MRI, could reduce the number of patients needed by an order of magnitude. However, any Alzheimer's disease biomarker must not only track the progression of the disease accurately but

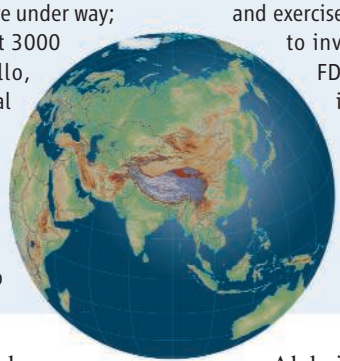
FDG-PET SCANS



Energy crisis. FDG-PET scans show reduced metabolic activity (warm colors) in the brains of people with Alzheimer's disease (*far right*).

Longitudinal Alzheimer's Studies Go Global

In the past few years, several international projects inspired in varying degrees by ADNI (see main text) have gotten off the ground. In Japan, neurologist Takeshi Iwatsubo of the University of Tokyo leads a national Alzheimer's neuroimaging study very similar to ADNI. In China, where the population over 60 is expected to triple by 2050, three large-scale longitudinal studies are under way; each plans to enroll at least 3000 people, says Maria Carrillo, who helps coordinate global Alzheimer's studies as senior director of medical and scientific relations for the Alzheimer's Association. Plans for a Europe-wide ADNI-like effort appear to have fizzled for political and logistical reasons, but several counties have their own projects, many of which have adopted ADNI methods, says Giovanni Frisoni of Fatebenefratelli Hospital in Brescia, Italy.



The Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing (AIBL) will examine the role of lifestyle factors such as diet and exercise in cognitive aging, in addition to investigating blood biomarkers, FDG-PET, MRI, and PIB. The study is not modeled on ADNI, but researchers have adopted some of its methods so that all the neuroimaging data will be compatible, says AIBL Director David Ames of the University of Melbourne. **–G.M.**

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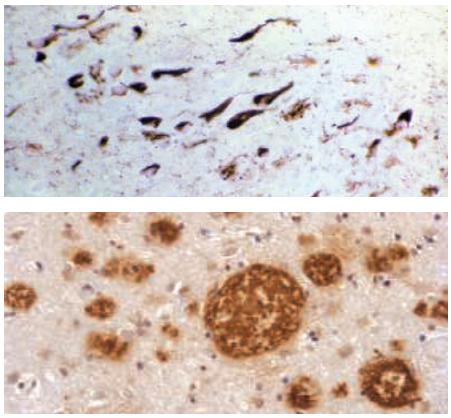
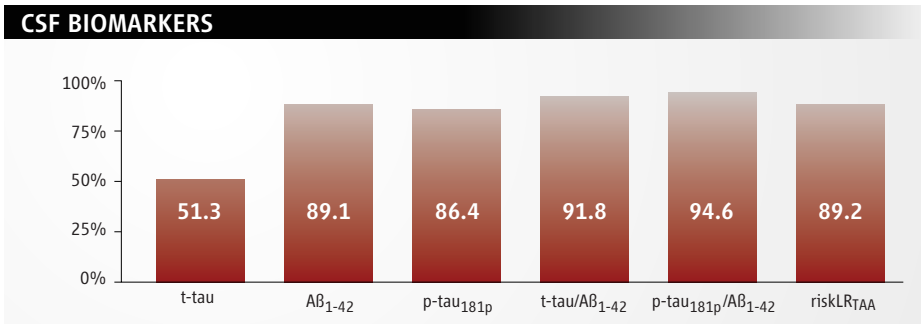




Predicting trouble. A high percentage of ADNI-MCI subjects who progressed to Alzheimer's disease had abnormal CSF levels of various versions of tau (*top left*) and β-amyloid (*bottom left*), two biomolecules thought to play a role in Alzheimer's pathology.

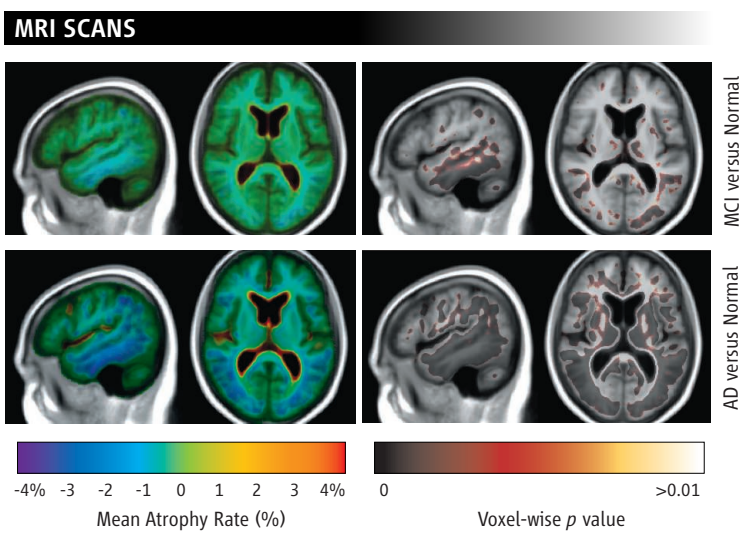
also respond to treatment in a way that mirrors actual clinical improvements, says Russell Katz, the director of the division of neuropharmacological drug products for FDA. It's an exciting possibility, Katz says, but "we're nowhere near there."

Even so, companies are already incorporating ADNI-vetted biomarkers. "Every company that's working in AD [Alzheimer's disease] drug development is designing trials based on ADNI data right now, not as the only tool but as a significant tool," says neurologist Paul Aisen of UC San Diego, who co-chair's ADNI's clinical core and oversees government-sponsored clinical trials as director of the Alzheimer's Disease Cooperative Study

At least one company is already using CSF biomarkers to screen subjects for a clinical trial, and others are considering it, says Aisen. Including only those people who show both β-amyloid aberrations and memory problems may help weed out misdiagnosed Alzheimer's cases and provide a better test of the proposed therapy.

Some companies anticipate biomarkers will help establish that their treatments strike at the roots of the disease. Eli Lilly, which has two compounds in phase III trials for Alzheimer's, is using several biomarkers—including MRI, FDG-PET, and β-amyloid CSF and PET—in hope of demonstrating that these treatments provide biological as well as clinical benefits. "Our studies are set up so that they look quite a bit like ADNI," says Eric Siemers, the medical director of Lilly's Alzheimer's team.

Such evidence won't directly influence the decision to approve the drug. But demonstrating a positive change in a biomarker—in addition to establishing a clinical benefit—might earn a company the right to claim its drug slows the decline of Alzheimer's disease, something no drug currently on the market can claim. Says Katz: "You can imagine the marketing advantage to the first company that gets a drug whose label says it's approved to slow the progression of Alzheimer's disease."



Atrophy analysis. Paul Thompson and colleagues at the University of California, Los Angeles, have developed a tensor-based morphometry technique to measure brain atrophy in the brains of MCI and Alzheimer's patients.

Different trajectories

The 2-year followup data for ADNI subjects has just come in, and Beckett says she's been "going mad trying to compile the data and bring some order out of the chaos." She says what's most striking about the analysis so far is that although the individuals in the normal, MCI, and Alzheimer's groups were intentionally chosen to be homogenous in their clinical profiles, within each group there is considerable diversity in the baseline biomarker profiles of different individuals and in the changes that have occurred during the first 2 years of the study. And that diversity has predictive value, Beckett says. "We are definitely seeing subtle changes in biomarkers that foreshadow both the cognitive outcomes and brain changes."

And the data will continue to roll in. Plans for ADNI2 include a greatly expanded β-amyloid–imaging arm. Because PIB is based on the short-lived Carbon-11 isotope, it has to be made on site, which limited its use to the 14 ADNI centers with their own cyclotron. If approved, ADNI2 will use a newer PET ligand based on Fluorine-18, which has a longer half-life, allowing it to be shipped to centers that can't make it themselves.

ADNI2 would also include a beefed up genetics component, which, like PIB, was a late add-on to the first ADNI study. Researchers published the first work from this effort, a genome-wide association study in ADNI subjects, in August in *PLoS ONE*, reporting several genetic variations linked to hippocampal atrophy in Alzheimer's patients. Several more studies are nearing publication and many more are just waiting to be done, says the head of ADNI's genetics core, Andrew Saykin of Indiana University in Bloomington. "Investigators around the world are going to be chewing on this very rich data for a very long time."

–GREG MILLER

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Published by AAAS

Science

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Science **326** (5951), 386-389.
DOI: 10.1126/science.326_386

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