A new century of Alzheimer's disease research

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Imagine the day when a routine visit to the family doctor includes a simple blood test to predict the risk for developing Alzheimer's disease (AD). If the test returns a worrisome result -- too many sticky brain proteins that might begin to gum up memory and thought in 10 to 15 years -- a person could be offered an aspirin-like pill to keep those proteins in check.

That is the future a visionary team of researchers at Mayo Clinic's campus in Jacksonville aims to reach.

"It will be very straightforward, like today's blood cholesterol test to gauge risk of developing heart disease," says Steve Younkin, M.D., Ph.D., a Mayo Clinic neuroscientist. "If your cholesterol profile is out of whack, treatment with a simple statin drug can reduce that risk. Our goal is to develop a similar kind of testing and treatment to keep the brain in balance."

Researchers and physicians at Mayo Clinic's sites in Florida, Minnesota and Arizona are studying various aspects of Alzheimer's. When combined, the elements provide a comprehensive approach to unraveling the mystery of the disease: from understanding why it develops, to how it can be diagnosed early, treated effectively and, ultimately, prevented.

Much of the basic lab, animal research and drug discovery occurs in Jacksonville. Mayo researchers in Jacksonville, Rochester, Minn., and Scottsdale, Ariz., are studying aging's effects in thousands of elderly

individuals. Researchers want to know how aging changes brain structure, thought processes and blood chemistry, so they can model and predict progression to Alzheimer's disease.

"Whether it is working with people or doing lab science, we have really tried to focus our research on ways in which we can make a difference in the lives of our patients, both today and tomorrow," says Todd Golde, M.D., an Alzheimer's disease researcher who chairs the Department of Neurosciences at Mayo Clinic Jacksonville.

And, by all accounts, that focus will likely begin to pay off in this second century of Alzheimer's research. Until 1986, some 80 years after German physician Alois Alzheimer discovered the brain abnormalities associated with the disease, physicians understood little about Alzheimer's disease. But several decades ago, the pace of discovery began to accelerate, says Ronald Petersen, M.D., Ph.D., a Mayo physician in Rochester who directs the Mayo Clinic Alzheimer's Disease Research Center (ADRC), encompassing the research programs in Jacksonville and Rochester.

"We have moved a great distance forward in understanding what might be the key, or, in the least, an important aspect of this disease," Dr. Petersen says. "And we are at the threshold of developing therapies that we hope will eventually impact Alzheimer's disease."

"We are not slogging through a fog anymore," says Dr. Younkin, who has helped define the direction that Alzheimer's research has taken in many of the world's research labs. "We can see the top of the hill for the first time, and while we probably won't get where we want to be for many years, it is really exciting." Dr. Younkin helped discover that a single brain protein, known as amyloid-beta 42 (AB42), appears to be the central player in the disorder. And much of Alzheimer's drug research is focused on different ways to attack Aâ42, believed to be the

most vulnerable target -- the Achilles' heel -- of Alzheimer's disease.

"We know AB42 is always on the scene and is clearly important," says Richard Caselli, M.D., who heads Alzheimer's disease research at Mayo Clinic in Arizona. "So the prevailing model is that AB42 is it, and if you can somehow control AB42, you can control Alzheimer's disease."

Protein provides initial "insult"

Today, an estimated 20 million people worldwide have Alzheimer's disease. Within the higher-functioning portions of their brains (the areas responsible for thought and memory), twisting tangles of threads made up of chains of tiny "tau" proteins are being assembled inside billions of nerve cells (neurons). Outside the neurons, other amyloid-beta (AB) proteins are fusing together into sticky clumps (plaque) -- akin to the substance that clogs heart arteries. Together, these tangles and plaques disrupt the normal functioning of the nerve cells, destroying the pathways along which packets of chemical "information" move. Memories cannot be stored or retrieved, and, eventually, the brain cannot control the body. Each year about 4.6 million more people develop Alzheimer's worldwide, and that number is escalating rapidly. As many as 4.5 million people in the United States have Alzheimer's, according to the National Institute on Aging, and experts predict that by 2050 that total will rise to approximately 15 million people.

To find out what causes Alzheimer's -- plaques, tangles or both -- researchers first began studying people who developed the disease early, before age 65. A breakthrough came when the gene that produced the AB fragments (amyloid-beta precursor protein, or APP) was found on chromosome 21. This made sense, because patients with Down syndrome, all of whom inherit an extra chromosome 21, typically develop early brain plaques and tangles.

Then scientists linked mutations in two other genes to early-onset Alzheimer's, and these two genes were involved in the production of AB. In 1995, Dr. Younkin and Harvard researcher Dennis Selkoe, M.D., independently found that all three of these mutations increase the production of either AB in general, or a particular type of AB that is made up of 42 amino acids -- just slightly longer than the typical 40 amino acid AB fragment.

Dr. Younkin's finding was pivotal, made just as the scientist moved his laboratory from Case Western Reserve to Mayo Clinic's campus in Jacksonville. An avalanche of confirmatory studies was soon published, and the Alzheimer's research world quickly turned its attention to figuring out ways to disrupt AB production. Some researchers, such as Dr. Younkin, believed that in the brains of people who have Alzheimer's, AB42 is deposited first, providing the initial toxic damage that leads to plaque formation, and then to disruption of tau inside neurons. The concept is known as the amyloid cascade hypothesis and is now accepted by many Alzheimer's researchers almost as a gospel truth.

Early laboratory analysis of AB42 showed that the extra two molecules seemed to form a hook on the amyloid protein, making it more likely to stick to other amyloid proteins in the brain. Thus, researchers concluded that AB42 is highly prone to forming deposits. Synthesized particles of AB42 will fuse to each other within hours in an animal's brain, but weeks are required for AB40 to adhere. More recent research has shown that the AB42 protein folds in such a way that it creates a pleated-sheet-like "template" that acts to chemically attract other proteins, and together these proteins grow in a crystalline fashion like a snowball emerging from a single icy flake.

"With a potential target, many in the pharmaceutical industry who want to design treatments for AD began bearing down on the issue, and that effort has completely turned around the prospects of finding something

that could eventually help our patients," Dr. Younkin says.

Now more than 100 mutations have been found in the three genes that cause early Alzheimer's, and all increase production of AB42.

Of the AB produced normally in humans, 5 percent to 20 percent is AB42. As people grow older, small numbers of plaques and tangles form. The risk that these lesions will cause dementia increases with age; half of all people 85 and older are believed to have some stage of Alzheimer's. Researchers think this common form of Alzheimer's is triggered by a combination of normal genetic susceptibilities and other damage, such as from head trauma or unknown environmental insults. Slowly, AB40 and AB42 build up in the brain and begin to disrupt the thoughts and memories that define who we are.

Ratios predict risk

Dr. Younkin joined a core group of researchers and physicians at Mayo Clinic already collaborating to study the basic biology of the disease and methods of caring for patients who have the disorder. Based on the knowledge that Alzheimer's is a disease of tau tangles as well as AB plaque, these scientists were already developing a mouse that spontaneously overproduces tau proteins.

Mayo Clinic researchers were the first to genetically engineer a mouse to express a mutation of the gene that controls tau production, and in 2000 they reported in Nature Genetics that the "tau" mouse develops the same kind of neurofibrillary tangles seen in human dementia. In 2001, the Mayo Clinic team produced another new engineered mouse, the first to exhibit tangles as well as the two forms of plaque (AB40 and AB42). In the journal Science, Michael Hutton, Ph.D., Dennis Dickson, M.D., Jada Lewis, Ph.D., Shu-Hui Yen, Ph.D., and Eileen McGowan, Ph.D., presented the mouse model, saying it is the best animal model possible to

test therapies aimed at slowing down, or halting, neurodegeneration.

The engineered mouse strengthened the notion that development of tangles followed that of plaque. The tangle pathology was enhanced in regions where the plaque occurred, says Dr. Hutton, a neurobiologist. But what was also interesting was that these mice, the ones that also developed plaque, produced more tau than did mice with only a tau mutation. “That proved that there is an interaction between tau and amyloid, and it is that interaction that causes cognitive deficits,” he says.

These Mayo mice are offered to any scientist studying Alzheimer’s disease for just the cost of producing them. They are also made available to pharmaceutical companies to help them test whether the drugs they are developing could reduce the production of tangles and/or plaque.

The mouse models helped provide a breakthrough discovery for the Mayo Clinic researchers.

Physicians at the three Mayo Clinic sites have been collecting blood from thousands of Alzheimer’s patients, as well as study participants who do not have the disease, to determine how blood chemistry changes over the years (see associated story, Defining Alzheimer’s disease risk with the help of thousands). With support from the National Institutes of Health, they had been examining blood serum for evidence of protein “markers” that could help predict which people would develop the disease over time. One marker is AB.

Although no one knows what the normal function of AB is, the Mayo Clinic researchers found that it could be measured in blood, and that levels of both AB40 and AB42 varied in people who developed the disease. What they discovered through this analysis, however, surprised them, says Neill Graff-Radford, M.D., who heads the ADRC’s Memory Disorder Clinic and has led the work on a blood test designed to predict

a person's risk of developing Alzheimer's.

"Levels of both AB40 and AB42 in the blood rise as a person gets older, but then, in some people, AB42 decreases," he says. Turning to the transgenic mice, the researchers found that as soon as plaque began to develop in the brain, levels of AB42 decreased in the blood and spinal fluid.

Drs. Graff-Radford and Younkin had expected aging and genetic-related overproduction of AB42 -- the insult that leads of Alzheimer's development -- would be reflected in blood samples. But sitting together in a room, looking at the charts that lead statistician Julia Crook, Ph.D., put together, the researchers experienced a classic "a-ha" moment. They saw it. The researchers realized that levels of AB42 had dropped because the protein was being sopped up, absorbed, by quickly forming plaques. In contrast, they discovered that at the same time, plasma levels of AB40 either continued to increase or decline much slower than AB42.

Drs. Graff-Radford, Younkin and Crook found that a low level of AB42 and a higher level of AB40 in blood could be seen three to five years before symptoms of the disease occurred. From these data, the Mayo Clinic researchers determined a scale of ratios for determining when symptoms will begin: two, four, or eight to 10 years.

"This blood test reflects some of the risks of who is going to develop the disease and when it is going to show up," says Dr. Graff-Radford. "The crucial point is that it could eventually offer us a predictive test."

The Mayo Clinic team is continuing to "follow the blood" of 2,000 participants in Rochester, and 1,000 in Jacksonville.

But the researchers know that if their AB40/AB42 ratio blood test ultimately can predict who will develop Alzheimer's disease, people

won't be interested in knowing their risk unless something can be done to reduce that risk.

A pill a day keeps Alzheimer's away

In the late 1990s, Dr. Golde's research group as well as other investigators discovered that compounds that inhibited production of AB actually inhibited AB40 more than AB42. As AB42 appeared to be the real culprit in Alzheimer's, Dr. Golde was convinced that a systematic search for compounds that preferentially lowered AB42 would be successful. However, a two-year effort did not find such a compound.

Then in 2000, Dr. Golde and Eddie Koo, M.D., who worked at the University of California, San Diego, screened several nonsteroidal anti-inflammatory drugs (NSAIDs) at high concentrations. To their surprise, they found that while some NSAIDs, such as naproxen and aspirin, had no effect on AB42, others, such as ibuprofen and indomethacin, did.

The possible significance of this finding was immediately apparent, Dr. Golde says. Large population studies had hinted that people who have used NSAIDs had a lower risk of developing Alzheimer's. While scientists thought these NSAIDs might be reducing inflammation in the brain -- and there is a lot of it in a brain with Alzheimer's -- Drs. Golde and Koo wondered if any might be working to prevent the development of Alzheimer's by selectively inhibiting production of AB42.

Still, Drs. Golde and Koo realized that, regardless of how NSAIDs might be working to decrease the risk of developing Alzheimer's, conducting clinical trials of NSAIDs in populations at risk for Alzheimer's or in those with the disease would be difficult. Long-term use of high-dose NSAIDs can cause stomach ulcers, kidney damage and gastrointestinal bleeding in anyone, and those side effects would be even more prevalent in the elderly. Moreover, if NSAIDs were working by lowering AB42,

Dr. Golde knew very high doses of the NSAIDs would be needed to make a difference in Alzheimer's risk.

This meant that a compound that could successfully and significantly lower AB42 must be one without such severe side effects. So, the first NSAIDs that Drs. Golde and Koo screened were known as COX2 inhibitors because they were believed to be safer. (NSAIDs reduce inflammation because they target enzymes that are known as cyclooxygenases or COX, and classic NSAIDs, such as ibuprofen and indomethacin, nonselectively inhibit the two types of COX enzymes, COX1 and COX2.)

But, again to their surprise, Drs. Golde and Koo found that many COX2 inhibitors actually had the opposite effect on AB42 -- rather then decreasing it, they increased it. The investigators then expanded their search to look more closely at compounds related to NSAIDs that might lower AB42 but result in greatly reduced COX activity.

So they tested a compound called r-flurbiprofen.

R-flurbiprofen is the mirror image of the COX-inhibiting drug s-flurbiprofen, but because it is structurally distinct (much as a person's right and left hands have the same overall structure but cannot be superimposed on each other), it does not inhibit COX enzymes. The result was, finally, encouraging -- r-flurbiprofen inhibited AB42 production both in cells and in the brains of mice.

As it happened, the biotech firm Myriad Genetics was testing r-flurbiprofen to treat prostate cancer, because the agent had shown it could reduce the size of tumors in mice studies. Armed with additional data that r-flurbiprofen decreased AB levels in an Alzheimer's mouse model and improved the cognitive deficits found in that model, Drs. Golde and Koo personally approached the drug company to encourage

them to test
r-flurbiprofen in Alzheimer's disease.

Myriad Genetics agreed, and in 2006 the company reported results from a phase II clinical trial enrolling 207 patients with mild Alzheimer's. The study found that r-flurbiprofen produced functional and cognitive improvements, ranging from 34 percent to 48 percent, in patients who took the highest dose, 1,600 milligrams a day. "And it was remarkably safe," says Dr. Golde. "It was much better tolerated in humans than it was in mice." There was also evidence that the drug not only improved symptoms but may have actually slowed the course of disease, he says. Current drugs offered to Alzheimer's patients only relieve symptoms.

Based on these findings, Myriad Genetics launched a 1,600-participant phase III clinical trial in the summer of 2006, describing it as the largest placebo-controlled study ever to be undertaken of an investigational medicine in patients with Alzheimer's. Patients will use r-flurbiprofen (known now as Flurizan) for 18 months.

Dr. Golde, who is not involved in this trial, suspects that r-flurbiprofen will show some benefit, but that newer, designer AB42-lowering agents might be better. "A more potent drug would likely be more effective, but it will take a long time to develop such a second-generation drug," he says. "The beauty of r-flurbiprofen is that it can be on the market quickly."

Dr. Golde stresses a cautionary note. He worries that because of these findings, people with Alzheimer's, or those who are at risk for developing the disease, might decide to take high doses of an over-the-counter AB42-lowering NSAID, such as ibuprofen. Because of the side effects associated with NSAID use, this could be quite harmful, he says. Indeed, because it does not inhibit COX at therapeutic levels, r-flurbiprofen is not an NSAID, whereas flurbiprofen is, he adds.

AB42-lowering agents may turn out to be “either a magic bullet or a magic shotgun,” he says. “They might be lowering AB42, reducing inflammation and doing five other things that we don’t know about.”

But to Mayo Clinic researchers, the big question is whether this compound, or any other similar kind of agent, can be used much earlier in people deemed to be at risk of developing Alzheimer’s.

“I think Alzheimer’s is going to be much easier to treat if you can prevent accumulation of AB in your brain, than if you try to treat it once plaques form,” Dr. Golde says. “We know that statins don’t work very well if a heart artery is 99 percent blocked, but do if they are taken earlier. The same thing would go for a drug designed to prevent Alzheimer’s.”

If r-flurbiprofen shows solid benefit in the phase III clinical trial, then it could be tested as a preventive agent, Dr. Golde says. But he adds that this “could possibly be the costliest trial ever to be conducted,” because it would take decades and involve thousands of people. However, Dr. Golde and his clinical colleagues share a common goal: to eventually conduct cost-effective prevention trials.

Restoring memory via tau

Mayo Clinic researchers also are working to prevent additional damage from occurring and to repair existing lesions in people who already have symptoms of Alzheimer’s.

In the process, they are attempting to answer the question that has stumped the Alzheimer’s research world: to what degree is AB responsible for the neurodegeneration seen in the disease"

No one knows what AB “normally” does inside the brain. “That is the

biggest secret in Alzheimer's disease research," says Dr. Caselli. "We'd like to know what role it plays."

And no one understands how tau interacts with AB.

Mayo Clinic researchers know a lot about tau, which helps stabilize the roadlike microtubules that run inside nerve cell bodies. In the world of neurobiology, tau is the big player, responsible for about 30 forms of neurodegeneration, including frontotemporal dementia, the second most common form of dementia after Alzheimer's.

Alzheimer's disease is the only form of dementia in which AB is involved.

As Alzheimer's develops, the shape of tau molecules inside neurons changes; they begin to come off the microtubules they had once supported, and bind together into paired and twisted filaments. "The hypothesis is that AB stresses neurons, releasing cascades of signals that affect the phosphorylated state of tau bound to microtubules, causing them to be released," says Dr. Hutton. This process proves to be toxic to the microtubules, which in turn cannot transport the molecular cargo needed to keep the neuron alive.

"Either the roads provided by the microtubules break down because of loss of tau, or tau accumulates into tangles that block these roads," he says. "We don't have evidence as to whether it is the tangles or the loss of tau that is causing cell death.

"The tangles we see are an end-stage event, whereas there is plenty of tau aggregation that occurs before these roadblocks appear," says Dr. Hutton. "In any case, the brain can't cope without tau."

Because of the connection between AB and tau loss, the Mayo Clinic

researchers believe that if AB is treated before the onset of tau damage, progression of the disease can be prevented. “We also know that tau is responsible for neuronal death, so we also have been developing ways to prevent tau toxicity, which could cause a major slowing of the disease,” Dr. Hutton says.

So the researchers turned again to their tau transgenic mouse, which features a unique on-off “switch”¬ to control the expression of the mutant gene so that the disease could be studied at both early and late stages.

During these experiments, the Mayo Clinic group and their collaborators were stunned to find that they could reverse tau pathology early on, and restore memory to mice that had started to develop cognitive problems.

But researchers were in for an even bigger surprise, Dr. Hutton says. “What was amazing, absolutely staggering in fact, is that when we aged the mice further -- to the point where the pathology was quite severe, a lot of neurons had died, and the mouse couldn’t remember any of its tasks -- when we hit this molecular switch, the mouse recovered a lot of its memory.”

To the research team, this demonstrated that Alzheimer’s is potentially a reversible process: that if deposition of AB is not stopped in time, then it may be possible to halt tau degradation and restore damaged nerves. “Once you get the disease, the effectiveness of AB therapy may be limited, so we hope tau will be potentially a more exciting target,” Dr. Hutton says. “If we are able to remove the blockage that is clogging microtubules, it may be that the system will just start again, with neurons back functioning normally.”

Dr. Lewis says the studies suggest that toxicity to neurons caused by tau begins before tangles develop. “If so, we may be able to repair that

process so that the neuron can rebound," she says.

Their achievement was reported in 2005 in Science.

"These tau findings changed our ideas about what the potential for recovery is in Alzheimer's, but also about what is causing memory loss in the patients in the first place," Dr. Hutton says. "Our mice lost between 30 percent and 50 percent of the neurons in the parts of the brain that are responsible for memory function. But, still, sufficient numbers of neurons were left so that some memory function was actually recoverable. The neurons began to work properly once the disease process was halted."

Dr. Hutton says the tau research is five to 10 years behind AB, and the focus of the "tauologists" at Mayo Clinic is to study how tau tangles disrupt microtubules as well as how the brain recovers and removes those tangles. What they find out can be applied to all diseases of dementia in which tau is involved -- and that is the majority, if not all.

Researchers also are busy using the tau mouse to test small molecules that have already been developed for other diseases that may stop tau from initially changing its chemical shape. One design for a therapeutic drug could be to inhibit the molecules involved in the abnormal phosphorylation of tau, and another might be to find a way to stabilize the microtubules. Amazingly, a cancer drug, Taxol, works to do just that, Dr. Hutton says, because stable microtubules cannot divide -- which a cancer needs to do. He is working with a pharmaceutical company to see if such a cancer treatment might work for Alzheimer's disease.

All in the genes

Many diseases spring from a person's unique mix of genes, the variations that flow down the generations through combinations of eggs and sperm.

And given the progress science has made in decoding the human genome, Dr. Younkin is convinced that some day soon researchers will have a blueprint of all the genes that raise a person's risk of developing Alzheimer's, even if by just a little bit here and there.

"In the world of complex genetics, this is a very exciting time," Dr. Younkin says.
He is part of a team of scientists from four institutions who just reported locating the 14th gene that has a statistically significant association with Alzheimer's disease.

In a January 2007 online issue of Nature Genetics, the researchers reported a new gene called SORL1 (sortilin-related receptor). They found that people who inherited certain variations of SORL1 appear to have an increased risk of developing the late-onset form of Alzheimer's. Although they have not pinpointed the exact variations, the researchers connected the gene to disease in six different groups of people, finding that Caucasians who have Alzheimer's displayed a variation in one area of the gene's sequence, while African-Americans, Hispanics and a group of Arabs with the disease displayed variations in a different location. Almost 7,000 people, of whom about half had the disease, were included in the analysis.

In cell culture studies, the researchers found that decreasing the amount of SORL1 protein increased the cells' production of AB.

While SORL1 will likely turn out to be a minor contributor to Alzheimer's disease in general, adding all such players together could ultimately provide the missing puzzle pieces that solve the disease, Dr. Younkin says.

"Alzheimer's is a great disease for doing genetics, because there are clear indications that a person has the disease, which makes it possible to test

that individual's DNA and RNA," he says. Those genes never change, so profiling the more than 300,000 functional inherited variations in the approximately 30,000 genes each person has can define Alzheimer's disease's complex genetic signature, he says.

"We can now look at the difference in gene variants between a person who has Alzheimer's and a person who does not; an analysis like that would only take several days," Dr. Younkin says. "If we can find those variations in thousands of people, we could begin to see which genes play important roles in Alzheimer's disease, and these genes could possibly be targets for novel therapeutic agents."

"It is all possible to do, which is wonderful," he says, but adds that while Mayo Clinic is doing such analysis with the thousands of patients the institution cares for across its three sites, many more people would need to be involved.

As much as Alzheimer's disease research has advanced in the past 20 years, Mayo Clinic researchers say caution is warranted about the future prospect of breakthrough drugs in this decade, or even the next. Dr. Petersen expresses this hesitancy. "There are a million studies that describe how things could be happening, and they make sense, but we don't know that they are true," he says. "We have to keep an open mind."

Still, there has never been a better time, or a brighter outlook, for Alzheimer's disease researchers who spend their careers trying to find an answer to this most devastating of diseases. "Before, there was a lot of faith and not a lot of science. It was like you were leading a detective-like investigation into the Alzheimer's killer using chisels and hammers to chip away at deeply buried clues," Dr. Golde says.

"Now we have the scientific tools and fancy machines that allow us to be so much more productive and to progressively solve this mystery," he

says. “It’s a new century.”

Defining Alzheimer’s disease risk with the help of thousands

As much as investigators worldwide are betting that the sticky plaques made up of amyloid beta (AB) fulfill the role of central villain in Alzheimer’s disease, all researchers know about cognitively normal people who, during an autopsy, were found to have brains full of the plaque.

These patients may not be as sensitive to AB’s toxic effects as others are, some scientists speculate.

But really, scientists can’t explain it.

That is why Mayo Clinic researchers in Minnesota, Florida and Arizona are enrolling thousands of individuals, including patients who do not have memory problems, people in mild cognitive decline and patients with the disease, to participate in what collectively is one of the biggest Alzheimer’s disease epidemiological research efforts in the nation.

In Rochester, which is in Olmsted County, Minn., more than 2,000 residents from 70 to 89 years old have been randomly selected and have signed up. And in Scottsdale, Ariz., 600 asymptomatic adults in their 50s and 60s are enrolled in an effort to define “normal aging.” In Jacksonville, Fla., over 1,000 individuals, including more than 350 African-Americans, are participating. Hundreds of Alzheimer’s disease patients being treated at the three Mayo campuses are also taking part.

With the generous permission of participants, researchers are routinely collecting blood samples to define genetic profiles and look for changes

in blood chemistry, including proteins that are sent floating downstream from the brain.

“We want to put all this information together to create a predictive equation that can determine an individual’s risk of developing Alzheimer’s disease,” says Ronald Petersen, M.D., Ph.D., director of the Mayo Clinic Alzheimer’s Disease Research Center. “The whole idea is to move back detection of the disease process earlier and earlier.”

Such biological profiling could also help in the effort to develop and test therapeutic drugs, he says. “If we have clarified who is more likely to develop the disease, we can allocate treatment appropriately,” he says.

Much of the blood collected by Mayo Clinic in Rochester and Scottsdale is shared with researchers at Mayo Clinic in Jacksonville. “The cross-talk between these three centers is really advancing Alzheimer’s disease science,” says Richard Caselli, M.D., who heads Alzheimer’s disease research at Mayo Clinic’s campus in Scottsdale.

The patients also undergo periodic cognitive testing, and many of them offer to participate in a bevy of different imaging studies. Based on the pioneering imaging work of Clifford Jack, M.D., in Rochester, patients may undergo magnetic resonance imaging (MRI) to examine brain structure, including changing volumes in white matter and hints of vascular damage; MR spectroscopy to assess chemical processing; functional MRI to look at the brain’s reaction to stimulus; positron emission tomography (PET) and glucose PET scanning to examine the functional aspects of performance; and the newest modality, amyloid imaging, which can provide a picture of amyloid deposition in the brain. Dr. Jack’s research has formed the basis of a $60 million, five-year grant, funded by a partnership of industry and the National Institute on Aging, to study these techniques nationwide, according to Dr. Petersen.

Through these studies, Dr. Petersen hopes doctors will be able to provide answers to those worried about developing Alzheimer's disease -- something no one has ever been able to do.

"Having a predictive equation will allow us to say, 'You have a certain probability of developing Alzheimer's,'" he says. "And if the probability is high, and if the therapy is risky or expensive, this information may help us determine how to intervene."

Source: Mayo Clinic