

Stopping Alzheimer's Before It Starts

Three new clinical trials expected to begin next year will attempt to prevent dementia by treating people at risk for the disease before they develop symptoms

ALZHEIMER'S DISEASE HAS STALKED MATT Reiswig's family for generations. His grandfather developed dementia by age 42. "My grandfather had 13 brothers and sisters, and of the 14 kids, 10 developed early-onset Alzheimer's," says Reiswig, a creative director at an interactive firm in Tulsa, Oklahoma. "It's been devastating to my family." Reiswig's father and uncle had symptoms of dementia by age 50, and at age 38, he knows he has a 50–50 chance of developing the disease, probably in the next decade. Those are the odds that he has the gene mutation that runs in his family.

For most people, Alzheimer's disease is a cloud on the distant horizon, a storm that may or may not materialize in old age. But roughly 500 families worldwide live with a more immediate threat: an inherited form of the disease that strikes in the prime of life. Each of these families, like Reiswig's, has a unique glitch in one of three genes. These mutations are cruelly deterministic; those who inherit them are assured of their fate. These families are now the focus of a crucial new stage of Alzheimer's research: They will be subjects in the first clinical trials aimed at preventing the disease by treating people who show no outward signs of sickness.

These trials come on the heels of a decade of bitter disappointment for Alzheimer's researchers, who've seen one promising therapy after another fail in late-stage clinical trials. The latest blow came just last week when Pfizer and its partners announced that they were suspending development of the once-promising treatment bapineuzumab after two large trials found no bene-

fits to mental function in people with mild to moderate Alzheimer's disease. Such failures have raised doubts about the field's guiding hypothesis: that the accumulation of a protein fragment called β amyloid in the brain is a key step in the disease process that ultimately kills neurons and robs people of their memories and the ability to think clearly. Another interpretation, however, is that anti-amyloid therapies have so far disappointed because patients got them too late. If these same therapies could be given years earlier, before irreversible brain damage occurs, perhaps the disease could be prevented.

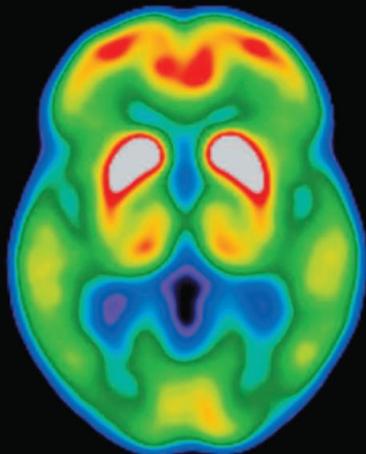
The new trials will put this idea to the test. They will be funded through a combination of support from pharmaceutical companies, the National Institutes of Health, and private philanthropies. Reiswig and his brother plan to participate in a trial affiliated with the Dominantly Inherited Alzheimer Network (DIAN), a consortium led by researchers at Washington University School of Medicine in St. Louis in Missouri. Another trial, the Alzheimer's Prevention Initiative (API), will focus on an extended family in Colombia. A third trial, dubbed Anti-Amyloid Treatment of Asymptomatic Alzheimer's (A4), will take a different tack, treating adults without gene mutations whose brain scans show signs of amyloid accumulation. All three trials are expected to get under way next year in what should be the sternest test yet for the amyloid hypothesis.



Family portrait. Matt Reiswig (second adult from the left) and his brother Marty (red shirt, just right of center) plan to enroll in the DIAN clinical trial. Their father, Lawrence (top), has early-onset Alzheimer's disease.

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Gathering storm. Brain scans of people with a gene mutation that causes early-onset Alzheimer's disease, taken at 5-year intervals, show evidence of amyloid accumulation (warmer colors) up to 20 years (*far left*) before the expected onset of symptoms (*far right*).

Fighting *la bobera*

Alzheimer's disease affects more than 35 million people worldwide. With that number projected to triple by 2050 as populations age, a preventive treatment would be an enormous boon to public health, not to mention a financial blockbuster. But testing preventive treatments in the general population isn't feasible, for practical and ethical reasons. Because any individual's risk of Alzheimer's disease is relatively low and impossible to predict, such a trial would have to enroll thousands of people and would subject many who would never have developed the disease to the unknown long-term risks of taking anti-amyloid drugs. That's where families like Reiswig's come in: Their deterministic gene mutations make it clear who stands to benefit from an experimental treatment and easier to tell if it's working.

Among the coffee plantations and rural mountain pueblos surrounding Medellín, Colombia, neurologist Francisco Lopera has worked for decades with the largest of these families, which will be the focus of the API trial. Lopera saw his first patient, a 47-year-old man with *la bobera*—the foolishness, as it's called locally—in 1984 as a neurology resident at the University of Antioquia Medical School in Medellín. In the 1980s and 1990s, Lopera traveled extensively through the region, braving drug cartels and guerilla fighters to piece together genealogies. In the mid-'90s, he struck up a collaboration with Kenneth Kosik, a neuroscientist at the University of California, Santa Barbara, that ultimately led to the discovery of the cause of the disease in these families: a mutation in a gene called *PSEN1*. Of the nearly 5000 family members, roughly 1500 carry the mutation.

The API trial in Colombia will test the preventive powers of crenezumab, an anti-

amyloid antibody developed by Genentech, a biotech subsidiary of Roche. One hundred mutation carriers will receive an injection of the antibody every 2 weeks, say API co-directors Eric Reiman and Pierre Tariot of the Banner Alzheimer's Institute in Phoenix. Reiman and Tariot say API chose crenezumab because animal studies suggest it effectively mops up several different forms of β amyloid. Also, crenezumab was designed to avoid an infrequent but potentially worrisome side effect of other anti-amyloid therapies: swelling and micro-

hemorrhages in the brain caused by leaky blood vessels. Genentech's clinical trials in mild to moderate Alzheimer's patients have so far found no evidence of this side effect, suggesting it may be possible to give higher doses safely, Reiman says.

In Colombia, a control group of 100 mutation carriers will receive placebo injections, as will another 100 family members without the mutation. This latter group is necessary because the vast

tests, but the team will also collect biomarkers, including scans that show amyloid deposition in the brain. The trial is designed to last 5 years. Lopera says the families are eager to participate. After years of studying these families and watching helplessly as people succumb to the disease, Lopera says his team has a new sense of optimism. "For the first time we will be able to offer a therapeutic option," he says.

A multipronged attack

The DIAN trial that the Reiswig family plans to enroll in has a different design. It will include people with mutations in any of the three genes linked to early-onset Alzheimer's: *PSEN1*, *PSEN2*, and *APP*. The first stage of the trial, scheduled to last 2 years, will test three treatments, says the trial's director, Randall Bateman of Washington University. The final decision on what those

compounds will be has not yet been made, Bateman says, but all will target β amyloid, either by slowing its production or clearing it from the brain.

This first stage of the DIAN trial will rely heavily on biomarkers. Recent work by DIAN researchers has begun to provide a picture of the pathological changes in the brain that pre-

S Video featuring the progression of amyloid accumulation in the brains of gene mutation carriers at www.scim.ag/amyloid_vid.

Alzheimer's Prevention Trials at a Glance

Trial	Participants	Treatment	Outcome Measures
API: Alzheimer's Prevention Initiative	300 members of Colombian families, including 100 carriers of a mutated <i>PSEN1</i> gene	Crenezumab (Genentech)	Primary: Cognitive. Secondary: Biomarkers, including brain scans to measure amyloid accumulation and brain atrophy
DIAN: Dominantly Inherited Alzheimer Network	240 members of families with early-onset Alzheimer's; 60 have a mutation in one of three genes	Three anti-amyloid therapies to be determined	An initial phase will use biomarkers to identify the most promising drug candidate for a follow-up phase to examine cognitive effects
A4: Anti-Amyloid Treatment of Asymptomatic Alzheimer's	1500 healthy seniors, including 500 with amyloid-positive brain scans	One anti-amyloid therapy to be determined	Primary: Cognitive Secondary: Biomarkers

majority of participants don't want to know whether they carry the mutation, Reiman says. Including the noncarriers makes it possible to blind the trial so that neither the participants nor the doctors treating them will know their genetic status. Mutation carriers as young as age 30 can receive crenezumab if they are within 15 years of their parents' age of onset.

The primary measure of the drug's effect will be changes on a battery of cognitive

cede cognitive problems in people with inherited early-onset Alzheimer's. A study of 128 DIAN participants, reported on 12 July in *The New England Journal of Medicine*, found that concentrations of β amyloid in cerebrospinal fluid dip up to 25 years before the onset of Alzheimer's symptoms. This dip is thought to indicate that the amyloid is being taken out of circulation as it begins to build up in the brain. Brain scans reveal amyloid accumulation and atrophy at least 15 years prior to

onset of symptoms. During the first stage of the clinical trial, researchers will monitor these and other biomarkers, as well as the participants' cognitive performance, and then choose the drug—or drugs—that look most promising for extended testing.

Like API, DIAN will also enroll family members without gene mutations so that participants can remain ignorant of their genetic status. But both trials will pay for genetic testing and counseling for participants who want it. Reiswig is one of the few who's decided to take them up on it. He says he's long assumed he has the mutation and he and his wife have lived accordingly, taking vacations and saving little for retirement. If he tests positive, he says the main thing he'll do is have the kind of heartfelt talks with his children that people often put off. He'll make a video, too, so they'll have a reminder of what their father

was like with a healthy brain and clear mind. They never got that chance with their grandfather, Reiswig says, nor he with his.

Scanning ahead

Unlike API and DIAN, the A4 trial will attempt to prevent the far more common form of Alzheimer's disease that's not caused by

a gene mutation. The trial will enroll people age 70 or older who test positive on a scan of amyloid accumulation in the brain, explains Reisa Sperling of Harvard University, one of the principal investigators.

A4 will enroll 500 amyloid-positive participants and 500 amyloid-negative controls in a 3-year double-blind trial that will track changes in cognition. Another 500 people with amyloid-negative brain scans will participate in a parallel "natural history" study of aging and cognition. Sperling says the

group plans to select a drug by December, by which time more details should be available from the bapineuzumab trials as well as another closely watched phase III clinical trial for solanezumab, an anti-amyloid antibody developed by Eli Lilly. Even if both drugs fail in people who've already been diagnosed with Alzheimer's, they might still work prophylactically—or at least that's the hope.

A4 will also include an ethics arm that will examine the psychological impact of disclosing information to individuals about their risk of developing Alzheimer's disease (see sidebar). "This is a really important opportunity to study what people hear when they get this information," Sperling says.

High stakes

A great deal hinges on the outcome of these trials. If they fail, it would be a major blow to the near-term prospects of a disease-altering treatment for Alzheimer's disease and perhaps even spell the beginning of the end for the amyloid hypothesis.

Almost any degree of success, on the other hand, would be a major victory. Although the extent to which the early- and late-onset forms of Alzheimer's involve the same mechanisms is still somewhat controversial, many researchers think there are enough similarities that any therapy that prevents or mitigates the early-onset form would at least be a strong candidate for trials in a broader population. A logical step in that direction would be a trial in people with *ApoE4*, a generic variant that increases the risk of late-onset Alzheimer's disease.

Whichever way these pioneering trials turn out, millions of people who aspire to a sound mind in old age have a stake.

—GREG MILLER



All in the families. Neurologist Francisco Lopera (left) and his collaborator, neuroscientist Kenneth Kosik, pore over genealogies in Colombia.

How to Talk About Alzheimer's Risk

If Alzheimer's disease were written in your genes, would you want to know? Most people do not, say researchers leading two upcoming clinical trials that will try to prevent Alzheimer's in people with gene mutations that cause an early-onset form of the disease (see main text, p. 790). To accommodate the participants' wishes, those trials will not reveal genetic testing results. But what about less certain risks?

Many people do want to know if they have the so-called *ApoE4* genetic variant, which triples the risk of developing Alzheimer's disease in old age, says Robert Green, a medical geneticist at Harvard University and principal investigator of the Risk Evaluation and Education for Alzheimer's Disease study. Over the past decade, Green and his colleagues have looked at the impact of telling people their *ApoE* status. When people who are psychologically healthy find out they're *ApoE4*-positive, they handle the information fairly well, Green says. "Whether they can do something medically about it isn't as important as you might think," he adds. People who find out they are positive often take other measures, such as buying long-term care insurance or joining an advocacy group, Green says.

A third upcoming trial, the Anti-Amyloid Treatment of Asymptomatic Alzheimer's (A4), will enroll people with a different risk factor: evidence of β amyloid accumulation in the brain, widely thought to be an indicator of the disease. In contrast with genetic testing, however, the predictive value of a β amyloid-positive brain scan is not well understood, says Jason Karlawish, a professor of ethics and health policy at the University of Pennsylvania, who will lead an ethics arm of the A4 trial. To enroll in the trial, participants must agree to find out their amyloid status, and Karlawish says he and colleagues are working on how to explain the scans and convey the uncertainty. Researchers will monitor participants for mood and lifestyle changes and examine how β amyloid test results affect their perceptions of their cognitive abilities and future risks.

With the approval earlier this year of florbetapir, a radioactive compound that binds to β amyloid in the brain and makes it visible on a positron emission tomography scan, more and more doctors will start ordering these tests, Karlawish says. He hopes his study will provide guidance for doctors on how to deliver the news, and on how patients are likely to take it.

—G.M.