

## Alzheimer's Talks with Dr. Eric Reiman June 13, 2016

Note: This transcript has been edited for content and clarity.

Welcome to Alzheimer's Talks, a monthly teleconference series presented by [UsAgainstAlzheimer's](#) where we connect you with leaders in the research field who are working to stop Alzheimer's.

My name is [George Vradenburg](#), Chairman and Co-Founder of UsAgainstAlzheimer's which is a patient-centered venture philanthropy, an entrepreneurial and innovative organization, seeking to transform the fight against Alzheimer's.

Just a quick update on some matters. [The key Senate appropriations committee last week recommended to the full Senate an increase of \\$400 million in the base budget for NIH devoted to research into Alzheimer's](#). That would raise annual Alzheimer's investments at NIH from about \$991 million a year to close to \$1.4 billion a year. That budget has to be approved by the full Senate in adopting a full United States government budget. That will be a bit of a challenge given the partisan politics for the rest of this year but we're hopeful that that will eventually end in an approved Congressional budget sometime by the end of the year or early next year.

Also, I'm pleased to announce that a spinoff organization from UsAgainstAlzheimer's called the [Global Alzheimer's Platform Foundation](#) has launched a \$70 million five-year project to reduce the time, cost, and risk of clinical trials by expediting the start of clinical trials and by having a standing network of clinical trial sites committed to faster recruitment and faster trial starts. That has launched now and will continue now, hopefully indefinitely into the future.

Third quick update: [ResearchersAgainstAlzheimer's](#), one of the family of networks that make up UsAgainstAlzheimer's, recently published a [report that seventeen drugs are in Phase III testing](#)—the last stage of testing before presentation to the regulatory agencies here and around the globe; seventeen drugs in Phase III trials which are on pace to be on market in the next five years if successful in Phase III, if approved by regulators. That's all very exciting and what it does is put all the regulators and all the payers like Medicare and all the physicians on notice that we may have some Alzheimer's innovative drugs on market in the near future and that they'd better be ready to address those drugs in a regulatory payer and a clinical context. It's a very exciting time, a great deal of momentum in the field.

And one of the reasons for that momentum is the guest that we have on the line today, [Dr. Eric Reiman](#). He's one of the top researchers in the country. He has masterminded two very, very interesting and important clinical trials in persons at a much higher risk of this disease, introducing a therapy before they get symptoms of the disease to see if we can find methods to actually prevent symptomatic Alzheimer's in those populations. He is also home to one of the, if not the, largest, [registry of individuals](#) who expressed interest in participating in clinical trials. One of the chief barriers, or the chief slowing factor in getting innovative drugs to market is the fact that we need to recruit more people into clinical trials. Dr. Reiman has been a real innovator in thinking through how to use various registry techniques to interest people in participation, and then to get them to sign up.

Just a little background on Eric Reiman: He has an impressive resume. He is the CEO of [Banner Research](#) and Executive Director of the [Banner Alzheimer's Institute](#). He is also the

clinical director of the [Neurogenomics division at the Translational Genomics Research Institute](#), Professor and Associate Head of Psychiatry at the [University of Arizona](#) and Director of the [Arizona Alzheimer's Consortium](#).

Today he is joining us to talk about his work leading the [Alzheimer's Prevention Initiative](#) and what work he is doing at Banner, and some exciting new studies they are working on as well as the registry.

Just as a reminder to everyone. If you have a question at any time during this call, please press \*3 on your phone. By pressing \*3 you will be placed into the question queue. Please have your question ready to share briefly with a member of our staff, or if you are listening to us online you can type your question in the box, and we will get to as many questions as possible after the opening presentation by Dr. Reiman.

Eric, thank you for joining us today, thank you for your extraordinary work, and thank you for what you do every day to try and get innovative medicines to market.

**Dr. Reiman:** Thank you so much, George. I want to begin by thanking [Elizabeth Plant](#), the director of [Alzheimer's Talks](#), for helping to set the stage, for the chance to speak with you, and I want to thank George Vradenburg and UsAgainstAlzheimer's for all they are doing in the fight against this disease. I have known George and a colleague of George's, Meryl Comer, and others for a number of years, and I can tell you that we share a passion for trying to address this problem in the most fundamental way, a sense of urgency, and an impatience for the status quo as we all seek to find new ways to work together and in support of some common goals.

As George mentioned, I'm privileged to talk to you about the Alzheimer's Prevention Initiative, what's happening in the effort to find effective prevention therapies in the shortest possible time and indeed the possibility of finding and maximizing the availability of effective prevention therapies by 2025. I'd also like to tell you about the Alzheimer's Prevention Registry which George mentioned, and if you haven't done so already, to encourage you to take a minute to sign up.

Allow me to begin by underscoring what most of you already know: Alzheimer's disease is an unacceptable problem. It takes a devastating toll on the afflicted person, it takes an intolerable and often under-appreciated toll on family caregivers and with the growing number of people living to older ages, it's projected to take a financially overwhelming toll around the world by the time today's thirty-year-olds become senior citizens. We need to find a way to address this problem and indeed prevent it as soon as we can.

I am a psychiatrist and brain imaging researcher by background, who became interested in the scientific study and prevention of Alzheimer's disease research in 1993, when Duke University researchers discovered the major genetic risk factor for developing Alzheimer's disease at older ages. Inheriting one copy of the APOE4 gene increases the chance of developing Alzheimer's disease at older ages; inherited two copies of the chance increases the risk even further. It led me to think that it might take too many healthy people and too many years to evaluate promising but unproven prevention therapies in trials, waiting to see who might go on to develop memory and thinking problems; it led my colleague Richard Caselli and me to consider the possibility of using brain imaging techniques to detect and track Alzheimer's changes before the onset of memory and thinking problems; and it led me to consider ways in which to set the stage to rapidly test promising prevention therapies in people at risk for Alzheimer's using brain imaging and other relevant measurements.

I was interested in the problem of Alzheimer's prevention for three reasons, and those reasons have become more compelling over time. First, there is a growing number of promising but unproven treatments to postpone, reduce, or maybe completely prevent the clinical onset of Alzheimer's disease. Second, some of these treatments may need to be started even before the onset of memory and thinking problems, when the disease is already extensive, in order to have their most profound benefit. Finally, an even modestly effective treatment could have a profound

public health benefit. For instance, an “Alzheimer’s procrastination therapy” that delayed the clinical symptoms of Alzheimer’s disease by only five years without also increasing lifespan, could reduce the number of affected persons by nearly half.

The growing list of promising but unproven prevention therapies, includes investigational medications and immune therapies that target the accumulation of a protein called amyloid, the major constituent of plaques; a smaller number of investigational immune therapies that target the accumulation of another protein called tau, the major constituent of tangles, another component of Alzheimer’s disease; and other investigational treatments with the potential to interfere with progression of the underlying disease. The list also includes medications that are marketed for other reasons, dietary supplements, and health-promoting diets and lifestyles, which have been suggested but not yet proven to reduce the risk of Alzheimer’s disease.

I am often asked what one could do today to reduce the chance of developing Alzheimer’s disease. While we have a large number of promising treatments, none of those treatments have yet to be proven to be effective, because to prove that they’re effective we actually need to do rigorous trials that compare the investigational treatment to a placebo in a rigorous fashion. Meantime, several of the proposed interventions may have other health-promoting benefits and, like chicken soup, may not hurt. For those reasons, a number of my colleagues and I would typically recommend 1) regular aerobic exercise, 2) social and intellectually stimulating activities, 3) heart healthy diets (e.g., the Mediterranean diet or DASH diet), 4) treatment for diabetes, 4) maintaining a healthy blood pressure, cholesterol levels and weight, and 5) no smoking. Above all, I would like to suggest joining in the effort to find demonstrably effective prevention therapies as soon as possible.

As I mentioned, I have been thinking about what it would take to rapidly evaluate the range of promising prevention therapies since 1993, we decided to get a sneak peek at some of the biological changes that occur in healthy late-middle-aged people at three levels of genetic risk, and we tried to set the stage for future prevention trials. Instead of needing to conducting twenty-year prevention trial in 50,000 healthy late-middle-aged people, waiting to see who might go on to develop disabling memory and thinking problems, we introduced the idea of conducting two-year prevention trials in several hundred healthy late-middle-aged APOE4 carriers using brain imaging techniques to see if they slowed down the decline in brain activity and brain shrinkage that are associated with the loss of brain cells and the accumulation of amyloid.

So we started a nonprofit organization called [Banner Alzheimer’s Institute](#) with the accelerated evaluation of prevention therapies as our primary goal. To begin, we proposed the idea of using brain imaging techniques to evaluate the ability of a cholesterol-lowering treatment to slow down the brain changes associated with Alzheimer’s in healthy late-middle-aged APOE4 carriers. As it turned out, our colleagues in pharmaceutical industry were not yet ready to embrace that idea. They noted that even if we could show that the treatment slowed down brain imaging “biomarkers” of Alzheimer’s disease, the FDA would be unlikely to approve the treatment based on the treatment’s biomarker effects alone.

As the FDA has long noted, there are examples from other areas of medicine in which a treatment’s biomarker effects failed to predict a clinical benefit (e.g., treatments that increased biomarker measurements of bone density failed to reduce the risk of fractures). For those reasons, the FDA has noted that it would be unlikely to approve a treatment based solely on its biomarker effects unless one could show a relationship between clinically proven treatment’s biomarker and clinical effects. At first blush, that sounds like a “catch-22:” If one could clinically proven treatments, why would we need the biomarker in the first place?

Rather than give up, my Banner Alzheimer’s Institute colleagues Pierre Tariot and Jessica Langbaum and I decided to up the ante by proposing a more ambitious research program, called the Alzheimer’s Prevention Initiative (API), to help establish both the scientific means and the accelerated FDA approval pathway needed to rapidly evaluate the range of promising treatments and help the field find ones that work as soon as possible. API includes two

complementary five-year trials in healthy people who, based on their genetic background and age are at particularly high imminent risk for the onset of memory and thinking problems due to Alzheimer's disease. It also includes the development of unusually large registries to inform potentially interested volunteers about emerging prevention trials and help speed up enrollment in those trials.

The Alzheimer's trials that we had in mind were to study people at high imminent risk based on their genetic background and age; we thought we would start with anti-amyloid treatments that are now in development to really not only evaluate these treatments that have a lot of promise but to provide a better test of the leading idea of what leads to Alzheimer's disease and the accumulation of amyloid, then failed trials in the later stages of the disease where one begs the question, were we too little, too late, such that even failed studies would help to advance the field and provide encouragement to target other elements of the underlying disease.

The first study we proposed, we proposed a study of people who carried a rare misspelling of a gene that caused them with virtually 100 percent certainty to develop Alzheimer's symptoms and to do so in their thirties, forties, and fifties. And it turns out about 500 extended families around the world carry one of these rare misspellings. This causes them to develop Alzheimer's symptoms early; their children have a one in two chance of developing the gene; and if you meet these families they underscore the urgency we all have in the fight against Alzheimer's disease.

Since we were interested in conducting this study in a way that would be sufficiently large to see if the treatment would work, we wondered where we could do such a study—and by the way, the Alzheimer's Prevention Initiative is co-led by my Banner Alzheimer's Institute colleagues, [Pierre Tariot](#), [Jessica Langbaum](#), and me, and it's just a privilege to work with them and so many other wonderful people in this effort—in any case, it took us to Medellin, Colombia. And work that Dr. Francisco Lopera's colleagues were doing and people with the world's largest extended family who are affected by this unusual form of Alzheimer's disease that we call early onset autosomal dominant Alzheimer's disease.

Think of your largest family reunion and now think of families, distant relatives all descended from the same ancestor, in which we now have cognitive testing in over 5,000 of these family members including identification of this mutation in more than 1,000 of these individuals who are destined to develop symptoms at the average age of 44.

So we began a five-year study with funding from the National Institutes of Health, from a philanthropy, and from a partner. We had a selection committee help us to find the most promising anti-amyloid treatment we could; in this case the partner is [Genentech](#) and it is an antibody therapy that targets amyloid and so far has shown a lot of safety. When the study was announced as part of the national plan to address Alzheimer's disease, it helped to galvanize interest and support for the feasibility of doing prevention trials.

It's more than a prevention trial, in that it's not only trying to evaluate a treatment in a way that might lead to approval if the findings are compelling in this group, but it includes all of the best established biological measurements of Alzheimer's disease at baseline two years and five years so that if we're lucky enough that the treatment works and gets approved in this group, it would be nice to show which treatments, which biological measurements respond to treatments and which biological effects predict a clinical benefit such that it might be possible to have an approval pathway just based on biological effects in those two year prevention trials we've been talking about.

Our next study for which we've got funding from NIH, philanthropy, and our partners [Novartis](#) and [Amgen](#), is of two different treatments, an amyloid active immunotherapy some would consider that to be a vaccine therapy that's administered in this case four times a year, and an oral medication we call a BACE inhibitor that interferes with the production of amyloid providing a more diversified approach among these different approaches to see if we could reduce the

risk of Alzheimer's disease by targeting amyloid in these ways. And it has many of the same data and sample sharing elements.

So both of these trials are intended to evaluate investigational anti-amyloid treatments and the treatments that might lead to approval in these populations provide the best possible tests of the amyloid hypothesis, which we need to know one way or the other. But we also consider these biomarker development programs in which we hopefully can provide the evidence needed to support the conduct of two-year prevention trials in people at increased risk for Alzheimer's disease, based on genetic background or biological measurements.

These studies are thought to provide a foundation for other trials, we are privileged to do them in a way that complements, supports, and benefits from other prevention programs such as the [Dominantly Inherited Alzheimer's Network, or DIAN](#), which is also in people who have these rare mutations, and [the A4 trial in older adults](#) who have biological measurements of amyloid accumulation which is present in about thirty percent of all older adults over the age of thirty.

What we're proud of is the idea of getting an agreement to share these data and biological samples after the trial is over. That was not conventional wisdom when it was proposed. More programs have to do that. And we think that sharing that information will help the field develop faster ways to test prevention therapies.

To help support these programs, we developed a program called the [Alzheimer's Prevention Registry](#), an online resource where it takes less than a minute to sign up, and provide one's email address, some other contact information and general demographic information; it doesn't require participants to do anything, or to sign up for future studies, but they have an opportunity to learn about the latest developments in prevention research, and if they're interested, follow up with one of the studies we mentioned that may be available for people like themselves or people they know. [Click here for more information and to sign up](#).

And as a related part of the Registry, we've recently developed a program called [GeneMatch](#) in which individuals who are fifty-five to seventy-five years of age could sign up to receive a kit in which they can swab the inside of their mouth, return it to the lab for genetic testing. The genetic test results are kept private and secure and are not returned back to the participant. However, the genetic results are used to help match people to studies, and those studies may require people to learn their genetic test results. GeneMatch participants are never under any obligation to join a study.. Part of the rationale for GeneMatch was our second prevention trial, the [Alzheimer's Prevention Initiative's Generation Study](#) in people who are in the highest imminent risk for developing the more common form of Alzheimer's disease that begins at older ages, and that's people with two copies of the APOE4 gene, which is about two to three percent of the population. We have recently just begun a study of these two other treatments in people with two copies of the APOE4 gene. This will be in more than ninety sites on three continents and you can imagine the amount of work it has taken to get to the point that we could do these studies.

In each of these API trials we want to see if we can slow memory and thinking abilities progression to the clinical stages of Alzheimer's disease and learn how these biomarkers behave. Unlike the API ADAD study in Colombia, where family members do not receive information about their genetic status because there's not a standard for disclosing this information, and historically only ten percent of families have wanted to know about that, in that case we study people who carry the mutation and another group of individuals from the family who don't, all of whom get placebos. In the API Generation Study, we are planning to study more than 1,300 people with two copies of the APOE4 gene between sixty and seventy-five years of age.

To give you an idea of how large that is, we in Arizona follow the largest group of people with two copies of the APOE4 gene in longitudinal studies, that's about 100 people. So the effort to

find more than 1,300 people who would be interested and eligible for this study is an ongoing effort. We're excited about that.

We think the study of these people at the highest imminent risk could provide a foundation to support the identification of treatments for everybody and to do so we have in mind the idea of doing so by 2025. So how do we do that?

What we suggest is now that we have a plan to try to share these biological measurements that could be used to evaluate promising prevention therapies in a way that could lead to marketing approval, it is time to start doing two-year prevention studies in a wider group of people at risk for Alzheimer's disease now, since the data is available while we're waiting for the results of these longer-term studies. So imagine two-year prevention trials in people with either one or two copies of the APOE4 gene, at younger or older ages; people who have evidence of amyloid in their brains, older adults; [patients with Down Syndrome, all of whom develop amyloid plaques in their brain and are at risk for developing Alzheimer's now that they're living to older ages](#); and those individuals with those rare misspellings of the gene.

We are extremely excited about the opportunity to participate in this effort. We feel also a tremendous responsibility to get it right. There's a lot of collaboration and interaction with other groups. We believe a win for one is a win for all and we need to get there. We need to investigate not just these investigational treatments but also those lifestyle interventions that I've mentioned along the way and we need to keep the pressure and momentum up so that we continue to move in this direction. We cannot guarantee that any of the proposed treatments will actually work but we think there's a fifty percent chance that one or more of them will, and we would argue that there's only one way to find out.

Thank you for your interest and your time. I really appreciate the opportunity to talk with you today.

**George Vradenburg:** Thank you very much, Eric. What you're doing is exciting and of course the whole concept that one might be able to take some sort of therapy at a time that you didn't have the symptoms and defer, delay, or prevent the symptoms from developing is really quite exciting in what you would have thought was a dream only five years ago. The fact that you're investigating that approach is really quite exciting for the whole field. We did get, from James Benfield, a request that we send or repeat the registry address so I'm going to repeat it: [www.endalznw.org](http://www.endalznw.org) is the registry address. Please, everyone write that down, go, and sign up and as Eric has mentioned, it's one minute to sign and you'll get information about what's going on in the field as well as information, if you're interested, in what else you might be able to do to participate in trying to find a cure.

Just so that I understand, I'm going to call it the Medellin trial, the trial in those individuals with this mutation, Eric, you said the average age of onset of symptoms in this population is roughly forty-four years old. You introduced this therapy in those individuals at what age?

**Dr. Reiman:** Thank you for asking, George. Our colleagues in Colombia have demonstrated that the average age to develop what we refer to as mild cognitive impairment is forty-four. The average age at which one develops dementia, the term we use for disabling impairment in memory and thinking abilities is forty-nine. We are studying people who are cognitively unimpaired and are thirty to sixty years of age.

**George Vradenburg:** Thirty to sixty. So let me just assume that you introduce this into people at thirty years old, and that half of them are getting placebo and half of them are getting the interventional therapy. How long are you going to have to wait in order to see whether there is a higher rate of progression to MCI and then to dementia, in order to tell whether or not the drug is having a positive effect?

**Dr. Reiman:** That again is a great question. So our primary endpoints that we're using in this study, the main measure of success, is actually a combination of memory and thinking tests that

we developed in using longitudinal data for other groups that helped to provide the most sensitive way to track subtle memory and thinking problems that subsequently led to the clinical stages of Alzheimer's disease, and which we then confirmed using longitudinal data in Colombia. We call that the API composite cognitive test score, which we think has added value and there are elements in a number of prevention trials as well. But we're also looking at time of the progression to mild cognitive impairment or dementia. And we believe that we have adequate power to detect an effect within a five-year study with a number of participants in this study. If the treatment had an even more profound effect one might be able to see that change earlier, and stop the study if the data were compelling. In prevention, in clinical trials, there's an independent group known as a data safety monitoring board that assesses both potential benefits and adverse effects during the course of the trial so that they can decide, they can tell the investigators who know none of this information whether to continue the trial or stop it. And we have those programs in place. But we anticipate the study will continue for five years and we think we have enough power to detect that effect over five years.

What we're concerned about is the idea of being able to have the power to detect the slowing in memory and thinking programs in the broader group of people at risk for Alzheimer's disease, like people with one copy of the APOE4 gene which causes some people to develop symptoms but not others. So for studies like those, we just think that the future is going to be these even shorter studies with biological measurements that don't fully depend on slowing down memory and thinking problems and we need to develop the means to do that. If it turns out that we provide compelling evidence, that these biological measurements should be used, regulatory agencies like the FDA will still want to follow people over time after they are approved and already out there helping people, just to confirm that the biological measurements were predictive of clinical benefit but I think that's where we need to get, ultimately.

**George Vradenburg:** Well, as you know, the current standard by which the FDA evaluates a drug is whether or not it has a clinical meaningful benefit in both cognition and in daily functioning, so we are at the moment a fair place away from getting to the promised land that you describe of being able to evaluate a drug based upon either improvements in cognition or simply improvements in a biological marker.

**Dr. Reiman:** Again, a great question. So when we first started raising these ideas, one of the really valuable things we did was to convene, continue to convene, unusually large groups of stockholders, patient and family stakeholders, federal stakeholders, industry representatives, and regulatory agency representatives including leaders at the FDA and I think one of the most important developments in advancing prevention research when we were raising these issues and the approach we were taking in API using these cognitive endpoints was the encouraging feedback we had in public meetings about the possibility that endpoints like these might be of benefit depending on what the data look like at the end of this study. And that encouraging feedback, I think, is what has led a growing number of private and public stakeholders to start planning prevention trials on their own. What we raised during that vetting process with the group including the FDA is imagine you're studying people in their 30s and 40s and they are declining. There's no other reason that they're declining in their memory and thinking abilities at that age, other than this gene. And we have a treatment that slows down those memory and thinking declines. Do we really need to wait until we have dementia and some more marked evidence of an impairment in their activities of daily living? I have been consistently encouraged by the feedback we've had from regulatory agencies that they are prepared to look at that data, understand the issues, and consider the possibilities once the data are available.

**George Vradenburg:** That's part of our job, to try to persuade the FDA to begin to alter its thinking based upon the advances in regulatory science that you're developing.

We do have a question here from Steve Lawrence and I'd be curious as to your answer. When you're asked, what do you say when people ask, "Is Alzheimer's hereditary?"

**Dr. Reiman:** So, scientific studies suggest that about seventy percent of a person's risk of developing Alzheimer's disease may be attributable to genetic factors. We now know that the APOE4 gene is the major genetic risk factor for developing Alzheimer's at older ages; we know of about twenty other genes, common genes, that very modestly affect a person's risk, not have any utility in predicting a person's risk but provide information about maybe how to target treatments based on knowing what those genes do. And we have those less common genetic causes of Alzheimer's, with Down Syndrome and autosomal dominant Alzheimer's disease. But even if genetic factors account for seventy percent of the risk involved Alzheimer's disease overall in the general population, that leaves thirty percent of non-genetic risk factors that could be used, that might be targeted in ways to delay the onset of the symptoms. And if we can find the right kind of interventions, whether they are investigational treatments as we try to go for a home run, or lifestyle interventions that may have substantial delay in symptoms. If we could delay the onset beyond a person's life span, wouldn't that be great? We think there's an opportunity to do that.

**George Vradenburg:** Laura sent one online. Given your expertise on APOE4, what is your view on the possibility of gene editing such as with CRISPR to convert APOE4 to APOE3?

**Dr. Reiman:** First of all, there have been remarkable developments in genetics including what has been up until now primarily research techniques like CRISPR to really make these refined edits in one's underlying genetics. I don't think that they're going to be ready for prime time in the foreseeable future for Alzheimer's disease. They're going to have, in Alzheimer's disease, more of a role in the research setting. But I do think that in the meantime there are ongoing efforts to try to develop treatments that modify the APOE protein that is produced by these genes and get them to be more like APOE3 and APOE2, the other common forms of APOE that are associated with a lower risk than APOE4. So we do think that modifying the APOE, the protein itself, may be a valuable way to proceed.

**George Vradenburg:** I've got a question here from Paula. What's the advantage of finding out now, if you're prone to developing Alzheimer's if there are no known therapies currently available? I feel it would simply cause one to be depressed if one was to find out that they may have a high risk of getting the disease.

**Dr. Reiman:** That is a great question and that's one that is a major focus of our API study in people with two copies of the APOE-4 gene, and by the way, that study is called the [API Generation Study](#). One of the goals in that study is to learn what the impact of receiving genetic information is, in this new era in prevention research. There was a study called the [REVEAL Trial](#) a few years ago led by Boston University in which they provided genetic information and looked at the impact on a person's life and it turned out to be more tolerable than many consensus groups had thought about. But what we've argued for some time is that there are three eras when it comes to risks versus benefits and disclosing a person's genetic status. There's the current era which doesn't tell us with certainty whether or when we might develop symptoms; while we're protected against discrimination for medical health insurance we're not yet protected for long-term care insurance or disability insurance or life insurance. There's also the question of what you would tell family members.

That said, some people have found it valuable to learn their genetic status, they have argued that the approach the Alzheimer's community has taken has been overly paternalistic and it is available for people who want to know, with what I would argue the proper genetic counseling so that they could understand the benefits and risks. But it is uncertain and somewhat controversial.

There's another era in which we have an effective prevention trial and it becomes more of a no-brainer whether you should consider getting genetic testing if it tells you what to do to prevent your chances of developing Alzheimer's disease. But what we've argued is that there's this third in between era that we've now entered and that's the era of prevention research. So imagine in our trial the risk of learning one has two copies of the APOE4 gene which doesn't determine for sure that they're going to develop it, but it could be sobering information, raises questions about



what to tell one's children for instance. But on the other hand, if I was sixty to seventy-five years of age and I had two copies of the APOE4 gene, I'd want somebody to point me to a prevention trial so even though these treatments aren't proven yet, it could help to empower me to participate in trials I might not otherwise participate in.

So one of the goals of the API Generation Study is to learn as we disclose this information to a subset of individuals in GeneMatch who are eligible to participate in these trials, is to learn what it means to get this information and to understand the impact. And we think that will be valuable to the field. We think it will be valuable because we anticipate there will be a time when there are demonstrated effective prevention therapies and we need to find the right ways to disclose information, provide genetic counseling, and to make that available for a much broader population even though it's not necessarily ready for prime time, not today.

**George Vradenburg:** Eva Ambrose asks a closely related question. How do we determine who should take a preventive treatment if successful? Will a doctor need to diagnose you with something in order to prescribe the treatment once it's approved? And assuming since you've indicated with the exception of some autosomal dominant individuals that there's only a higher risk but not a determining characteristic to the genetic information, is simply your genetic status going to be a basis for whether or not you should take a treatment or would you want something else for the doctor to do before prescribing?

**Dr. Reiman:** So that is a wonderful question, a very important one. And the answer is that it depends, in part, on how effective the treatment is, what is known about its tolerability and safety, and perhaps, to some extent, its cost. If it turns out a treatment can be as effective after somebody has amyloid in their brain—and by the way we've shown in Colombia and colleagues from DIAN have shown, in other groups, that amyloid accumulation begins more than two decades before the onset of symptoms on average—if we can show that you're as likely to respond to treatment after you have biological evidence of amyloids in the brain than if you have it earlier, then you can imagine the possibility that there will be biological tests, whether it's an expensive PET scan or lumbar punctures as available today or less expensive tests in the future, you can imagine the potential to monitor the onset of, for instance, amyloid accumulation so that, not unlike getting a mammogram or colonoscopy, hopefully less invasive, and determining when to begin. But it may be possible for some treatments that you need to begin even before the onset of a lot of amyloid accumulation and so it may be a combination of factors such as one's genetic status and age. For instance studying, introducing APOE4 carriers prevention therapy say starting at the age of fifty. All of this will depend on what we learn from these trials and the features of the particular medications themselves. If we had a treatment like a cholesterol lowering treatment perhaps, or let's say a healthy lifestyle intervention that had other health promoting benefits, and was safe for all, we would encourage the opportunity to make that available to all. Then the question comes up, how do we support adherence to treatments like that, that we think would work.

**George Vradenburg:** Question from Dirk Walter about the status of the A4 study and how the A4 study relates to the studies that you're doing in APOE4 and autosomal dominant population?

**Dr. Reiman:** [The A4 study](#) was the first prevention trial to introduce another anti-amyloid antibody treatment, called solanezumab in older adults who have evidence using positron emission tomography of amyloid plaque accumulation in the brain, which I mentioned is found in about thirty percent of people older than the age of seventy who are cognitively unimpaired. And so the advantage of a study like A4 is that if they find an effective treatment in that group, it could be generalizable to a much larger percent of the population from the beginning. The challenge with that study all by itself is that if it failed to work, it would beg the question, were we too little, too late even in healthy individuals once somebody had extensive amyloid accumulation and so the advantages of the genetic studies that I've described is that they have an opportunity to study people who we know are developing Alzheimer's disease, about a third of whom in our trials do not yet have a lot of amyloid and may provide a better test of the

amyloid hypothesis. So by doing these studies, by having a range of studies like these happening, these are greater than the sum of their parts and have added value for all of us.

The other advantage of the genetic studies is we just have a lot more longitudinal data to date, on what happens to people over time, what happens to their biological measurements, their memory and thinking problems. So we have a little bit more confidence about how powerful our studies are to detect an effect. I am thrilled that our colleagues are doing the A4 trial, that our colleagues are involved in the DIAN trial. We and other groups continue to learn from each other, to chart new territory together, to address not only scientific issues but ethical issues, social issues, cultural issues, so that we maximize the chance that we get it right and not inadvertently set the field back as well as to advance the conversation.

**George Vradenburg:** We have a number of questions here about non-pharmacological interventions specifically, I guess, an opinion from you about coconut oil, flax seed, omega 3 and DHA supplements, and neurofeedback mechanisms or some sort of brain stimulation. I'm curious about your views about each of these sort of non-pharmacological interventions and the prospect of preventing Alzheimer's or Alzheimer's symptoms.

**Dr. Reiman:** In each of those cases, there is either biological evidence, in the test tube or animals, or in community based studies, epidemiological studies, to raise the possibility that these and other interventions may have a role, but there is not yet compelling data in clinical trials for any of them. If one asked my colleagues in the field what they themselves would do based on the availability of information, I think many of us would suggest getting your omega 3 fatty acids, through fish, in diet, and we might be less likely to be taking dietary supplements right now. But imagine the potential to set the stage to do two-year prevention trials, say in APOE4 carriers or amyloid positive older adults who are part of much longer term studies in older adults to determine whether these treatments are slowing down the underlying disease. I think we have an opportunity to find out.

So what I recommend for people who ask me what I would do, or in some cases when it comes to exercise, what I say and what I would like to do more of, are some of those other healthy lifestyle interventions that I've mentioned, with aerobic exercise possibly being at the top of the list. In terms of the dietary approaches, these dietary approaches typically include food with green leafy vegetables, fruits, and whole grains. The DASH diet which stands for dietary approaches to stop hypertension which has been suggested to improve cognitive aging, if not Alzheimer's disease, emphasizes vegetables, fruits, and fat-free or low-fat dairy products, whole grains, fish, poultry, beans, seeds, and nuts. The Mediterranean diet, which has also been studied in community based studies, limits red meat, emphasizes whole grains, fruits and vegetables, fish, nuts, olive oil, and other healthy fats. The caution I would draw from community based studies is that just because you see an association between use of one of these agents and lower risk doesn't mean that's what caused it. There can be other factors that cause certain people to use that, that might actually protect them, factors like higher levels of education, or other health factors.

An example of this came from the suggestion, years ago, that hormone replacement therapy would have a role in reducing the risk of Alzheimer's dementia by half based on several epidemiological studies and the Women's Health Initiative Memory Study conducted a study which they sought to do over ten years to see if it would reduce the risk of Alzheimer's dementia. To have any chance that they would see an effect they had to start at age sixty-five and to their surprise, to everybody's surprise, it actually was associated with a higher risk of dementia. That doesn't mean that a hormone replacement therapy still doesn't have a chance to work in late and middle age, or that we can find the right kind of hormone replacement therapy, but it does remind us that we need to be cautious about interpreting epidemiological data. So if I would recommend anything at this time it would be other heart healthy interventions that we know have other health benefits along the way.

I would argue, in terms of what you can do know, the best thing that I think people can do right now is to be vocal stakeholders when it comes to the fight against Alzheimer's disease and keep

the pressure up for all of us to be evaluating the range of these treatments and giving us the best chance to see if one works. Again, I think we have about a fifty percent chance that now one of these treatments will work and we'll be able to demonstrate its benefit, and for the larger at-risk population, by 2025. When we started this effort, there was no chance because it wasn't feasible.

**George Vradenburg:** My colleagues here at UsAgainstAlzheimer's repeatedly say, 'the first person cured of Alzheimer's will be in a clinical trial'.

So just as a reminder, if you want to know more about Eric's work, go to [www.endalznw.org](http://www.endalznw.org). Thank you very much, Dr. Reiman, I very much appreciate your time today, and everyone, we will send you this link in the recap message. We will also post it on our website. I'm sorry to those questions we did not get to today.

If you've not already joined UsAgainstAlzheimer's, please go to [www.usagainstalzheimer.org](http://www.usagainstalzheimer.org) and sign up. We'll send you a recap of this call, invitations to future calls, important updates, simple ways that you can get involved. I hope that you will join us.

Thank you to everyone on the phone or online for participating in Alzheimer's Talks today. In about a week, we'll have a copy of the recording and a transcript on our website for you to share with friends. As always please stay on the line if you would like to leave us a message with a question or a comment. We're particularly interested in what you'd like to hear discussed on future calls.

Thank you, Dr. Eric Reiman of the Alzheimer's Prevention Initiative, thank you very much, Eric for joining us, thank you all for joining us today, and have a good afternoon.