Alzheimer's Talks Transcript

with Dr. Randall Bateman

September 17, 2015

Note: This transcript has been edited for content and clarity

George Vradenburg: Welcome to Alzheimer's Talks, a monthly teleconference series presented by UsAgainstAlzheimer's where we connect you with the leaders in research and policy who are working to stop this darn disease.

My name is George Vradenburg, Chairman and co-founder of UsAgainstAlzheimer's. We are an entrepreneurial and innovative solutions-oriented organization, seeking to transform the fight against the disease by working broadly with all interested parties and with a certain passion and intense focus for ending the disease by 2020.

If you have not already joined UsAgainstAlzheimer's, please go to www.UsAgainstAlzheimers.org and sign up. And we will send you important updates and simple ways that you can get involved. We know we can stop this disease, but we can't get there without your help. So please join us. It's going to take—as our name suggests—all of us against Alzheimer's.

Thank you for joining us today to hear from Dr. Randall Bateman about some really important research.

We have about 800 people today who have signed up to be on this phone call or to receive the transcript. They're from thirty-nine states plus D.C., Canada, and Austria. So, willkommen. If you have a question during the call, please press *3 on your phone. You will be placed into the question queue. Please have your question ready to share briefly with a member of our staff; we'll try to get you live on the air as soon as possible with Dr. Bateman when we open it up for questions. Or, if you are listening online, you can type your question in the box, and we will get to as many questions as possible after the opening presentation. Unfortunately, we will not be able to answer personal specific medical questions during this call.

I do want to introduce you to Dr. Randall Bateman. He is the Charles F. and Joanne Knight Distinguished Professor of Neurology at Washington University School of Medicine, one of this nation's preeminent Alzheimer's disease research centers. Randy is perhaps one of the leading researchers in the field with a global reputation and a global reach with his trial and his work. He is working with UsAgainstAlzheimer's on a number of projects including reforming the clinical trial system so that we can speed up a search for the cure. He is also an investigator for the Charles F. and Joanne Knight Alzheimer's Disease Research Center and for the Hope Center for Neurological Disorders at Washington University.

He is also, importantly for today's call, the Director of the Dominantly Inherited Alzheimer's Network Trials Unit (DIAN-TU), which aims to prevent the onset of memory impairment and dementia by launching the first clinical trials in what is characterized as autosomal dominant Alzheimer's disease, or genetically inherited disease, which Dr. Bateman will describe in some more detail in just a second.

Randy, Dr. Bateman, we look forward to hearing more about your research, specifically about the DIAN Trials Unit, why it is unique, and opportunities for our listeners to get involved.

Dr. Bateman: Great. Thank you, George. I'm going to start by reviewing some of the background information about Alzheimer's disease and the different forms of the disease, and then I'm going to get into a bit of the history and some of the scientific developments that have occurred over the past several decades in Alzheimer's disease, before moving on to some specific studies in this autosomal dominant Alzheimer's disease.

Alzheimer's disease has likely been known by society and in history for at least several thousand years. There are texts that date back in Chinese and Egyptian text, of people who were afflicted with a disease that caused loss of memory as well as loss of cognitive function and ability to take care of themselves associated with increasing age. These clinical descriptions that have been found almost certainly were describing what we today call Alzheimer's disease. Many people ask: what is Alzheimer's disease, and when did it start, and where did it come from? The answers to those questions are still being sought, but Alzheimer's disease is a form of what we call dementia, and dementia means some cognitive impairment and impairment of our ability to do the things we normally do, such as work, take care of ourselves and others, and our activities of daily living. This form of dementia has now become the most common kind of dementia in the world, largely because of the society—we're getting older, we're aging. Alzheimer's disease is remarkably age-dependent. Its risk doubles every five years past the age of sixty, so that by the time people are sixty-five years old, the risk may be only a few percent, two or three percent. But as we reach seventy-five years old, the risk increases upwards of ten percent, and by the time people reach eighty-five years of age or older, the risk can be as much as forty to fifty percent, or almost one out of two people being afflicted with Alzheimer's disease.

The disease was first described, by modern medicine, by Dr. Alois Alzheimer, after whom the disease is named, in 1906. He described the disease by looking at the brain, the organ that's afflicted by Alzheimer's disease, and by describing the pathological changes that are present in the brain that are associated with Alzheimer's disease. Two pathological findings were very key to the modern understanding of what causes Alzheimer's and these include something called amyloid plaques—these are microscopic protein plaques that deposit within the brain—and tau tangles. These tau tangles exist in the thinking cells, the neurons, of the brain. He described that in exquisite detail in 1906; subsequent to that, cases were reported and found all over the world in typically younger people where they were looking for these cases.

In the 1970s and 1980s, researchers made a very significant observation, which was that this disease, these amyloid plaques and tau tangles, could be found in *older* people, and as the population was aging at that time it was becoming quite common. Back then, people talked about senility, or hardening of the arteries, or dementia in general, as the reason for cognitive impairment and decline as people aged. But this insight led to the realization that Alzheimer's disease doesn't just occur in rare individuals at an early age but it occurs in older people. As we get older the same pathology appears and the same clinical symptoms appear. So with that realization, scientists began to focus more time and attention into understanding these amyloid

plaques, the tau tangles, and what causes the cognitive impairment and the clinical dementia of Alzheimer's disease.

Some 106 years after the very first patient, Auguste D., was described in Germany as having Alzheimer's disease, a sample of her brain tissue on a microscope slide was analyzed, and it was discovered that that first patient had a mutation and a gene that was thought to cause Alzheimer's disease. The first description of these kinds of mutations was made in the early 1990s, that mutations, which were discovered in genes called the amyloid precursor protein presenilin 1 and presenilin 2, were found to be sufficient to cause Alzheimer's disease at a relatively young age, in people in their thirties, forties, and fifties, who carried these mutations. And that really launched the modern molecular biological revolution of Alzheimer's disease research, by understanding what genes were involved, which proteins were involved, and how Alzheimer's could be caused in people. The scientific and medical fields began to, in earnest, develop treatments, which were targeting the underlying process of Alzheimer's disease.

Starting really in the 2000s, clinical trails have been designed and some have been launched and run, targeting these proteins, and targeting the causes of Alzheimer's disease. At the time, the patients who were enrolled in these trials had mild to moderate Alzheimer's disease, and what we mean by that is, when people have problems taking care of themselves or taking care of others, we call that mild to moderate Alzheimer's disease. But in fact, what our research and others' research have clearly demonstrated over the past ten years, is that Alzheimer's disease starts long before people are not able to work or drive or complete a checkbook. It begins likely some twenty-plus years before that happens, and the progress, the changes that occur in the brain that lead to that impairment, are now beginning to be better understood.

And so one of the key questions is: how do we treat Alzheimer's disease? How can we cure Alzheimer's disease? How can we prevent Alzheimer's disease? These questions are difficult to answer because one needs to stop a process, a disease process, that occurs in people and has occurred for many hundreds of years, and the way we do that is with a scientific approach. We've had excellent strides and advancements made in other diseases. For example, cardiovascular diseases, stroke, migraines, multiple sclerosis, and now, cancer, have all had significant wins in countering these diseases with scientific advancements targeting the causes of these diseases at their root. And by the same token, we think that Alzheimer's disease is well on this path of understanding what causes the disease, developing treatments which can specifically target it, and then treating patients in a way to get a clinical benefit.

There are many questions that still need to be answered. Some of these questions include: who do we treat; at what stage of the disease should we treat them; and what do we treat them with? Another large question is, at what dose should we use drugs which are designed to change the process of Alzheimer's disease? It's an interesting historical precedent that penicillin is a fantastic wonderful drug. But it failed its first few clinical studies because in one case it was administered through the wrong route, and in another case it was given at too low of a dose. So even a fantastic medicine like penicillin can fail if it's not administered at the right dose or in the right patients. And so with Alzheimer's disease, what our research has been focused on is trying to determine when is the ideal time to treat the disease and with which drugs and at what dose and which patients.

I'm going to come back to these patients that harbor these mutations that cause very early onset Alzheimer's disease as being a key not just for understanding Alzheimer's disease, which they've greatly helped, but as a key to being able to treat and even prevent the disease from coming on in the first place.

So this autosomal dominant form of Alzheimer's disease turns out to be quite rare. It's less than one percent of all Alzheimer's disease, and its presentation however is quite similar to what we call sporadic or late onset Alzheimer's disease, that typically occurs after the age of sixty-five. These people will begin with amnestic symptoms, difficulty remembering things in the recent past, which progresses to forgetting more things in the recent past, including longer term memories, cognitive deterioration including making decisions, generalized cognitive decline, language can be affected, and during these cognitive and clinical changes, there are changes that also occur in the brain that can now be monitored in the clinic as well as in research.

For example, MRI scans can measure the shape and the size of the brain to determine parts of it that are shrinking in what we call atrophy. Newly developed scans now can see the pathology of Alzheimer's disease, the amyloid plaques in the brain through these PET scans that use tracers that bind to amyloid plaques, and very recently-developed scans can now see these tau tangles, the second pathology of Alzheimer's disease, in living people. And so whereas ten to twenty years ago, we used to teach our students that you can only diagnose Alzheimer's with one hundred percent certainty with a brain biopsy or an autopsy, now there are these tools that can detect the pathology of Alzheimer's disease while people are still alive. And these advancements have led to breakthroughs in our understanding of when these changes occur, both as people have the symptoms but also well before it. And in our study of dominantly inherited Alzheimer's disease, the Dominantly Inherited Alzheimer's Network, we've found that these changes of amyloid deposition start fifteen to twenty years before the very first symptoms occur. Similarly, studies in sporadic Alzheimer's disease suggest similar findings, that this amyloid deposition likely occurs many years before the first symptoms begin.

Other scans looking at how the brain utilizes energy and glucose, a sugar that it consumes, as well as biomarkers of these proteins that deposited amyloid plaques and tangles found in cerebrospinal fluid, the fluid that surrounds the brain, can be determined by research and have been shown to not just help diagnose patients with Alzheimer's disease but even predict those who will go on to get Alzheimer's disease. And so the field is rapidly moving to an era where we can diagnose and now even partly predict who's at risk for getting Alzheimer's disease. All of this is critically important and our goal is of one day treating and preventing Alzheimer's disease.

The Dominantly Inherited Alzheimer's Network is a large global network of families who inherit this rare form of the disease, of a mutation that causes in them with near one hundred percent certainly that they will get the disease. Now these are mutations in APP, PS1 and PS2, these are not the common genetic variants risk factors such as APOE. There is an APOE-4 allele, for example, that increases one's risk of Alzheimer's disease but it doesn't guarantee that one will get the disease. It simply increases the risk above what a person who has a different APOE allele such as 3 or 2 might have. In contrast, mutations in APP, PS1 and PS2 that cause this dominantly inherited Alzheimer's disease nearly universally cause the disease and do so at a very young age. People will have their first symptoms on average at about forty-five years old. Some people may get symptoms in their thirties. Others may get it in their fifties, and it appears to be specific to both the mutation as well as the family that has that mutation, in terms of age of onset.

But, there's a silver lining in this, in that it provides a way to predict not just who will get the disease but about when they will get it. So by knowing about when someone will get the disease, that has allowed us to develop and launch one of the first prevention trials in Alzheimer's disease. By prevention, what we mean is that in people who carry this mutation, we're now testing drugs to see if we can stop the Alzheimer's process before any symptoms or

cognitive loss occurs in these individuals. By treating what we think are the underlying causes of Alzheimer's in these individuals, the prediction is that if those drugs work and are safe and well tolerated, they will be able to stop the onset of Alzheimer's and prevent the disease from starting in those individuals.
In order to do this, it's taken quite a global effort of many different partners from all over the world and this includes support from multiple groups such as our pharmaceutical partners, that have formed a pharma consortium, the National Institutes of Health and the National Institute on Aging have supported this research, as well as other partners, both foundation level, such as the Alzheimer's Association, the GHR Foundation, and other supporters such as Cogstate, AVID, and specialized NIH programs developing new biomarkers.

So what are the goals of this trial? Well, the main goal in this trial is to try to prevent cognitive and clinical loss due to Alzheimer's disease in individuals who have the mutations who are destined to get it at a young age. If we're able to do that, the information that we obtain in these trials with all of these PET scans, MRIs, cerebrospinal fluids through lumbar punctures, as well as clinical and cognitive measures we think will be essential and valuable for accelerating the treatment and prevention for all of Alzheimer's.

For example, if one of these biomarkers is associated and correlates with how well a drug can prevent cognitive loss, we may be able to then use that biomarker as a shortcut to accelerate trials to find even better drugs. That kind of biomarker we call a surrogate biomarker. It means we may be able to use a biomarker that predicts a beneficial drug effect to cut the time it takes to do Alzheimer's trials from many years to much less. And so what that means is, it's much faster. It may be smaller, less expensive, and then we can test many more drugs. Currently the world can only really test so many drugs at a time, because of the incredibly large expense it takes to test drugs in Alzheimer's disease. But if we can speed up this process and accelerate it, we think we will quickly be able to move towards highly effective drugs with the goal of one day being able to prevent and cure Alzheimer's.

The DIAN-TU trial, or the DIAN Trials Unit trial, was launched with two different drugs. One was gantenerumab from Hoffman-La Roche and the other is solanezumab from Eli Lilly. The trial aims to enroll approximately 210 people and we're now nearing completing of that enrollment over the next one to two months, for this initial part of the trial to test whether these drugs can slow down or stop the progress of Alzheimer's disease. And so people who come from families who either have these mutations, or can be tested to test whether they have a mutation, can enter the study, and there's a website to find out more information about this. It's www.DIANexr.org, and this information will be made available after this call, so if you think that your family has a high prevalence of Alzheimer's disease that strikes people at a young age, typically less than the age of fifty-five, then this may be something that you want to seek more information about.

The current trial with the first two drugs is well on its way to completing its enrollment but we're now planning for the next stage, the next generation of drugs to enter the trial in 2016 to 2017. So we expect that there will be an opportunity for enrollment in the future.

In addition to that, there's another study, the DIAN Observational Study, that launched in 2008 under the leadership of Dr. John Morris, and that study has led to much of the information that has informed us about the Alzheimer's process and what changes before people get symptomatic, and has enabled these prevention trials to move forward. That study is also open for enrollment and recruitment so if people are interested, they can go through the expanded registry and indicate their interest. Currently the studies are running in the United States,

Canada, Australia, London, Germany, and other countries are joining the study including Argentina, Japan, Korea, and Italy and other areas of the world will also be joining the study. So I want to emphasize that this is a large global effort and that many of the researchers at universities, doctors, and scientists around the world who both work for companies, as well as universities, have made all of this possible.

I want to thank George for your time to review this information and I think if there are questions, we'd be happy to discuss them.

George Vradenburg: Thank you very much, Randy, that was very clear and very direct.

A couple of things. If I am in a family in which I have Alzheimer's at my parents level or my grandparents level but the symptoms of that Alzheimer's didn't occur until they were in their sixties, seventies, or eighties, can I be confident that I don't have this particular mutation that you're studying?

Dr. Bateman: George, it's very likely that if someone has a family history where most of the people had Alzheimer's in their sixties, seventies, or eighties, it's very likely that that is not caused by one of these very rare mutations. Now, it's not zero percent chance, because some of these mutations can cause a late onset form, but I want to emphasize that the vast majority of families that have Alzheimer's disease in those later years is not caused by the mutation. Typically it's caused by this one genetic variant I referred to, APOE-4.

If there is a high prevalence of APOE-4, there is now a study which is being developed and launched to study people with the APOE-4 allele, and to determine if Alzheimer's can be prevented in those individuals. That study is led by the Alzheimer's Prevention Initiative led by Eric Reiman and Pierre Tariot out of Arizona and their website is www.endalznow.org. So if you know that in your family there's a high incidence of late onset Alzheimer's, or you know that your family has the APOE-4 gene, that's an opportunity to participate in research.

George Vradenburg: Is the Alzheimer's Prevention Initiative Trial now recruiting?

Dr. Bateman: They are now recruiting into their registry and their cohort. I'm not aware that they're recruiting directly into the trial yet but my understanding is that that is likely to start relatively soon.

George Vradenburg: Great. One other question and then we'll turn to some of the people that are sending in questions and are ready to talk to you. You're studying a possible means of prevention in populations that have this particular presenilin or amyloid precursor protein gene, which represent only one percent of the total population of all of the people in the world estimated to have Alzheimer's. So what relevance, if any, is the work that you're doing in this particular population to the ninety-nine percent who have Alzheimer's but don't have this gene?

Dr. Bateman: Right. That is a great question. The relevance is on several levels. The first level is that the dominantly inherited Alzheimer's disease, clinically, cognitively, biochemically, the changes that occur in the brain, all appear nearly identical to that of the later onset much more common form. And because of that, any findings that we have in the dominantly inherited Alzheimer's disease will likely be directly applicable to the much more common later onset form of the disease. And in particular, in a trial where we're testing different biomarkers and different drugs looking for an effect on prevention and treatment, if a test is developed that can predict whether a drug helps Alzheimer's disease, and this trial may provide that, what I called a

surrogate biomarker or a shortcut way to do trials in the future, and that would be a fantastically huge success for Alzheimer's, because as I said we're greatly limited in the numbers of drugs that we can test in any given time, to determine whether they have an effect. But if we have this surrogate biomarker, we can increase the number of drugs we can test by multiple folds. And so the DIAN-TU trial may be able to help provide and support some of those surrogate biomarker developments, and it's one of the main aims, it's why we have those biomarkers.

But there is a second translatable component to the trial and that's that, for example, if a particular drug or drugs are shown to be beneficial in dominantly inherited Alzheimer's disease, that may help support approval of that drug for use for everybody. Let me give you an example. In order for tests or treatments to reach patients, they have to be approved by the national regulatory authorities that are responsible for approving those in each country. If a treatment is found to have an effect, the regulators look at all the data that's available about a drug. And so one can imagine a scenario where you have, say, a trial with a drug in late onset sporadic Alzheimer's disease and you could also have a trial of that same drug in early onset dominantly inherited Alzheimer's disease, and if both of those trials point to the same thing, that the drug is beneficial, then both of those pieces of information could be used to help support approval of a treatment or a prevention for Alzheimer's disease. This is part of the coordination that goes on in the field. There are several other large prevention studies ongoing; one is the Anti-Amyloid Alzheimer's disease study, that's led by Reisa Sperling and Paul Aisen, and that one, they're testing a drug, solanezumab, and solanezumab is also in the trial of dominantly inherited Alzheimer's disease, and if both of those studies align, then that is highly supportive data that regulators need to be able to approve a drug for use in the general population.

George Vradenburg: So we have an interesting question here from Kimberly Brown Azzarello. Basically, if this particular disease condition, this mutation form of Alzheimer's is so rare, what were the advantages or what drew you to doing a study in this population, as opposed to the much broader population? What was either interesting to you, from a scientific point of view, or otherwise of interest to you in studying something that is, on the face of it, so rare, and why not test in the broader, more general form of Alzheimer's?

Dr. Bateman: George, there are several reasons why we—and I want to emphasize that there are hundreds of researchers around the world at academic centers that are involved in the DIAN studies—and so there are several reasons why we really were excited about this particular population, and helping them. One was actually because many of us saw these families in our clinics and saw them in research studies but they were largely excluded from participating in clinical trials to develop treatments because of their age or because they had a mutation. They were not allowed to participate in the very trials that they really helped set the stage for, by participating in research early on in providing those breakthroughs that I had talked about, the mutations and the molecular biology, the development of models of Alzheimer's disease all really came about because of their mutations and their participation in research. So there was this large unmet need within these families who, their cases of Alzheimer's were specially tragic, striking at such a young age while they were working and raising their children, striking down half of the family members with the disease, that they would not even be able to participate in clinical trials. And so that was a strong motivating factor.

But there was also a very strong scientific and medical motivating factor, and the scientific factor that I mentioned was that we know, ahead of time, we could tell from birth, that if someone has that mutation, they will get Alzheimer's disease. And we can tell about when they'll get it. And so when you're designing a prevention study, that knowledge, that information is very powerful in the ability to design a prevention study.

The other points are that drugs were largely developed on these mutations because the Alzheimer's models that are used to screen for these drugs all contain mutations from these families. So, in fact, this is a pure form of Alzheimer's disease that is most likely to respond to the treatments, these disease-modifying treatments, that have been developed. And because of their age, these individual tend to have less other problems—heart disease, strokes, or other things that can impair cognitive thinking—and so it really makes them a pure population of Alzheimer's disease to help study.

So those are some of the reasons why many of us think that this is an incredibly powerful and important population to offer these kinds of studies and trials for. I'd like to throw in another historical precedent which is, back in the 1970s and 80s, there was a thing called the cholesterol hypothesis, where people proposed that high cholesterol levels could increase the risk of heart attacks and strokes. And one of the very first clinical trials which demonstrated a drug called compactin would work, lowered the cholesterol deposits that occurred in the skin. These family members would die of heart attacks and strokes in their thirties, forties, and fifties, and had terribly cardiovascular disease, very high cholesterol levels, and when they were given this drug, those cholesterol deposits resolved, they melted away. And that was really the first clinical sign that a class of drugs would be highly successful in preventing heart attacks and strokes. These class of drugs are called statins. And so that historical precedent, I think, offers several insights including that young families with mutations that have aggressive forms of the disease can point the way to highly effective therapies that can work for all of us, and that these families can benefit greatly, these individuals now are living into their seventies and eighties, gaining decades of life, having dramatic clinical responses, and that these young families can be included in trials to be highly important.

George Vradenburg: That was really clear, thank you for that. There are a number of people who sent in questions before, who actually are in your trial, and were quite interested in the notion of how their trial with respect to their somewhat unique or at least unusual condition was going to benefit the broader community so it was really very clear.

So we have a question here from Sue Halliday online, who asks: So, are you saying there's a pure form of Alzheimer's, early onset, and the sporadic form is more complex?

Dr. Bateman: Yes, I think that's correct. The sporadic form of Alzheimer's disease, late onset form of Alzheimer's disease, we know in addition to Alzheimer's disease, has some other pathologies, other findings that are very common. In fact, it may be that half or even more of the people with Alzheimer's disease also appear to have some other co-morbidity that could contribute to their clinical cognitive impairment, their dementia.
In particular, things like very small strokes, these micro-infarctions, changes in other proteins or deposits that occur in the brain, hippocampal sclerosis, a form of Parkinson's disease that can deposit within the cortex called alpha-synucleinopathy, or dementia with Lewy bodies, and other diseases, commonly come with advancing age. So the drugs that have been developed against these amyloid plaques and these tau tangles we think could be developed to be highly effective against amyloid plaques or tau tangles, but we don't expect them necessarily to improve these other co-morbidities, these other diseases such as small strokes or hippocampal sclerosis. And so what I mean by pure Alzheimer's disease, I mean that without having these other diseases, these other processes present, in a younger population, that the reason that they're having cognitive decline is almost solely due to the Alzheimer's process. Whereas in patients who are older, with Alzheimer's disease, much of it may be due to Alzheimer's disease but we think some of it is being contributed by other processes as well and so even if we're able to

successfully treat the Alzheimer's process we still think there will be some room for improvement by targeting these other disease processes.

George Vradenburg: That's quite interesting. We've had a couple of people online just asking again for the site for the late onset trial out in Arizona, www.endalznow.org for those people who have been asking that online to have that repeated.

Dr. Bateman: George, let me just add to that. There's also the A4 study, that's recruiting people over the age of sixty-five and that's www.A4study.org. That's a trial for people who don't have symptoms but they want to try to see if they have amyloid in the brain, and if they do, they may be eligible to enter a prevention study with a drug.

George Vradenburg: We have a question that came in before the call. The question was really sort of a two-part question. Is there a greater incidence of this genetic mutation that you're studying in men and women, or minorities and whites? And if there is a differential, is there an understanding of why?

Dr. Bateman: The distribution of these vary rare mutations does not seem to segregate at all by whether a person is a man or a woman, and that's what we mean by autosomal, it's not inherited along the lines of sex, nor does it seem to segregate at all between different cultures or races. These mutations are found all over the world in similar prevalence numbers. For example, there are people throughout Europe and the United States, Canada, Australia, aboriginal tribes, Japanese people, Koreans, Chinese, it doesn't really seem to matter, the background of where these mutations arise. What is interesting is that all over the world, in all of these areas, amongst all of these people, these same mutations in these three same genes keep turning up. Alzheimer's in many ways is a uniquely human disease, and there really aren't animals that get what we call Alzheimer's disease, a progressive cognitive dementia that impairs someone to the point of not being able to take care of themselves and leads to death, universally leads to death, caused by amyloid plaques and tau tangles. There aren't other animals that really get that kind of disease, and so in many ways, it's remarkable that amongst all human people that we all are at risk for Alzheimer's disease.

George Vradenburg: We do have a question from James Boland who has a question, and he's in the 208 area code; I don't know where that is. James, do you have a question?

Caller: To clear that up, I'm in Idaho, it's a very low population state, we have no access to any clinical trials of any sort, anywhere, any time, anywhere. There is, in the UsAgainstAlzheimer's talks, there have been referenced several of these things, for people who have found if they take coconut oil, for example, well, there are a couple of trials now using high dose omega 3 and high dose vitamin D with regard to heart attacks, strokes, etc. One very interesting one is out of University of California, can't remember where, where this doctor took ten people who had various things, treated them with all sorts of things, and had outstanding results. I have not seen any follow-up on that, by the UsAgainstAlzheimer's organization.

George Vradenburg: That's Dr. Dale Bredesen's work. I'd be interested in your comments, Randy, on this notion that in fact there are some natural products which taken in either high doses and/or in multiple different variations, different natural products might have an impact in reducing your risk or preventing Alzheimer's?

Dr. Bateman: So, I don't want to comment on any particular study or particular treatment that's happening now, but I will provide my perspective on trials in general and what's come out over

time. Many of you may recall, that back in the late ‘70s, ‘80s, there were concerns that aluminum pots and pans and cans and things of that nature, aluminum in the drinking water and other things, caused Alzheimer’s disease and that was based on some basic studies. That has been completely debunked. Aluminum does not in any reasonably carefully done study cause Alzheimer’s disease. At that time, and since that time, there continue to be periodic changes in attention of nutritional supplemental vitamin based things where people are trying to treat serious diseases including Alzheimer’s. Alzheimer’s is one of these diseases, that it’s so terrible, it’s the most feared diseases in people over the age of sixty-five, for which we don’t have highly effective treatments, we don’t have great treatments yet, that people are desperate and are constantly searching and seeking. And that’s a good thing. It’s good that we’re searching, it’s good we’re seeking for ways to treat these things. However, my perspective is that, over the years, as gingko biloba, as a root of this, or vitamin of that, or these different things have been tested, that these things gain attention in very small studies that are not necessarily carefully controlled, that as they reach larger studies and as the studies are carefully done, every time that these kinds of naturalistic approaches, it hasn’t worked. The only drugs that have really been shown to help are drugs that target a neurotransmitter in the brain called acetylcholine and another one called NMDA, and these drugs have a modest clinical benefit but, in every study that they’ve done that’s carefully controlled they’ve shown a consistent modest benefit and that’s in contrast to these other supplements, where every time they’re studied, they don’t show any benefit at all. So, when I advise my patients who ask me about this, I say, look, it’s fine to try anything you want as long as it’s not harmful, if you want to try it and see if it works, that’s fine. My patients and myself, I would say, we have not found or noticed that any of these vitamin supplements or nutritional supplements have been highly effective.

George Vradenburg: We have another question, from Hanson Clement in it looks like Colorado. Hanson, do you want to ask your question?

Caller: Thank you. I’m a retired physician. The blood brain barrier is certainly appropriate and good to prevent toxicants from getting into the brain, but on the other hand, how much does the blood brain barrier prevent medicines from coming across the blood brain barrier to get into the brain?

Dr. Bateman: That’s a very insightful question; thanks for asking it. You’re right, the blood brain barrier is a wonderful thing, it protects the brain from anything that should happen to come into our blood stream, from everything from infections to poisons that we may consume, things like that. It does its job so well that it’s a major challenge in any kind of brain disease where you’re trying to get the medicines, the treatments, into the brain. In particular, it’s very good at blocking some of the medicines that we’re trying now, larger medicines called antibodies that try to get in to remove some of these things, the blood brain barrier only allows 0.1 percent of them to get in at any given time. Part of the challenge of drug design is you not only have to design a drug that does what it should do and not do things it shouldn't do, not have side effects, and be absorbed, and to be distributed and cleared properly and not have metaboloids, but now you have to also design it to get across this tricky blood brain barrier that’s designed to keep those things out. It is a major challenge in the field of Alzheimer’s to deal with the blood brain barrier but many hundreds and thousands of scientists and doctors have been working on it over the past two decades and have found ways to get these drugs across the blood brain barrier to have an effect.

George Vradenburg: I’m going to ask a question, there are always two or three people who ask this, either before the call or online: What is your best judgment about when we’re going to get, on the market, a means of prevention or effective treatment of Alzheimer’s?

Dr. Bateman: George, as you know, that is an incredibly difficult question, asking someone to predict the future of when a discovery or a breakthrough will be made. That is the hardest question to answer because we're looking for something that hasn't been done before. It's not like running a marathon where you know how far you are. You don't know where the finish line is. We don't know if the next drug will be the next breakthrough. But we have clues that are pointing us, I think, in the right direction. And the clues are, that several of these drugs that are targeting this protein, amyloid beta and amyloid plaques, have now started showing signs and signals that they are improving the cognition and the clinical outcome of patients who take them. And so that, I think, points us in the right direction. Now, when these drugs will prove to be good enough to be approved for use by patients, that is an uncertainty. But if I were to put an estimate, a range, I would say it could be as soon as a few years. I would be surprised if it took us longer than ten to fifteen years, with the right resources, to have a new and effective treatment or partial prevention for Alzheimer's disease.

Now, I also would be surprised if within ten years, we had the perfect cure for Alzheimer's, a medication that completely stopped all Alzheimer's, where no one else would ever get it again, like polio. And so what I think we're going to need, is we're going to need to double down our efforts, put forth fantastic research, bring together our public-private partnerships, our governments, our companies that develop these drugs, our universities and hospitals, that help run these trials, and bring forward more trials targeting, to develop the very best treatments that we can to help, because the Alzheimer's problem is a huge wave that's coming. George, I think you've been one of the most eloquent and outspoken advocates for this approach because I think you recognize, as well as anybody, the great importance our success in the next five to ten years has on society, given the many millions of people who are afflicted and will be afflicted with this disease.

George Vradenburg: One last question here from Carol. Carol, would you please ask your question?

Caller: Yes, hi. My mother had early onset Alzheimer's, diagnosed 52. Her mother, my grandmother, had sporadic later age, a cousin recently died at seventy-six, lung cancer and also dementia. I'm seventy-three, I see changes in me, my friends brush it off as age. I've contacted Stanford for a national study that I qualified for until they found out that I was left-handed. And I understand their reasoning. I called UCSF (San Francisco) and they said no, you have to have cognitive neurological testing and symptoms before you can get genetic testing for APOE-4 and so I'm at a loss as I'd like to have that testing, and I don't know what to do to get it. I'm still able to take care of myself, I still have a brain working, functioning, but at seventy-three, there's a lot of changes and it worries me with my family history. So I don't know how to go about getting the genetic testing. That's my question. Where? How?

George Vradenburg: There's a real practical question.

Dr. Bateman: Yes, that is a fair question. The short answer is, there is a way to receive genetic counseling and testing. We can provide a link to a referral, because other people may be interested as well. Genetics counselors can counsel you about the benefits and risks of that testing and can order those tests, and your doctor and that counselor can tell you about what your results are. So if that's something that you're particularly interested in, you can get that through your doctors who are familiar with it. Perhaps the fastest way is to talk to your doctor and talk to one of these counselors to have that set up. Research studies can also do it, and it sounds like you've tried those avenues. However, those research studies have strict

requirements for people who are eligible in order for them to be successful, and so if you really just want to know the answer to that question, I highly recommend you follow up with a doctor who's experienced with the genetic testing, and a genetic counselor.

George Vradenburg: We will, we'll put it in the transcript, but I'm going to also suggest, Carol, that you stay on the line after the call ends and leave us a message with your email. Don't do it right now, but do it when the call ends. We'll invite you to give us your email and we'll send you that link directly after the call.

Thank you, Randy, for this very, very clear and very important discussion. I want to give a special thank you to Karen and Chris Segal as well as the Zickler Family Foundation. Their contributions have made this call possible. So we're grateful for their support and grateful for the support of anyone on the line whose wish is to donate to permit us to continue these calls. They are very important, they reach a lot of people, and we bring you the best and most recent developments in the research space.

We did have a number of questions we couldn't get to today and for that I'm apologetic, but we do try to end this right on the hour.

As a reminder for those who think they might be eligible and interested in the DIAN Trials Unit study you can call: 1.844.342.6397 (1.844.DIAN.EXR) or email: Dianexr@wustl.edu. We will also include this same information on our website and in the recap message that we will send everyone who registered for today's call. Thank you to everyone on the phone and online for participating. In a week we will have a copy of the recording and a transcript on our website for you to share with your friends.

As a program note, our next call will be on October 13 and will feature the work of the LuMind Research Down Syndrome Foundation. Dr. Michael Harpold, Chief Scientific Officer and Chair of the Foundation's Scientific Advisory Board, will explain why individuals with Down Syndrome experience Alzheimer's disease earlier and at a much higher incidence and rate, and the latest research advances which will hopefully help find a treatment for individuals with Down Syndrome and, just like the specialized population Randy's dealing with, give us the implications for how to treat the broader class of individuals affected by Alzheimer's.

If you would like to register for this call on October 13 at 3 p.m. Eastern, please click here. As always, please stay on the line if you would like to leave us a message with a question or comment. We are particularly interested in what you would like to discuss on future calls.

Thank you for joining us today and have a good afternoon and thank you, Dr. Randy Bateman.