

## Alzheimer's Talks Transcript

Could repurposing drugs help us find a treatment for Alzheimer's?

With Dr. Steven Arnold, Penn Memory Center and Dr. Gary Landreth, Case Western Reserve University  
Wednesday, July 24, 2013

**George Vradenburg:** Good afternoon. This is George Vradenburg of [USAgainstAlzheimer's](#). We welcome you to today's Alzheimer's Talks. Thank you all for joining with us today in what should be a very interesting and hopeful discussion about our efforts to get a means of prevention and effective treatment to Alzheimer's.

As I say USAgainstAlzheimer's sponsors these calls. We are an organization that is mobilized of engaged and enraged individuals to try and stop this disease. Today's call is made possible with the generous support of the [Emmanuel J. Friedman Philanthropies](#) who share our goal of stopping Alzheimer's disease.

Just as a reminder for those of you who have been on these calls and a cue for those who have not - if you, during the course of this call, have a question for one of our presenters or for anyone presenting on this call, please press star 3 on your phone. By pressing star 3, you'll be placed into a question queue. You will not be taken off the call. So don't worry that if you press star 3 that you're going to lose the call, you won't. So, if you have your question ready, we will at the appropriate time when we go to your questions, call on you, and you will then live to be able to ask your question.

Today's call, we are joined by [BrightFocus Foundation](#), who is a great partner and collaborator in the fight to end Alzheimer's disease. They are a very significant and major funder of research in this field focusing on novel approaches to try to gain a means of prevention and effective treatment. So, Dr. Guy Eakin from BrightFocus will introduce our guests.

**Dr. Guy Eakin:** Thanks, George. Again it's a delight for BrightFocus Foundation to be able to work with USAgainstAlzheimer's to bring together this conversation about advances in Alzheimer's disease research.

We know that the average drug costs over 1.2 billion dollars to develop. This is not including the cost of all the other drugs that fail along the path to regulatory approval. That drug approval process is lengthy, it's resource intensive, and we quite simply do not have the resources or the time that the urgency of Alzheimer's disease demands. We have two scientists on the phone today who have been major players in asking a simple question that has a complicated answer. Do we already have a cure for Alzheimer's disease?

It's my pleasure to introduce Dr. Steven Arnold. He joins us from the University of Pennsylvania where he's a professor of Psychiatry and Director of the Penn Memory Center. Dr. Arnold's work has covered identifying new ways of diagnosing Alzheimer's disease. He's been developing the clinical trials designed to test new therapeutic strategies and in 2012, he discovered that insulin resistance, which is associated with diabetes, has also occurred in the brains of people with Alzheimer's disease. Dr. Arnold is a recent addition to the BrightFocus family, having received a grant to explore the crucial next question of whether anti-diabetes drugs might be used to treat Alzheimer's disease.

Then we will hear from Dr. Gary Landreth, who is a professor of Neuroscience and Neurology at Case Western Reserve University and Director of their Alzheimer's Research Laboratory. Gary's relationship to BrightFocus has also covered many years during which he made significant progress identifying how genes that determine risks for Alzheimer's disease might be manipulated to one day cure Alzheimer's. Last year his work culminated in a scientific report that gained national media attention that suggested that a treatment for Alzheimer's disease might be found in a previously existing anti-cancer drug. BrightFocus has been proud to contribute to this test of this idea and what's now an on-going clinical trial. So it's my pleasure to introduce both Dr. Landreth and Dr. Arnold. They've got a lot to talk about, so without further ado, it's my pleasure to turn the conversation over to Dr. Arnold.

**Dr. Steven Arnold:** Okay, well thank you very much Guy and thanks both George and Guy for the opportunity to speak with everyone in this forum. I was thinking about how to present the framework for why we're interested in re-purposing these drugs. I think Guy mentioned a few things, but I wanted to go over things in a little bit more detail in terms of the way many of us are thinking about Alzheimer's disease.

You know what we refer to as Alzheimer's disease in later life is really quite a complicated disease. We try to define it quite simply or simplistically by the presence of abundant amyloid plaques and how tangled these abnormal aggregations of proteins that form in the brain and are associated with the degeneration that occurs in Alzheimer's disease type dementia. You know, in rare cases, typically family cases of early-onset, this can be due to a major mutation in one of the genes that's involved in making amyloid and clearly that's very important and it gives us a lot of clues as to some of the mechanisms that may be involved in the way people develop Alzheimer's disease in their brain. But I think for the much, much, more common forms of Alzheimer's disease that occur in late life, the path to the disease and the dementia is much more complicated. And I think that if we start to take a look at some of the risk factors, aside from age and some of the genes that are involved, we can see that there are a lot of risk factors that may lead us to think about opportunities for treatment. So, I'm talking about some of the vascular risk factors that are increasingly associated with risk for developing Alzheimer's disease later in life - things like diabetes or even pre-diabetes, high cholesterol and other lipids, obesity, smoking, hypertension. There's a lot that I think we can learn about these risk factors and the exact mechanisms by which they promote Alzheimer's type dementia.

For instance, with diabetes or hyperlipidemia, high cholesterol and other fats, a metabolic syndrome, there's a whole host of biochemical factors that affect the brain. There's insulin resistance, so cells lose their ability to respond to the health-promoting effects of insulin, there's

inflammation that these risk factors promote. There's oxidative damage and a whole lot of different changes in proteins and lipids that actually can cause damage to the functioning of cells, including brain cells in the body. So if we look at these factors that seem to promote Alzheimer's disease and degeneration that occurs and also the way in which the brain responds to these things and amyloid intel. I think that we can see a number of opportunities that we can use drugs that have been developed for other purposes to see if they affect similar problems or mechanisms of disease that we think are important in the brain.

I hope I'm wrong, but I don't think that it's going to be one magic anti-amyloid pill that stops Alzheimer's disease but rather a combination of factors that manages these different disease processes and other factors that promote the brain's intrinsic healing abilities as well. And for this we already have a number of candidate medicines. Some very powerful medicines that are used for other illnesses like diabetes, like cancer, like heart failure or certain diseases like psoriasis and some of these medicines may ameliorate or help the metabolic, the inflammatory and other processes that are involved in Alzheimer's disease. So, I think that if we can take these other mechanisms and that's what, you know, I think Dr. Landreth and I have tried to do is to identify some of these medicines that are already used and actually available for other conditions, to actually see if they can work in Alzheimer's disease.

Now this re-purposing of drugs in Alzheimer's disease, it's not really new. There have been large-scale studies in years past of things like Prednisone or Estrogen or Valproate, another medicine that's been used for epilepsy, to see if those medicines can work. But these were long and expensive clinical trials that use these medicines in people with moderate or even advanced disease and the findings were largely negative and I think that we can understand a number of problems in the design of those studies that may have contributed to the negative findings. Since those studies, the field has really advanced tremendously and I think our understanding of the biology of Alzheimer's disease is much richer. I think that we have very, very importantly, the identification and capability to use biomarkers of Alzheimer's disease that are really transforming the field of clinical trials for Alzheimer's disease. So, certain aspects of MRI scans, different kinds of PET scans, spinal fluid testing. All of these give us windows into the brain that we never had before and because we realize that early diagnosis with these biomarkers can let us identify whether there's Alzheimer's disease in the brain even before someone has major symptoms of it. We can use that to intervene and hopefully change the course of the disease before the disease really, really takes hold. So we can think of novel approaches in medicines like Dr. Landreth's very exciting work or our own studies here and based on the availability of some of these biomarkers, we can identify the disease early and perhaps use the biomarkers to see if there is any response at all for good or ill when you give a certain drug to a patient.

We got very interested about a year or couple of years ago, we started studying the insulin signaling in the brain and we found that when we think of insulin, we typically think of diabetes and the amount of sugar that's in our blood, but insulin has a whole range of other properties and particularly in the brain, it's specially important as a growth factor and it's involved in a whole other set of metabolic activities in brain cells and what we found in looking at brain tissue from people who died with Alzheimer's disease, we found that even in people who never had a history of diabetes, that people with Alzheimer's disease their brain cells were resistant to the normal healthy effects of insulin in the brain. Diabetes of course is a very big and important

disease and there's a lot of drugs that are available that are very effective for diabetes and while they help regulate sugar in the blood for people with diabetes, they've never been really looked at to any great degree in the brain and there was a lot of resistance among some of the diabetes medicine companies to actually looking and trying to re-purpose their drugs for Alzheimer's disease or other neurologic conditions. I think there are a lot of economic forces that are stacked against re-purposing drugs that are already available and maybe we can talk about that a little later on as well.

Our idea was to take some of these anti-diabetes drugs, in particular we're looking at Metformin which is the most widely prescribed anti-diabetes drug in the world and to put this into a brief, economical, what I call a nimble clinical trial study design just to see, can it change any of the biomarkers relative to Alzheimer's disease? Can it change blood perfusion to the brain measured by MRI scans? Will it change amyloid or tau levels at all in the spinal fluid after someone is on this? Does it change a person's thinking and memory using very sensitive computer-based tests? So, that was our approach, based on some data coming out of our lab on brain tissue and then looking at what was already available in terms of available drugs and choosing the drug that might have a direct effect within the brain to see if it can be helpful.

So I think that kind of lays out our own rationale here for why we're so interested in this and I think that there are many, many other opportunities and Dr. Landreth is certainly exploring these and let me turn things over to him now.

**George Vradenburg:** If anyone has a question that they think they'd like to put to Dr. Arnold, press star 3. You'll be in a question queue and you'll have an opportunity to ask that question after we hear from Dr. Landreth. So, Dr. Landreth, would you offer your comments too.

**Dr. Gary Landreth:** I would like to thank you and Guy for the opportunity to discuss our work and re-purposing of drugs.

So, I'd like to have a bit more directed discussion towards the rationale for this idea about re-purposing drugs. This represents rather a fundamental rethinking of the traditional approach to drug development and it's driven to a large extent by the fact that it takes about 13 years from the discovery of a compound to its approval as a drug and this is associated with enormous development costs associated with most of just drug development, but then the clinical testing and safety. The other important factoid here is that most of these drugs in developmental programs fail at like the 99% level and so it is actually a rare event to have a drug succeed both in its effectiveness and approved to be safe. So, it's this background, which has driven the idea that if we have a panorama of drugs which have been partially through or completed this FDA approval process, to take advantage of those drugs and then think about their potential utility in other indications for which they were not originally designed.

And so, there basically has been two strategies which have been implemented and one of which is to go to the pharmaceutical companies and ask them what do they have on their shelves that have either been approved by the FDA and failed in their initial trials, or drugs that have been partially characterized and so there have been enormous resources put into developing these, basically having no utility, and so what the National Institutes of Health has done, is to develop a

brand new institute, it's called [National Center for Advancing Translational Sciences](#) or NCATS to do as one of its missions just that. To allow the scientific and clinical scientists and clinicians to go back into, look at these compounds, and ascertain do they have effects in other disease related assays and indeed there is a substantial amount of resources they have put in to this issue by the NIH.

The other strategy is that basic scientists like myself and Dr. Arnold who have tried to dissect the underlying mechanisms that are associated with disease and then once having gone through, basically, discovery processes, learned new things about the drug, go back into these libraries of compounds and try and pick one out that does the job you think needs to be done. That's the approach that we have taken over the last few years.

The major problem with developing new therapies for Alzheimer's disease is basically a fundamental ignorance of the underlying neurobiology of the disease and this is a work in progress and it takes a long time to figure this stuff out and then drug development is really complicated by, one, the long time course of the disease, that is once it's diagnosed, and its progression to increasing disability. But also we, through the wonders of modern medicine, we now have new imaging tools and biomarkers. So we now recognize that the disease process starts one to two decades in advance of these people showing up in their doctor's office with their memory problems. So, Alzheimer's disease represents a really difficult target for drug development. And I think one of the other issues, which is complicated, is up until the very recent past we have only been able to test drugs on people with frank Alzheimer's disease and I think one of the new advances is that within the last few months there has been a recognition that we need to be able to treat people who are cognitively normal but who are at risk of disease or show the early signs of the disease through their biomarkers. So, I think the landscape is basically changing even as we speak.

Now in our own work, we've been investigating whether the basic biology of why some people are at risk of the disease is specifically if you have an APOE-4 gene and we've, through this, investigate this very primary mechanisms of disease. We came to learn that manipulating the ApoE gene expression might be of utility and our contributions to this discussion has really been to sort of recognize how the body or how the brain normally clears amyloids from the brain and it's a normal product of activity of the brain and then the trick is how does the body efficiently dispose of it. And it was our good fortune to happen on to the mechanism for why that occurs and fortunately we were able to sort of dip in to the existing reservoir of drugs and pull one out that performs the exact test we needed to do and to a degree that was serendipitous. So, what we have is we have a rather nice drug that it gets across blood-brain barrier, it elevates brain ApoE levels and so in mice it has a variety of salutary effects. So, we are about to initiate having the first individuals into what's been termed a Phase 1B trial. So, we're going to test, does this drug work in human beings as it does in mice and that is a sort of a central prerequisite to any subsequent development of the drug. We're actually quite excited about that and those trials are currently underway and it's our hope and expectation that although this is one good example that there will be others following.

**George Vradenburg:** Thank you very much Dr. Landreth. Remember if you've got a question, press star 3. You'll be in the phone queue and we'll get to you in just a second.

I've got a question, I take it that one of the appeals of looking at drugs that have already been approved for one indication to determine whether or not they may be useful in treating Alzheimer's is that, in fact, having been through the clinical trial process they've been proven to be safe, at least safe with respect to certain patients and safe with respect to a particular dosage. And my question reflects some questions that we received before this call, if we were to find a re-purposed drug that in fact was effective against Alzheimer's, would it be able to get to market faster because we would be skipping some of the early-stage safety trials? And would companies be incented to develop it if they run out of patent life on those drugs? It's sort of a dual question, are the incentives right and then can it get to market faster? I don't know maybe Dr. Landreth...

**Dr. Gary Landreth:** Okay, so, I actually have an answer to that question. So, I can tell you that it is possible to maybe shave off a decade in drug development time with an FDA approved drug. Because most of the time and expense, especially with the drug development, is actually devoted to safety studies and the sub-score would just have to be tailored to the population you intent to treat. So, the answer is that there is a dramatic acceleration. I think a measure of this is that our work was published about a year ago and we're already into a Phase 1 clinical trial and this is sort of like moving at warp speed by conventional measures.

The issue of the economics of drugs though is actually really quite complicated. In our example, we have this drug Bexarotene, which ran off of patent in April of last year and I can tell you that there is little enthusiasm from pharmaceutical industry about developing this drug and as a consequence we have had to basically rely on public and philanthropic resources to get our initial trials underway. The business models for the pharmaceutical companies do not mesh well with re-purposing drugs and particularly when their patent life has expired.

**George Vradenburg:** So, we've got a number of questions that are coming in and so I think I'll start with Fariba Toofanian who has a question about whether these re-purposed drugs might be available today. Fariba, would you ask your question?

**Question:** Actually my question is regarding the existing drugs that are in the market right now and the efficacy of those drugs, how long can they be given to a patient and when do we stop giving it to them?

**Dr. Steven Arnold:** Okay, well this is Dr. Arnold. I can pick this up. It's a little complicated question. Many of these drugs including Bexarotene and Metformin and other drugs that are being re-purposed are already available by prescription for other conditions. The issue really is, do we understand the safety of these medicines in a group of people like say with Alzheimer's disease for whom it has never really been studied? So is it safe? And then the other question is, while it makes sense that this drug may work for Alzheimer's disease, we don't know whether it does or not and so is there enough reason for you to go to your doctor and say, you know, 'please write this prescription off label for me'? And I think that's the importance of doing these kind of Phase 1 or in our case a Phase 2 trial. These are drugs that are available already, but there's not an indication for them, there may be some conceptual rationale, but there's not really any demonstrated efficacy and that's what we're about is to see whether there are any safety concerns and are there any efficacy concerns.

**George Vradenburg:** I think Fariba's question may have been directed actually to the drugs on the markets today where they're indicated, targeted at Alzheimer's. You know, the existing drugs, symptomatic drugs. To what extent are they effective and how long might someone take them and so it's slightly off topic, but never the less an important question for everyone. So Dr. Landreth, do you have a...

**Dr. Gary Landreth:** Well, actually I think Dr. Arnold might be more appropriate to answer that, I mean the existing drug Aricept which is the most prominent certainly has a limited range of efficacy and period over which is useful in patients to which it does work.

**George Vradenburg:** Dr. Arnold, do you want to add to that?

**Dr. Steven Arnold:** All right. So you know, we have basically 4 approved medicines for the treatment of Alzheimer's disease: Aricept, Razadyne, Exelon, and Namenda are the major ones. Three of them are pretty similar, Namenda's a little bit different. I think in general they show a little bit of benefit for some people in terms of symptomatically delaying progression of the disease a little bit, but they are certainly not the answer to these medicines and many of us just do not know when's the best time to put someone on or take someone off these medicines is. I think that's the reason why we're so desperate to find drugs that both can change the course of the disease which these current drugs can't and to hopefully improve symptoms and a person's functioning as well.

**Dr. Guy Eakin:** George. This is Guy Eakin with BrightFocus. If I could add one comment to that last question. You know, Dr. Arnold mentioned these nimble trials that Dr. Landreth mentioned a low enthusiasm on the part of pharma. And this talk is all about creating an advocacy movement around Alzheimer's disease and this is exactly where the advocates have an opportunity. These nimble trials \$500,000/\$1,000,000 can run these early trials to gauge the early safety or early efficacy profile and this is exactly where we need philanthropic money going. Just wanted to throw that in right there.

**George Vradenburg:** Thank you Guy. I've got an interesting question here from Dr. Chris Carter about the potential sex differences in the effects of some of these re-purposed drugs, particularly in the metabolic space. Chris?

**Question:** Yes. My question relates to at least my reading that there are sex differences in the deposition of amyloid and tau on brain autopsies suggesting that it might account for some of the sex differences in the prevalence of the disease. So, Dr. Arnold, when you made that comment about the Metformin and the fact that the cells in your brain autopsies appear to be resistant to the healthy effect of insulin, my question is did you study this separately for men versus women?

**Dr. Steven Arnold:** Well, we actually looked at about 150 cases in our studies, both men and women, and we did look for sex differences and we did not find them. So, in terms of the way the brain cells were responding or not responding to insulin. And then we looked at many, many other signaling proteins in the insulin pathway. We did not see any major differences or significant differences between men and women, but you do raise an important point about

being aware that there may be sex differences and I think it is important to incorporate those kinds of analyses into any of the studies that we're doing.

**Question:** Thank you very much.

**George Vradenburg:** I'm going to turn to Joanne Hurley from Phoenix, Arizona.

I should mention by the way that we have representatives of people from 42 states, Turkey, Ukraine, and Canada on the phones. Just so that you doctors know that you're speaking to a wide, geographically dispersed audience.

Joanne Hurley's from Phoenix, Arizona and has an interesting question relating to nutritional products. So, Joanne?

**Question:** Thank you very much. Dr. Arnold your risk factors were wonderful and I wonder why when all of those risk factors—every single solitary one that he has mentioned—has a demonstrated nutrient solution that's already been tried and put into use. It's a matter of lifestyle choices and it's easily taught, it has practically no cost to it, can be implemented immediately, has nothing to do with poly-pharmacy or anybody else, any political group. Why are we ignoring these 18 or 20 scientists that are doing all the work on this.

**Dr. Steven Arnold:** Well I happen to agree with you in many regards. I don't think, you know, lifestyle is the whole issue here but it is a big issue and, you know, as Dr. Landreth had mentioned, you know, we're able to identify the seeds of Alzheimer's disease beginning probably a couple of decades before someone actually has the disease and that's why I think that looking at different aspects of nutrition, at physical exercise, at mental activity, if we can modify these risk factors, with the high blood pressure, the sugar diabetes.

**Question:** Well those have all been demonstrated, you know that.

**Dr. Steven Arnold:** Right.

**Question:** So why aren't we doing it?

**Dr. Steven Arnold:** They've all been demonstrated and I think that, but we have never really studied those over enough period of time to see whether you can improve them early on, 10 years later, 20 years later that your cognition, your brain health is going to be better. I think your prediction and my prediction and many of our predictions in the field, is that it will and I do think that what we do, you know, I'm in my 50's what I do now in my 50's is going to determine whether I develop dementia in my 70's or 80's. So, I think good attention to those factors is a major thing.

**Question:** Thank you very much for listening.

**Dr. Steven Arnold:** Sure.

**George Vradenburg:** Dr. Arnold there have been some recent press reports coming out of Lancet about the declining prevalence of dementia in certain older populations and the speculation is that because some segments of the population are doing a better job at controlling their other risk factors, on a population basis we are seeing a decline in prevalence of Alzheimer's in certain age categories. Would you comment on that?

**Dr. Steven Arnold:** Yeah, we've been looking at some of the large epidemiologic studies from Kaiser, from various places and some people have actually predicted or you know Kristine Yaffe had a nice paper a couple of years ago that if we could better manage the vascular risk factors in particular, that we could decrease the prevalence of Alzheimer's disease or delay it a couple of years, you know, by 30%, 40%, perhaps even 50%. Well, maybe that's what we're seeing with some of these new data coming out of Europe. We are treating these factors better, we're recognizing them better, we're more aggressive about managing them and maybe we are seeing some of the fruit of that aggressive vascular risk management in these decreasing numbers.

**George Vradenburg:** I'd like to go to Connie Donovan in Barrington, Illinois, who has a question about the clinical trials of these re-purposed drugs.

**Question:** Hi. Thank you. My question is for Dr. Landreth who referred to clinical trials currently underway. I don't know if they're being done at Case Western or somewhere else, but I am curious about the population that has been or is being recruited for these trials with the re-purposed drug that he mentioned. Knowing that the seeds are sown one to two decades before symptoms appear, are these trials involving younger folks, like the worried wells, the people who have first-degree family members who have been diagnosed already. Who is involved in these trials?

**Dr. Gary Landreth:** Okay. I can tell you, in our first trial, we're simply looking at normal individuals and, you know, probably mostly college kids to do basic safety studies.

But you ask an extraordinarily interesting question, is who should we be testing these drugs on? So I can tell you that we've had a room of trialists and there are as many opinions as there are trialists. But I think that the dominant opinion is, we should be looking at individuals who are at higher risk of the disease, that is individuals with genetic mutations and that's being done both in a study called DIAN and also the study in Columbia. There is a group of patients who possess the APOE-4 allele who are at higher risk and those patients are being targeted in another trial and would be an appropriate population for us to treat. So, I think what you're saying is exactly right. We need to get in and look at people in advance of frank disease, that is at the earliest stage of disease we can identify and ascertain whether we can either delay or prevent disease onset in those populations. And I think what you're saying is exactly right, that we really need to look at people that are younger and at the early stage of disease. I think we've rather conclusively demonstrated that we've had very little luck in treating people with diagnosed Alzheimer's disease.

**Question:** Right and the clinical trial databases that a lot of people go to are focused on people over 65 and as you said, we haven't seen much of anything that can be done for those folks. Delay of symptoms I guess maybe, but as you pointed out, the 4 or maybe it was Dr. Arnold, the 4 drugs

that are currently being used may help a few people a little bit. But that's why I'm excited about what you're doing and I'm curious about, you know, who is going to be recruited for those trials or who is currently in them. Obviously your baseline would be healthy college kids.

**Dr. Gary Landreth:** ...the landscape has just changed. The FDA has now rewritten the rules that'll now allow cognitively normal individuals to be tested on drugs and that was not previously possible. So, I think, this is a work in progress.

**Question:** Thank you.

**George Vradenburg:** There is a trial, called the A4 Trial, which will start recruiting early next year. In which an anti-amyloid drug, not a re-purposed drug but an anti-amyloid drug is going to be tested in people over 65 who are cognitively normal but who have a positive amyloid PET scan. So, there is a drug that is at least going to be tested in the older populations, but cognitively normal populations that have a positive amyloid PET scan.

I'm going to return to Pat Beekley who has a related question regarding Metformin and other diabetes drugs.

**Question:** Hi. I was curious about, I'm speaking now for my dad, who was recently diagnosed with early stages or moderate stages of dementia. But he also has Type 2 diabetes. Now, I didn't hear you mention Type 1 versus Type 2, if there is any difference in the drugs that used for them or not. But most of the drugs he was on and he was on Metformin at one time and he was on the whole gamut. He's now on Janumet. But he's always taking, been taken off of these drugs because of the government says no, it's bad for this, it's bad for that and Metformin was one of them that, they said wasn't good for you. So, he was changed. So, I'm just wondering about, if you're looking into like side effects of some of the diabetes drugs, as well as what it can do for Alzheimer's treatment.

**Dr. Steven Arnold** Okay. I do wanted to clarify, there is the Type 1 that used to be called juvenile onset diabetes and that's where the pancreas that makes insulin, stops making insulin and as opposed to Type 2 diabetes which is by far the much more common type of diabetes, where cells become resistant to the effects of insulin. And so, just about all of the data indicates that it's the Type 2 diabetes that is a risk factor for developing dementia in general and Alzheimer's type dementia in particular.

You are bringing up a good point. There are a number of medicines that are used for Type 2 diabetes. All medicines have some side effects depending on your age, depending on various other conditions. One medicine may be safe for you, and tolerable for you, whereas another medicine may not be. So, I don't, obviously I don't know your father's particular condition. Metformin, the reason why we chose it, is because we know the way it gets into the brain. It is the most commonly used Type 2 diabetes medicine in the world. There are some large epidemiology studies, from Taiwan and then recently, just presented last week at the Alzheimer's Association International Conference, from a large epidemiology study in California that diabetics who are taking Metformin have a lower risk, not a zero risk, certainly not. But a

lower risk of developing dementia compared to people who are on other anti-diabetes medicine and so, based on that, we chose the Metformin.

But it is an individual thing and now that we're testing this in non-diabetics, we need to really clarify what are the safety and tolerability profiles. So far, in our study that we're running, you know, most people are tolerating it pretty well. Some people are developing, some abdominal cramping or bloating, which is a common side effect. Some people may not be able to take the drug because of those types of side effects. But that's part of the work that we're, we're trying to do, that we need to do in re-purposing this drugs.

**Question:** Okay. Then another part of this is, are you advocating or recommending Metformin or those diabetic drugs as a proactive drug? Maybe for someone that's not diabetic but for someone like, I just buried my mother in December from Alzheimer's and now my dad was recently started on Aricept. Is there something I or my brother can do to be proactive?

**Dr. Steven Arnold:** Not until we have shown scientifically, through these types of clinical trials that it actually is helpful. We don't know whether Metformin is going to work or not. As I've said before, there's a rationale, conceptually it make sense. But we have absolutely no hard data that it does make a difference and so, I would not advocate you and your brother or anyone else going on this medicine until the data starts to show that there is a positive benefit to it. All you would be doing would be exposing yourself to the side effects or the risk factors without really any hard evidence that there's a benefit.

**George Vradenburg:** Thank you Ms. Beekley, I appreciate the comment.

We had a question submitted before the call from Nashua, New Hampshire. Which basically asks the question, recent reports about the fact that cancer patients might have a lower incidence of Alzheimer's and the question sort of relates to that and how chemotherapy affects the Alzheimer's risk. And so, what the relationship is between cancer and Alzheimer's? And perhaps Dr. Landreth, that's your court?

**Dr. Gary Landreth:** Well, so that's really a complicated question. Given the breath of the ranges of cancers involved. So, there is to my knowledge, there's no rationale for why chemotherapy would at least in principle be efficacious in treating Alzheimer's. Although they are select agents that have been used to treat cancer, which are of utility. But as a general mechanism of action, there isn't a strong rationale for that.

**George Vradenburg:** A question here from Lolita Harbit of Greenville, North Carolina regarding the populations in which these trials are been done. Lolita?

**Question:** Yeah. My question was, have you done any trials using racially diverse individuals and if so, what are your findings?

**George Vradenburg:** Dr. Arnold, do you want to try that one.

**Dr. Steven Arnold:** Sure. We are always trying to increase the diversity of our trials and actually seeing are there differences. Certainly we do see that some of these risk factors are more common in some populations. So, for instance, diabetes and metabolic syndrome are more common among Latinos. Hypertension is very common among African-Americans and so, we need to be sensitive to some of these differences and study whether a medicine has any differential benefit or risk for diverse populations. So, I think that is, it's an important question that you're asking and actually the A4 study that, I think George had mentioned before, that amyloid prevention trial, a requirement of that will be that every one in five people has to be from a minority. So, I think that there is a tremendous amount of interest in making sure that diverse populations are included in this trial.

**George Vradenburg:** We certainly have a range of questions that are coming in. It's rather fascinating. We have a question here from Oceanside, California. Joseph Potocny. Joseph, will you ask your question.

**Question:** Yes. What I was wondering is how the doctors are feeling about all the studies that are coming out Europe and out of the nordic lands about Alzheimer's possibly being an auto-immune disease. So, I happen to have Alzheimer's and I happen to agree with that theory and I have for some time. But I was just wondering how you feel about that, because I'm looking at everything that's being done, isn't doing anything.

**Dr. Gary Landreth:** So, there's very clearly an inflammatory component to Alzheimer's disease. But that involves an intermediary to the immune system in that the brain detects something going awry and mounts an inflammatory response. So, that's actually quite different from what you're talking about, these autoimmune diseases. It's my view that there's no clear and compelling evidence for an autoimmune involvement in the most common forms of Alzheimer's disease. I recognized that some people have been advancing that. But it is my professional opinion that the evidence is not compelling.

**Question:** All right. Thank you.

**George Vradenburg:** So, Bill Articola, I'm sorry if I've mispronounced your name. You have a question for one of our speakers. Bill?

**Question:** Yeah. Although Bloomberg BusinessWeek is nowhere near the same class of medical journal as say the Lancet or JAMA, they had a rather interesting and I would say influential article in late April called "Alzheimer's: The Costliest Killer" which certainly does bring to home a lot of the concerns of what this disease is going to do to us in the next 20, 30 years. Economically, if for no other reason. But one statement made, I think it's kind of relevant for today's discussion. It said that with respect to medical breakthroughs, up until last year, there were high hopes for a new class of drugs that sweep beta-amyloid protein from disease brains. The drugs reduced beta-amyloid as advertised but didn't improve patients' thinking. Well, this is kind of a rather dismal statement that they're making. They didn't cite any medical articles behind this but they were saying that this is a failure of these clinical trials. So, I was wondering if any of the doctors on the call have any insight into this particular statement about, you know, is reducing beta-

amyloid really going to help with cognition or improving cognition in folks who have Alzheimer's?

**George Vradenburg:** Dr. Arnold?

**Dr. Steven Arnold:** Okay. Well, I think that you are stepping into a still controversial area within the field here and I think that they are different viewpoints. There's no question that amyloid is a very important factor in Alzheimer's disease. But I think that Alzheimer's disease and the dementia coming from Alzheimer's disease is more complicated than just amyloid. Sometimes I use the analogy of smoke and fire, that amyloid maybe the smoke and you can clear the smoke and certainly a lot of people die from smoke inhalation but if you don't address the fire burning underneath, then you're still going to degenerate and so, I sometimes think about that metaphor for what's going on in Alzheimer's disease. So you know, I do think that this is a complicated disease, that there are a lot of mechanisms that are at play and that's why I said in my sort of preamble at the beginning of the call that while I hope there is a magic anti-amyloid pills that stops the disease. I think it is going to be more complicated than that. I don't know if Dr. Landreth wants to comment on this too. Because, you know, he may have some additional thoughts or different opinions.

**Dr. Gary Landreth:** So, I actually agree with everything you just said. So, the class of drugs they're talking about, they're antibodies. They're basically sort of a vaccination type of strategy and those have sort of failed in spectacular ways over the last few years and the strange thing is these drugs looked really fantastic on our animal models but it did not translate to human beings and I think we're all really quite worried about that. I would reiterate, the question is, is amyloid a legitimate target for drug development? And I think that is one of the \$64,000 questions for which we do not have a clear answer and I think this reflects our fundamental ignorance of the disease processes and what's really important in preserving memory and cognition. I think we simply don't know enough today to have a hard opinion about that.

**George Vradenburg:** So, there are number of questions that we haven't been able to get to. Quite a few relating to Metformin and Alzheimer's, whether it's a positive or negative and I think you responded to those. There are several questions here about how one might get into a clinical trial of a repurposed drugs and whether or not the presence or absence of Alzheimer's would be a factor in doing that. So, I guess I'll ask that question on behalf of the number of questions that are online.

How do you get into these trials and are there any trials of re-purposed drugs going on right now that people might get to participate in?

**Dr. Steven Arnold:** I think that there are a number of clinical trials going on around the country, many actually. Both small and perhaps some larger trials. You know, each trial has their own eligibility criteria based on safety considerations, based on what the target is. We happen to target people with mild cognitive impairment to early Alzheimer's disease and not beyond that. We do have some biomarker requirements for eligibility. A lot of the eligibility for participating in these studies does depend on the specific questions is being asked and how useful it is. With these smaller trials that we're talking about, if there is a positive signal, if it does look like it's

been beneficial, then it's going to be important to put it into a larger and more diverse clinical trial to actually prove that it can help in the more general population. I think you just have to be, on the [Alzheimer's Association website](#) or [clinicaltrials.gov](#). Be on the look out for the trials that are available in your area, look at the eligibility criteria and see if it's right for you.

**George Vradenburg:** I want to thank Doctors Arnold and Landreth for taking time to talk with us today and share some of their observations and their really interesting research, which as Dr. Landreth pointed out if we can identify some really possible and promising re-purposed drugs could cut significant time and expense out of the clinical trial process and get some of these drugs to market faster.

Also want to thank Guy Eakin and the whole BrightFocus Foundation for their rather intriguing, exciting, interesting funding strategies for important research and working with us so closely to advocate for an end to Alzheimer's.

This call highlights really the importance of our continuing to pressure Congress for increased research funding so that we can encourage and fund many more trials. So that we're not limited and constrained by the resource constraints that we have today in terms of the number and character of the clinical trials that we can fund in this important space in particular as researchers have pointed out, the difficulty of the economic incentives of the marketplace with respect to drugs that may have been either abandoned or repurposed and where the patent life has run out.

I want to thank finally the Emanuel J. Friedman Philanthropies for making this call possible. The Friedman Philanthropies are major active and very generous funders in this space. We're so grateful for their support.

Thank you all for participating in Alzheimer's Talks. In about a week we'll have a copy of the recording and a transcript on our website for you to share with your friends. As always, please stay on the line if you would like to leave us a message with a question or comment.

Thanks again to Doctors Arnold and Landreth and thank you all for participating today and thank you Guy Eakin of the BrightFocus Foundation. Take care. Have a good day.

*Transcript has been edited for readability.*