Alzheimer's Talks Transcript
Alzheimer's Drug Pipeline
with Drew Holzapfel and Dr. David Morgan
April 11, 2016

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 seek to connect you with leaders who are working to stop this damn disease.

My name is George Vradenburg. I'm Chairman and Co-Founder of UsAgainstAlzheimer's, an entrepreneurial and innovative organization, set up to, in fact, catalyze a change and transform the fight against Alzheimer's.

Thank you for joining us today to hear about a brand new analysis from our own researchers' network, ResearchersAgainstAlzheimer's, which looked at all of the Alzheimer's drugs in Phase 3, the final stage of clinical trials which could be available on the market in the next five years. You can see this analysis at ResearchersAgainstAlzheimers.org and we will also send a link in the recap materials to everyone who registered for this call.

We have two guests joining us today who both led this fascinating new analysis.

First, we will hear from Drew Holzapfel, Director of ResearchersAgainstAlzheimer's. He is also the leader of an industry coalition called the Global CEO Initiative on Alzheimer's Disease; it's a business coalition that is designed to partner with governments and with researchers around the world to speed clinical trials, to speed new innovative medicines to market. He previously worked at Pfizer as Director of Global Commercial Development for its Alzheimer's program.

And then we will hear from Dr. David Morgan, CEO of the Byrd Alzheimer's Institute at the University of South Florida, distinguished professor of molecular pharmacology and physiology at the Morsani College of Medicine, and a Founding Member and lead representative of ResearchersAgainstAlzheimer's.

We have almost 300 people registered for the call today from forty-one states, plus the District of Columbia, and also individuals as far away as England and Austria. There are an additional 650 people who couldn't join us today because of schedules but asked us to send them the recap along with a recording and a transcript—which we will also send to everyone who registered for this call.

Remember, for all of those of you who have been on this call or those of you who are new to the call, if you have a question during the call, at any time, 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 presentations.

First, let's have Drew Holzapfel, Director of ResearchersAgainstAlzheimer's, describe the analysis that he's just published. Drew.

Drew Holzapfel: Well, thank you very much, George, I really appreciate this opportunity and also thanks to Dr. Dave Morgan who oversaw the research. We were also fortunate to have the input of several other global experts like Dr. Morgan involved in this project, from Cleveland Clinic, Baylor, and Harvard University. And finally, thanks to all the companies who are investing in these drugs; they were incredibly responsive to our requests for information. So, thank you.

The headline of this report is that we have a reason for optimism today with the late stage pipeline with seventeen drugs that could be on the market in the next five years. So that's the headline, but I think that there's an important context that we need to set, so before we get deeper into the Phase 3 analysis, just a quick reminder of where we stand today with treatments. There are five treatments on the market today representing two types of medications: cholinesterase inhibitors and memantine. One of the products on the market is a combination of both these types of medicines. In total, these drugs are indicated for all the stages of the disease: mild, moderate, and severe. The first product launched to treat Alzheimer's was tacrine; it was approved in 1993 and it's been discontinued in the U.S. due to safety issues. But these drugs on the market today represent the best hope for the over five million people in the U.S. with Alzheimer's, and the approximately fifteen million caregivers who provide care. But given the growing incidence and high unmet needs from the current therapies, more innovation is obviously needed in Alzheimer's. And while we're optimistic about the future, we do need to acknowledge the recent past.

A few key points here: We've not seen a novel drug since Namenda was launched in 2003. Based on an analysis from Jeff Cummings at Cleveland Clinic, in a period of over a decade from 2002 to 2012, we saw a near 100 percent failure rate in Alzheimer's drug development. Moreover, successful clinical trials in any disease area are the exception rather than the norm. Overall, there's a ten percent success rate in drug development. In CNS, or central nervous system, which includes Alzheimer's, the success rate is even lower. So as we speak of optimism, we obviously do this with our eyes wide open. But our general philosophy is to prepare for success rather than to prepare for failure. So, it's actually that term failure that I think we also need to explain and perhaps using the word failure is just a little bit harsh. These are scientific experiments run to answer scientific questions. So while a particular compound might fail, the trial did not fail and that effort added the insight and built a foundation for future tests to consider.

So now with that, taking a look at the analysis. As I mentioned, we found seventeen drugs that could launch in the next five years. On the analysis you'll see we lay this out and look at when the trial will complete, when the regulatory filing will happen, and when the estimated launch date is. For these drugs and the timing, we based it on extensive research looking at clinicaltrials.gov, SEC filings, company reports, company interviews, news reports, etc. And when the information was missing or incomplete we applied our analysis and our experience in the field to determine key milestones. And as George mentioned in the opening, our analysis focused on just the drugs in Phase 3.

Accompanying the analysis, you'll see a detailed chart and I think there's one key thing to point out here. The chart will have nineteen drugs, so there are nineteen drugs in Phase 3. But just to repeat, there are seventeen drugs that we estimate could launch in the next five years. There are two more drugs in Phase 3 that launch outside that five year time frame.

So, much of the recent research and the late stage compounds have focused on amyloid plaques; the amyloid plaques are the sticky substance that abnormally accumulates in the brain of people with Alzheimer's. It's one of the two main pathological features of Alzheimer's. In

Phase 3, testing the amyloid hypothesis, we see a number of different compounds: Solanezumab from Eli Lilly, Aducanumab from Biogen, two from Roche, Gantenerumab and Crenezumab. Three of the four of these have the potential to be on the market by 2020, with Solanezumab potentially being on the market by 2018.

Also looking at the amyloid hypothesis, attempting to reduce the amyloid load, you see it in late stage development, BACE inhibitors. Merck is the leading candidate in developing a BACE inhibitor but as many of you surely saw last week, there was an announcement from AstraZeneca and Eli Lilly, where their BACE inhibitor moves into the final stage of drug testing later this year. And this again builds on the previous work around BACE inhibitors and it's that foundation of knowledge that also encourages us to think that there are new treatments that will make it into the hands of patients.

Testing the other pathological feature of Alzheimer's, which is tau, is a company called TauRx and their compound is reading out later this year with a potential launch in 2018. So when you continue to look at 2018, we've already mentioned Solanezumab and TauRx compound, you also see the potential of a total of six launches, so six out of the thirteen drugs. Three of these drugs, you'll see, come from a collaboration from Otsuka, and one other is from AB Science, it's an injunctive therapy that may play a role in the neuroinflammatory process.

Just moving from the late stage pipeline, to a focus on what are the barriers to accepting these drugs once they achieve regulatory approval: We need to start thinking about the health care system and ask the questions, is the health care system ready, and what is needed to be ready? There are a few things that we think are critical questions that have to be answered in this time leading up to 2018. First, we need physicians to diagnose. We see that there is approximately a fifty percent diagnosis rate in Alzheimer's, and when you compare that to other disease areas such as cancer, it's way lower than other diagnosis rates. This is true for Alzheimer's across the globe as well. We also need a medical system that treats this fatal disease with urgency and gets the patients to specialists when necessary.

Another question we need to think about is infrastructure. Future treatments and new diagnostics introduce new settings of care. Solanezumab, Aducanumab, Crenezumab, and others will require infusions. The question we have to ask is, are there enough infusion chairs, are the infusion chairs in places that are accessible to patients? Much of the work currently, today, around diagnosis, is focused on imaging. Another question we have to ask is, can the system be designed to allow better access to imaging agents and also to the imaging equipment? Diagnosis in Alzheimer's, as you know, is not easy; it's often said that the only definitive diagnosis for Alzheimer's can be given upon autopsy. That being said, diagnosis today is arrived at after documenting the deterioration through cognitive tests, neurological exams, patient and caregiver reported feedback.

Looking at this late stage pipeline, early diagnosis may become even more important than ever. Delivering these drugs to patients as early in the disease course as possible might be one of the most important lessons we've learned from the trials of the past. So again, access to imaging is a big question in terms of our health care system readiness.

And then finally, our final question is about both quantity and quality. We have a rapidly aging population; do we have the providers to support the number of seniors? Additionally, as we have a need to look for earlier detection, do we have the tools and the resources in the right place on the frontlines of care? I think these are the questions that this analysis helps us really focus in on.

So in closing, before I turn it back to you, George, I just wanted to offer that we realize it's been 100 years since Alzheimer's was first characterized, and over a decade since the last novel

treatment was introduced, but a foundation of research may have us in place to make rapid advances in coming years and it's our belief that we should be ready.

So George, with that, I turn it back to you.

George Vradenburg: Well, thank you very much, Drew. It's really an interesting piece of work and really quite a hopeful piece of work. We hear so much about drug failures, we hear so much about potential scientific discoveries, but we hear very little about the drugs that are actually on the way to those who need them, or are at risk for the disease.

So now we'll turn to Dr. David Morgan who, as I mentioned, is the CEO of the Byrd Alzheimer's Institute at the University of South Florida. Dave?

Dr. David Morgan: Thank you very much, George. I really want to commend Drew for all the work that he's done in putting together this document; while he gives me some credit, he's really the one who did all the heavy lifting on this and I think he's done a tremendous job of putting together a great summary of the current status of the Phase 3 studies going on in Alzheimer's disease.

I'd like to start just by talking briefly about ResearchersAgainstAlzheimer's. ResearchersAgainstAlzheimer's is an advocacy group. We're about 400 strong and we're growing. Our overall goal is to enhance the policies of our governments with respect to dementia and to memory care. One of the things that we're working to achieve is to bring the funding levels for research on Alzheimer's disease to a level that reflects its overall impact on our society. We've noted that while Alzheimer's disease costs more than cardiovascular disease or cancer in terms of medical costs—this doesn't even include lost productivity—Alzheimer's still receives only about twenty to twenty-five percent of the funding that those other diseases receive; and this is after a sixty percent increase at the NIH in funding for Alzheimer's disease this last fiscal year. Alzheimer's is a very underfunded disease. Part of the problem that researchers face is getting the resources to carry out the scientific experiments and clinical trials needed to find the right drugs for Alzheimer's patients, get them through the pipeline and into the treatment of people who have this disease.

One of the questions I'm often asked is, why is Alzheimer's so neglected? Why, from a governmental perspective, haven't we been doing a better job? I think part of it is, a general ageist attitude that we find in some of our legislators. They think of it as "old-timers" disease. One problem is we don't have survivors of this disease who can come forward and tell the general public how important it was that they have access to state of the art medicines that led them to be cured. ResearchersAgainstAlzheimer's highly recommends that as many people as possible contact their legislators at the state level, and their representatives at the federal level, to share with them how important this disease is and how critical it is that we get the research funding that we need. The sixty percent increase that I mentioned brought us up to almost one billion dollars a year. We estimate that to really complete the development of many of these medications, we need at least two billion dollars a year, so our work is not done. Nonetheless, UsAgainstAlzheimer's and ResearchersAgainstAlzheimer's has had some level of success in helping move forward this increase in funding and we need to push this even harder and further.

I actually direct an Alzheimer's disease clinic, that sees patients on a daily basis and one of the questions that Drew raised, which I think is a very critical question, is trying to educate health care providers how to recognize and diagnose accurately Alzheimer's and other forms of dementia. We have about a six-month waiting period to come in to see our experts in our clinic. One big problem is we don't have sufficiently well-trained health care professionals who understand how to recognize, diagnose and treat Alzheimer's disease. Especially once we get

medications that will be useful in treating these individuals, the needs for accurate diagnosis are going to be essential.

One of the things that is being done, and I think needs to be expanded further, is that the United States Health Resources and Services Administration has restarted a program to increase the geriatrics training of health care professionals. It's called the Geriatric Workforce Education Program. In the fall of 2015, USF [University of South Florida] was awarded one of these GWEP grants with an addendum to specifically increase training in recognizing and diagnosing dementias. This, I think, is a very important issue as we move forward with the improvements in our ability to treat this disease.

Another major challenge to treating Alzheimer's patients, and this applies to geriatrics in general, is the Medicare payer levels are really very difficult to survive on. It's hard to run a sustainable medical practice with a 100 percent Medicare payer mix. These payment issues will be additional burdens that somehow need to be addressed appropriately so that we can bring these medications to the general public.

A final point is that this particular analysis is extremely important because it's the culmination of the progress that we have had over the last thirty years of doing research on Alzheimer's Disease. Many people in the general public don't understand how long the delay is, between the identification, in a research setting, of a potential treatment for a disease, and the time it takes to move those ideas into a clinical setting and ultimately through to the Phase 3 testing. This is at least a ten- to fifteen-year program and usually takes even longer.

But it's really telling us something very important, which is that hope is on the horizon. These are ideas that have been born over fifteen to twenty years ago and are now moving their way through the overall pipeline. I'm impressed that we're going to see what I think of as a graded series of improvements in our ability to treat this disease. We started off with some of the cholinesterase inhibitors which as Drew mentioned, the first one was sufficiently toxic that it's no longer even used. Yet at that point in time, it was all we had. And we've gotten better and better at developing these anti-cholinesterase drugs. We've added memantine, which also shows some improvement even on top of the improvements we see with cholinesterase inhibitors and we're likely to see more treatments like this.

There are some drugs that are anticipated to have what we call a symptomatic effect; that is, they are going to improve cognitive function without necessarily slowing the progression of the disease. Many of us think of this as not being a particularly effective approach to treating a disease; nonetheless, if we look at Parkinsonism and Parkinson's disease, the development of L-DOPA, which is largely a symptomatic treatment for that disease, has probably extended the lifespan of these people by at least ten years. So there can be major impacts and even some of the cholinesterase inhibitors—it's been identified that these can delay institutionalization of individuals who move towards late stage dementia by up to two years. So these are meaningful impacts and we're going to see continued improvements in our ability to improve symptoms.

We are also testing disease modifying therapies. When we consider disease modification, we need to pay attention to what stage of the disease these medications will be effective at treating. Look at the success that we've had in impacting other diseases. The one that's most remarkable has been cardiovascular disease where, on an age adjusted basis, we have cut by fifty percent the risk of dying from cardiovascular disease in the last fifty years. It wasn't that you just woke up one morning and read in the newspaper, *"Heart Disease Cured!".* Instead we've seen a graded series of improvements to treat and prevent the disease, using multiple types of medications, against things like high blood pressure, against things like blood cholesterol, against things like blood clotting, and delaying the formation of clots with daily aspirin tablets and more effective types of anticoagulants. It's also been a recognition of the benefits of lifestyle

changes and nutrition. Prevention is always the easiest way to fight a disease; to identify who's at risk and to find a means to mitigate that risk. Although they're not all represented in this phase 3 pipeline analysis, there are a number of ongoing prevention trials that are testing agents intended to slow the progression of the disease, possibly arresting it. The goal is to take people who are at risk for the disease, because of biomarker measurements, and treating with these drugs to prevent them from ever getting the disease.

This is an exciting stage that we're at, at this point in time. It's quite conceivable that we may have some type of prevention treatment within the next several years, that we will find things that are capable of delaying, at least, the onset of the disease.

The second level of medication effectiveness after prevention is treatment. A number of these drugs are designed to be effective treatments, to take people who already have the disease and to give them an agent which will slow the rate at which the disease is developing inside their brain, and presumably that will also then slow the progression of the symptoms of the disease. Patients taking the drug may not immediately feel better, but a year from now, they will be much better off than they would have been without taking that drug.

Finally, we can talk about a cure. I've been doing research on Alzheimer's for thirty years and I think we can develop prevention treatments and therapeutic treatments without having any major scientific breakthroughs. I think that the science is there. All we really need are the resources to prove the science right. But if we're going to cure the disease, if we're talking about taking someone who is in an advanced stage of dementia and trying to bring them back into a more normal cognitive state, I think for that we're still going to need some breakthroughs. We're going to need to continue to fund the basic science that is looking at the underlying principles behind how the brain works and give us some further insights into how we can develop some newer and more effective medications or cellular approaches.

But I think this analysis really highlights how far we've actually come, and hopefully, it's pointing out how close we actually are to coming up with multiple types of meaningful treatments for this devastating disease.

George Vradenburg: Thank you very much, Dave. And of course, if we can get more than one out there, that works differently, we might even put them together in combinations to have multiple and multiplier effects so I think that might be on the horizon in the 2020 to 2025 area.

So we have a number of questions online, pretty interesting.

We have a question here about why only fifty percent of those that are estimated to have the disease are diagnosed with the disease. Why? What is limiting our access to earlier definitive diagnoses and treatments with imaging? Drew, you want to try? Why only fifty percent?

Drew Holzapfel: I have some guesses from being in the space; this is outside the analysis. I think that physicians feel reluctant to deliver the diagnosis, sometimes, because of the current treatments on the market and I do think that with additional innovations reaching the clinic, that physicians will feel more empowered to deliver the diagnosis. So that's just my guess, though.

George Vradenburg: Dave, do you have a view on that? What is the best differential diagnosis tool that we have today? How much does it cost and why don't we get something like a blood biomarker, a blood diagnostic test?

Dr. David Morgan: Well, there are a number of ways to detect dementia. The easiest one is to do memory screening evaluations, to start to identify who's beginning to have some kind of cognitive declines. When we go out in the community and do this we find about twenty percent

of people who are living at home, sometimes by themselves, score at a level that we suggest that they seek a more detailed evaluation of their cognitive status. Some of the time, what happens is people don't recognize that they're having memory problems. They almost intentionally try to cover it up and ignore it in certain stages of the problem and it's really going to be up to their relatives to bring them in to have a detailed evaluation.

But I think it's also the fact that our primary care physicians are not trained to identify this disease and they have so little time to spend with the patients, particularly their geriatric patients, that they're much more concerned about their cardiovascular disease risk and whether they've got cancer and whether they've got other types of organ failures, that they just simply don't have the time that it takes to do a meaningful analysis of what their cognitive status is. So I think it's a combination of all of those things that reduces the percentage of the general population that receives a diagnosis. Sometimes a physician is very suspicious that there's dementia, but given the limited treatment options and their failure to recognize that some of these do have long term benefits for the patients, they decide to just ignore that and not share that information with the patient, much like cancer, for example, fifty years ago.

George Vradenburg: There's also the fact, I believe, that an amyloid PET scan is a fairly expensive diagnostic tool, one that at the moment is not reimbursed by Medicare, making it a pretty high-priced tool for private payers, for only those who can afford it themselves. And I am aware that there are efforts to try to identify blood tests or retinal tests or some sort of electrical scan, that would be able to identify dementia, and, in the best of all cases, differentiate the source of dementia to Alzheimer's versus vascular dementia versus frontal temporal lobe versus Lewy body dementia. So we are working on better diagnostic techniques and less expensive diagnostic techniques than the current ones that we have on the market.

There's a general question here about how many of the seventeen drug compounds that are expected out in the next five years are oral or topical versus infusion?

Drew Holzapfel: So, I'll take a stab at that. There are a handful of these that are delivered via infusion, as I mentioned, so Solanezumab would be the first in that class. I would say close to ten of these will be oral compounds, so it is a mix based on the drugs in late stage compounds.

George Vradenburg: There is a question here—with the increase in younger onset diagnosis rates, why does it seem that most trials are designed for those living with the disease sixty-five and older, versus earlier populations? Dave, you want to take that one?

Dr. David Morgan: Well, I think part of the problem is that they're trying to look at groups of people who are more abundant, so that there are more of them so that when they evaluate those studies they can enroll adequate numbers. Often, the early onset cases are the familial cases; they have a known inherited component to the disease. Those are thought to be perhaps more aggressive forms of the disease and therefore would be more challenging for a drug to effectively treat. There isn't a particularly good reason. If someone is demonstrated to have a non-inherited form of Alzheimer's disease, to only evaluate an older group of patients is an error. Increasingly, studies are starting to recognize that, and are looking to expand the age range particularly in the younger ages of individuals who would qualify for the study itself. In the past, it could also have been that without a positive confirmation of Alzheimer's—by either an amyloid imaging PET scan or by a cerebral spinal fluid measurement of amyloid levels—that the earlier onset cases would have been more likely to be not Alzheimer's but some other form of dementia. And if that was true and you're using an anti-amyloid drug, then those people would not be responsive to the drug.

George Vradenburg: We have a question here from Ana Jessica Montells from Mooresville, North Carolina. Miss Montells, would you like to ask your question?

Caller: Yes, thank you. So my question was the genetic testing, the DNA sequencing, if the person has inherited possibly early onset, with the APOE and the C8C9 and all the genetics, does that prove—or not—conclusively that you have it? Or does this just state whether you have the gene?

Dr. David Morgan: This is Dave Morgan, I'll respond to that. There are two ways in which genetics can influence your risk of Alzheimer's disease. One way is if you have what we call familial Alzheimer's disease. Typically, this can be traced back over generations because it tends to be fairly early onset in the forties or perhaps the early fifties. And these are inherited in what we call a dominant fashion, so that an affected parent has a 50-50 chance of passing on the disease to one of their children. In those cases, if you happen to have inherited the specific mutant gene that caused the disease in your mother or father, then you also are at very high risk of developing that disease and also, interestingly, at roughly the same age that they developed the disease. There are clinical trials looking at individuals in these families and including them in prevention trials to determine if some of the medications that are in the Phase 3 study testing might also be effective in preventing the disease in people that don't even have any symptoms yet, but are known to be at risk.

The second way in which genetics influences the disease is to increase your risk. This is not a dominant inheritance. These people tend to have a little bit later onset of the disease in their families, let's say in the sixties and seventies rather than the forties and fifties. Here, having a copy of the gene doesn't necessarily mean that you will get the disease even if you live into your eighties or nineties. It does however indicate that you might have an increased risk. So, one of these genes is the gene for apolipoprotein E. There are three normal variants of apolipoprotein E in the human population; 2, 3 and 4. If you have one copy of the E4 variant, then you have about a threefold increased risk of developing Alzheimer's. But there are still people who have E4 variants and live into their nineties and don't develop the disease. Evidently they have some other genes that may be protective for the disease or they have lifestyles that have helped avoid developing the disease.

George Vradenburg: We have a question here from Dan Gasby. Dan is a caregiver for B. Smith, the model and restaurateur, so Dan, welcome to the call. Go ahead and ask your question.

Dan Gasby: My question is, I was able to afford the amyloid plaque test and in traveling around the country talking to people about being able to get a better handle on the potential of having the possibility of Alzheimer's, they said, "I can't afford the price." How do we help make it more accessible, more affordable?

Drew Holzapfel: Dan, thanks for the question, it's great to hear your voice. I think it's a larger question around advocacy in this space. I really like the point that Dave made about the increase in funding from 500 or so million to about 900 million at the NIH and I think that speaks largely to the increased advocacy we've seen. And so, as we look at these future innovations that start to make it into the clinic, access is going to be a key issue, and advocates like you, Dan, and the work that you're doing with B. are going to be incredibly important in making sure that this final step of actually having access by a patient is taken. So I think that it really speaks strongly to the role of advocacy.

George Vradenburg: I'd say that there are really two ways, Dan, to lower the cost to the individual patient. One is through innovation. That is, we find newer products that can do the same or better jobs at lower prices. Or, if we can't do that, we get the help of Medicare to reimburse for some or all of the costs of that diagnosis. So, advocacy will work on the latter

question, and innovation and the marketplace should work on the first question, but it's a combination of the two that we're going to need: Much more innovative ways of identifying amyloid, for those drugs which are shooting at amyloid as the target; for finding tau for those drugs that are shooting at tau as their target; or other aspects of brain impairments for other methods of action. And then, finding more innovative lower-priced ways of detecting those conditions so that we get the right drug aimed at the right population with the right target as we go through time.

Dr. David Morgan: George, can I comment on this also?

George Vradenburg: Absolutely.

Dr. David Morgan: One way that you may be able to get access to amyloid imaging is a trial which is just about to get started, that's called IDEAS. This is being partially sponsored by the Center for Medicare and Medicaid Services (CMS), that is the agency that reimburses for Medicare. This study will provide for, I believe, up to about 2,000 people, a reimbursed amyloid imaging scan in order to develop evidence whether amyloid imaging improves the clinical care outcomes for memory impaired older adults or not, compared to the historical CMS data for people diagnosed with Alzheimer's disease. There are going to be at least sixty sites throughout the country where these scans can be performed. The amyloid imaging information will be shared with the medical provider. This will permit individuals that are being initially evaluated for dementia to obtain an amyloid imaging scan without having to pay more than the copay that you would already have to pay if it was routinely reimbursed by Medicare.

Dan Gasby: One of the things that I'm seeing out there, that, once people get over the fact of not feeling uncomfortable about knowing there's this test out there, I think it will have if not exponential, a geometric effect of people wanting it. There are some people that will be fearful, but I think the more people that realize it, and are ambassadors for taking or participating in finding out on a long-term basis that they potentially have this plaque build-up and there are things that they can do immediately to start the process, like exercise and changing their diet, and all of the things that are now being talked about in certain holistic ways to go about it through meditation. I think this will have a multiplier effect on making and driving local and state and maybe federal legislators to realize how important these tests are.

George Vradenburg: I think that's right, Dan. I would also say that, if one of these drugs in the next year reports success, that is, if the treatment has successfully worked in Phase 3, and they're seeking regulatory approval of its marketing, that we're going to have a lot of people go to their doctors and a lot of doctors who may now be willing to talk about Alzheimer's and diagnosing Alzheimer's because there will then be some anticipation that there will be some treatment on the market. So, I do think that we're going to see a dramatic change in attitudes once we get a report of a successful Phase 3 test.

Let me move on to Geraldine Carolan, is that right, from Peachtree City, Georgia. Geraldine?

Caller: Yes. My question is, do you recommend testing for the APOE-4 gene, if you are a child of a parent with the disease?

Dr. David Morgan: This is Dave Morgan again. It's not a straightforward question to answer. In general, if we knew that we had a medication that I could offer you, that would prevent the disease, I would without hesitation recommend being tested. At this point in time, without having such a medication, it's a mixed response that you get from the general public. Some people want to know if they have the increased risk. If they do, it may lead them to adopt these healthier lifestyles that Dan Gasby was talking about. That at least is one thing you could do. It might also modify how you view your life course in the future. On the other hand, there are

individuals who really don't think that they would be positive, that were they to find out they were, may in fact be quite devastated by this information. Other people prefer to remain unaware of what their overall risk is, and lead their lives the way that they would have led their lives anyway. So I don't think that there's value in knowing your ApoE status in a pre-symptomatic individual. Once someone has the disease, very often physicians will test for an APOE-4 variant. It turns out half of all dementia patients have an E4 allele, whereas only about fifteen percent of the general population, that's 15 percent, have that variation. So it's not a simple Yes or No answer to your question. I apologize, but at the same time, my suspicion is, it's probably better not to do it, until we find that we have something that can reduce your overall risk. Because you should lead a healthy lifestyle anyway and you should probably make certain that you try to accomplish everything you want to accomplish before you die anyway.

George Vradenburg: Next question here from Jamie Zimron, from Redwood City, California. Jamie, would you please go ahead and ask your question?

Caller: I'm wondering about, I've seen a lot of brain supplements, brain food kind of things, in health food stores and even online, being talked about. Not only for better memory function, that sort of thing, in the immediate, but potentially to help keep the brain healthy, the brain matter healthy. Just wondering if you all have any knowledge or experience with these kinds of natural based supplements and if they may be of some help in keeping the brain healthy and preventing the onset of dementia or Alzheimer's.

Dr. David Morgan: In general, there has been very little evidence on a scientific basis that any of these supplements have impact on your risk of developing age-associated memory decline. There's one thing that we do know is extremely powerful in human medicine and it's called the placebo effect. I think a lot of people who take these do in fact feel better, and I don't deny that that can be a useful outcome. Nonetheless, when tested in what we call a double blind placebo controlled trials, where we essentially eliminate the placebo effect as a possible cause of the benefits that we would see in the study, none of these agents met the rigorous criteria that we would require to say that they're having a significant benefit. We do know that the best evidence, really, comes from having a healthier lifestyle which means, in general, eating better, eating less, having fewer refined carbohydrates, having diets that are varied in their overall content, and exercising. Those are the things that I think have the best evidence to support trying to minimize your risk of developing these diseases.

George Vradenburg: We have a couple of questions online here that may be a quick response. Of the compounds discussed, the seventeen compounds available on the market in the next five years, we hope, how many also can be used for other types of dementia other than Alzheimer's? The question is, are there other drugs in the pipeline that are aimed and targeted at Lewy bodies and other forms of dementia other than Alzheimer's?

Drew Holzapfel: It's an interesting question. I think if you look at the analysis, and you look at Brexpiprazole and Aripiprazole, those are being studied for, and in some cases, indicated for other uses. So, treatment of depression, schizophrenia, bipolar. Then also further to your point, one of the compounds in development is also being tested for treatment of dementia with Lewy bodies and that effort is being led by Axovant. We also have a compound in here that has a trade name of Ritalin, a common treatment for ADHD, that's also being studied. So I think there is an opportunity to look at drugs that have other indications, and test them in Alzheimer's and potentially add value to patients with Alzheimer's disease.

George Vradenburg: I've got a question here from Nelly Leap, I guess this is probably for you, Dave. Is there any hope of stem cells clinical trials?

Dr. David Morgan: At the present time, as far as I know, there are no active stem cell clinical trials. But I there's a number of them that are in various stages of planning. They may be in Phase 1; they haven't gone into any efficacy testing. I think it's a very interesting question. We generally think of stem cells from the perspective of replacing the missing neurons. But that doesn't seem to be the direction these trials are taking. Instead, it turns out that the stem cells have a normalizing influence on the immune system and on inflammation. They may be effective in ways that we don't yet fully understand, such as regulating the inflammation that we think contributes to some of the amyloid and the tau pathology that we find in Alzheimer's disease brains. So there may be some stem cell studies in Phase 1. They haven't gotten to the larger scale studies yet but they are certainly in planning.

George Vradenburg: Question online here from Sharon Fratepietro. I'm a volunteer in the A4 research study, starting my second of three years in particpation. Is recruitment for this study still going on, and if so will the report on the results be delayed? Will there be an interim report?

Dr. David Morgan: The trial is still ongoing, and recruiting patients. It is a prevention trial, I suspect they will have an interim analysis at some point, in the trial, before it's fully completed, just to identify if they are seeing a significant effect. They'll probably end the trial at that point in time and release the results. But I don't know that for certain; I do know that they are still recruiting. I think they're past the halfway point in recruiting for the trial. These trials do take a long time to recruit and especially a prevention trial. Interestingly, one of the challenges right now is finding participants—we have dementia patients coming in to the clinics so for trials for mild to moderate dementia we have these people showing up at our doors. However, we don't have normal people coming to our clinic for dementia because they don't have dementia. So recruitment for these trials is not as straightforward as some of the others. Nonetheless, I think we'll see that trial through to completion. I don't think it will be terribly delayed because of the delay in recruiting, although all trials would like to recruit as quickly as possible.

George Vradenburg: So since it didn't pop out in our analysis, we know that it is not on a pace that would get it through the pipeline and through regulatory approval before the first quarter of 2021. So, if everything proceeds in the normal course, it will be some time in 2022 or 3, before the drug would be available in preclinical populations. It is the same drug that's being tested in the Solanezumab trial by Eli Lilly which is scheduled to be out in 2018. That drug is being tested in persons diagnosed with mild dementia. That same drug is being tested in individuals before they have any symptoms and for that indication, not until 2022 or 23. Now, as Dave mentioned, if it's really powerful, it may be that it will get terminated early and potentially get evaluated at the same time as the Solanezumab drug, I guess evaluated for use in mild patients, and if in fact it's proven to be efficacious in mild patients, and the trials in preclinical patients are positive, based upon some interim analysis, it could be that the drug would be evaluated in both mild dementia patients as well as preclinical dementia patients, before symptoms appear, at the same time.

We only have a few minutes left so let me just say I want to thank both Drew and Dave Morgan for their work in putting this analysis together and for leading ResearchersAgainstAlzheimer's. ResearchersAgainstAlzheimer's has been active in advocacy in this town but I think we'll increasingly begin to figure out how to do these kinds of reports on the state of the pipeline, and on another critical issues in the development of innovative medicine for Alzheimer's.

And if you are a researcher who is interested in joining ResearchersAgainstAlzheimer's, please go to www.ResearchersAgainstAlzheimers.org for more information or to sign up.

I'm sorry that there were a number of questions that came in over the phone and online that we didn't get to today. It is the nature of a fascinating topic like this to generate a lot of questions.

If you've not already joined UsAgainstAlzheimer's, please go to http://www.usagainstalzheimers.org and sign up. We'll send you a recap of this call, invitations to future calls, and important updates and simple ways that you can get involved in doing precisely what Dave Morgan suggested, and that is, advocate for increased resources and increased attention to this disease. I hope that all of you will join us.

Thank you to everyone on the phone or online for participating in this 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 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 would like to discuss on future calls. Thank you for joining us today. Thank you, Drew. Thank you, Dave Morgan. Have a good afternoon. Bye.