UsAgainstAlzheimer's

Alzheimer's Talks
with Dr. Laurie Ryan
June 28, 2017

Note: This transcript has been edited for content and clarity

Welcome to Alzheimer's Talks, a free monthly teleconference call presented by UsAgainstAlzheimer's.

My name is George Vradenburg, Chairman and Co-Founder of UsAgainstAlzheimer's. Thank you so much for joining us today to hear about how we can improve the pace, the speed, and the quality of Alzheimer's clinical trials. We have with us today a real expert in this space, Dr. Laurie Ryan from the National Institute on Aging.

Very briefly, before Laurie starts her comments, I want to share a couple of top-line items with you: I have just come from an UsAgainstAlzheimer's board meeting, our first meeting with Greg O'Brien as a board member. As many of you know, Greg is living with Alzheimer's and is the author of On Pluto: Inside the Mind of Alzheimer's. He brings an important perspective to our work but also provides us an immediate and personal incentive to continue our efforts to speed up the search for a cure. We are glad to fight this disease alongside Greg and the millions of people who are experiencing this disease who are living it every day, and the carers that provide services to them. So, it is great to have Greg on board.

One other thing: As many of you may know, just from listening to the news, we are engaged in Washington in a broad and deep and somewhat intense discussion about amending the health care act, ObamaCare, whether to repeal it, replace it, and if replace it, by what. There is a pending Senate health care bill, which UsAgainstAlzheimer's has opposed, in its provisions that would reduce commitment to Medicaid and to reduce the services that are so needed by individuals with dementia and their families. The Congressional Budget Office has estimated that 22 million Americans would lose their health coverage in the next 10 years, under the plan being considered by the Senate. The Medicaid cuts are particularly significant because they would produce a large impact on individuals with Alzheimer's, as one in four individuals with Alzheimer's in this country relies on Medicaid. CBO estimates that Medicaid spending would decline by 26 percent and enrollment would fall by 16 percent by 2026.

So, I would encourage all of you to call your senators and ask them to assure, that in whatever bill emerges, that adequate Medicaid investment is made, in order to assure that the persons in this country with dementia and Alzheimer's continue to get adequate care and services.

With that said, let's turn to our guest today. We're honored to have Dr. Laurie Ryan as our guest today.

She is Chief of the Dementias of Aging Branch in the Division of Neuroscience at the National Institute on Aging, which is part of the National Institutes of Health (NIH). At the National Institute on Aging, Dr. Ryan directs Alzheimer's disease clinical trials research. After receiving

her Ph.D. in clinical neuropsychology, Dr. Ryan joined the Defense and Veterans Brain Injury Center at the Walter Reed Army Medical Center in Washington. This background is particularly interesting, given our new Veterans Against Alzheimer's network being led by UsAgainstAlzheimer's board member Shawn Taylor.

Dr. Ryan served as the clinical neuropsychologist for the Walter Reed Site and worked on issues with traumatic brain injury. She became the Assistant Director for Research and senior neuropsychologist for the national Defense and Veterans Brain Injury Center where she was responsible for overseeing clinical research development and implementation with a particular focus on clinical trials. In September 2005, Dr. Ryan joined the NIA with this focus on Alzheimer's disease clinical trials. Dr. Laurie Ryan, in her position at NIA, is working on bringing together all of the stakeholders needed to create a national strategy to improve Alzheimer's disease clinical trials, particularly coordinating strategies for recruitment— recruitment which will speed the search for a cure.

Before I turn this over to Laurie Ryan, just remember, if you have a question during the course of the call, please press star 3 on your phone. By pressing star 3 you will be put into a queue and talk to a member of our staff, who will make sure that we have the question that we can put to Dr. Ryan, and when we get to the question period, we'll make sure that you'll have an opportunity to ask your question directly of Dr. Ryan. If you are listening to us online, you can type your question in the box. We will get to as many questions as possible during the question phase. Please remember that Dr. Ryan, like all our guests, is not able to answer personal medical questions on this call.

Laurie, thank you so much for joining us today, we're very pleased to have you and we are great admirers of your work, your dedication, and your commitment at NIA.

Dr. Ryan: George, thank you very much and thanks to UsAgainstAlzheimer's for inviting me to do this. I'm really happy to be here to talk about this important topic and I'm going to focus on Alzheimer's disease and related dementias, our national recruitment, and strategy efforts for clinical research, clinical trials in particular but also just clinical research.

So, I'm going to hit upon a few things today. One are the recruitment challenges that we face, what are some of the NIH research implementation milestones and other efforts that are focused on recruitment and how we can really build public and private sector efforts at the national and local level.

As I think probably many of you on this call are aware, we face a number of recruitment challenges, one of which, of course, is the need for large numbers of participants. The goal of the national plan is to prevent and treat Alzheimer's by 2025 and so we're going to need large numbers of individuals to participate in research. And from clinicaltrials.gov, you can see that there are about 150 or more trials seeking about 70,000-plus volunteers and we actually need 10 times that number of individuals to be screened to actually find the right participants for each study.

And when we're looking at Alzheimer's and related dementia studies, there are a number of unique challenges:

- One is that our primary care providers are really those that are on the front lines, and they need support and resources to help them assess cognition, and then to refer appropriately to studies.
- Researchers themselves need tools and resources to apply best practices to recruitment.
- There are a number of barriers to participation that we could have a whole session on, particularly for underrepresented and minority communities.
- Many of our studies require partners, study partners, if you have dementia or mild cognitive impairment, even in some of the preclinical studies.
- There are invasive procedures that occur in some of the trials, you have lumbar punctures for CSF studies, infusions for some of the different immunotherapies.
- And of course, now that we're focusing a lot of our attention to prevention and pre-symptomatic trials, we need large numbers of cognitively healthy volunteers, people who don't have a diagnosis.

We have to reach out.

I'm going to highlight, next, a couple of the large studies that NIA is participating in; these are not the only ones but these are ones you may have heard of, and that are looking for large numbers of volunteers. One is the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease, or the A4 trial[1]. And that is a secondary prevention trial, in clinically normal older individuals, ages 65 to 85, who have evidence of amyloid pathology one of the hallmarks of Alzheimer's disease on PET imaging, PET scans. So it's a randomized double blind placebo controlled Phase 3 trial, using the anti-amyloid drug Solanezumab. It's recruiting over 100 participants, 500 per arm. There's also an observational component, an observational study for people that are not eligible for the trial. There's also an ethics component. It's over 60 sites in the U.S., Canada, Australia, and Japan and it's a large public private partnership so there's NIA funding, there's the company funding, in this case Lilly, as well as philanthropic support, things like the Alzheimer's Association. This trial actually has been going on for a number of years now and actually enrollment is almost complete so that's very heartening.

Another study that again is a public private partnership that NIA helps to cosponsor, is the Generation Study[2] and it's a five-year trial involving more than 1300 cognitively again healthy older adults ages 60 to 75 who are at high risk for developing the late onset most common form of Alzheimer's disease because they have two copies of the APOE-4 gene, which puts them at a higher risk. And there are actually using two different drugs from Novartis; one drug is an active immunotherapy, and the other is what we call a beta-secretase, a BACE inhibitor. And this is also going to be at over 60 sites in Europe and North America. They began enrollment in December of 2015 and they're also looking for large numbers of volunteers.

Just to kind of give you a little heads up of what NIA is doing outside of those very large public private partnership studies, we recently did a tally and currently we have about 59 ongoing clinical trials, some just recently funded. Most are in what we call the early stage clinical drug development Phase 1, Phase 2, and there are 23 of those. They are focused on a number of areas,

[1] For more information on the A4 trial, click here to listen to the Alzheimer's Talks with Dr. Reisa Sperling.
[2] For more information on the Generation study, click here to listen to the Alzheimer's Talks with Dr. Eric Reiman.

not just amyloid but things like metabolism, growth factors, oxidated stress. We have late stage clinical drug trials—we're talking about Phase 3 here—we have five of those, amyloid as well as things looking at vascular factors. We also do a number of non-pharmacologic lifestyle interventions, for example, exercise, diet, cognitive training, and it makes sense that NIH funds most of these because these are not patentable, these are not a drug that can be marketed but they are all obviously very important and we have 23 of those. And then we also look at treatments specifically that focus on the behavior or the neuropsychiatric symptoms of Alzheimer's, things like agitation, things that actually really affect people's quality of life and often these are the things that lead you to go into a nursing home, when families cannot handle people who are very agitated and aggressive. So we have a number of those, we have eight of those, some are pharmacologic and some are non-pharmacologic. So that's just the NIA-funded trials in Alzheimer's and related dementias.

What I wanted to segue now was, well, what are we doing about this? How are we going to hopefully help improve recruitment because we need large numbers of participants?

Difficulty in recruiting, I should mention, is not specific to Alzheimer's; other disease areas also have difficulty. There's been studies, cancer studies, for a long time, showing roughly three percent of individuals actually will enroll in a trial, so it's not unique to Alzheimer's but it is such a big problem and the fact that we're seeking individuals who are cognitively healthy in many cases, adds to the burden so we're really struggling, but we're very hopeful and we're working together not just the NIH but also UsAgainstAlzheimer's, the Alzheimer's Association, and other philanthropic groups, and even companies are coming together to ask how can we improve this for the field as a whole.

So I wanted to start with touching on the NIH research implementation milestones, and these really came from the national plan which everyone is aware of, and they were actually developed from the two summits that we held at the NIH, Alzheimer's Disease research summits in 2012 and 2015 (I should mention that we'll have the next summit on March 1 and 2, in 2018, and that will be open to the public). Based on the recommendations, based on the national plan, the recommendations from the research summits, we developed these research implementation milestones that cover a variety of areas, how we're going to get to our goal of 2025, and there are 86 individual research implementation milestones focused on specific research topics across 15 different implementation areas. And actually people can look at these on the NIA website if they're interested.

What I want to focus on today are—we have a number of those research implementation milestones that are focused on recruitment, obviously because we cannot meet the research needs if we don't have volunteers. So one of the areas is called recruitment and citizen engagement, and we've built a number of milestones, and I'm going to talk about the ones that we're kind of doing right now, the 2016-2017 activities.

One of those was talking about establishing partnerships among NIH and other federal agencies to develop national public education campaigns and we do have an example of that. We're working on some other areas, but one of the ones that we have done has been fairly successful. It's called Recruiting Older Adults into Research, or ROAR, and that's between the NIH and the Administration for Community Living. And that is trying to get the network of community sites that are part of what we call the ACL—Administration for Community Living—to really

understand research and help provide information to the constituents of people that use the services, about how they can get involved in research.

Another area that we're looking into is how can we maybe provide supplemental funding to research studies to help build diverse community partnerships. And that's one of the things we can certainly do on a regular level, when studies need additional support, but also how can we actually really put that out there. So that's in development.

Another is using technology to reach more individuals. We have one pilot use of electronic consent. And you might say, "electronic consent, how can that improve recruitment?" Well, if we're going to be seeing individuals not at all these kinds of big medical centers, but we really need to actually access people in their communities, one of the ways to make that easier would be to have mobile consent, and also to make the consent forms much more user friendly. Right now many of them are multiple pages long and you really need almost a law degree to understand it, so the idea is how can we utilize these new technologies. And that actually was a funding opportunity announcement or FOA that came out actually earlier this year, and we've gotten applications in for that.

We have another one that's going to be coming out; the concept was cleared by the NIA council, but the FOA as we call it, the funding opportunity announcement, has not come out yet, but that's going to be looking at how we can utilize mobile technology, again, to actually assess everyday functioning in someone's home, or as they move around the community, because again, how can we get information on how people are doing and utilize that in trials in a much more efficient manner than having to bring everyone into a large medical center that they may not live closely to.

Then there are some NIH-specific areas; what can the NIH do in terms of our research, in terms of looking at how we can change grant mechanisms, how we can do targeted outreach, how we can help convene and facilitate. One of the things that we're doing at the NIA/NIH level, is looking at, how can we make a repository for the researchers, how can we provide a resource, an online portal, for researchers in different areas who are trying to do trials, can look at best practices, what has worked in other areas, basically a clearinghouse. Because right now, not everybody may know about all the potential strategies that one can use. Obviously people know things about advertising in the newspaper and online, but there are other ways, community outreach, going to different community centers, involving the local community, churches, for example, so we're really trying to have this recruitment repository available to researchers.

We'd also like to bridge the gap between research and clinical care with outreach tools and information to clinicians, and some of that is going to be using digital and other communications. Doing that cross-agency, I mentioned the Administration for Community Living, well, they have two websites, BrainHealth.gov and Alzheimers.gov and actually NIH is going to be bringing that under our umbrella of scientific outreach tools so we'll be able to make sure that there are a number of places people can go, and of course convening and facilitating is one thing that we can do, and I'm going to talk about what we've done recently to spur this national effort on recruitment strategies.

Before I touch on those national recruitment efforts I also want to talk about some NIH policy changes that are hopefully going to bring more attention to recruitment. One of the things that

NIH is doing is, and you may have heard of this, we are going to be requiring a single institutional review board of record—that's the body that does the ethical review of human subjects research, not just funded by the NIH but each individual local level there's an IRB that reviews the protocol to make sure everything is above board. Really the goal of a single IRB is to enhance and streamline the IRB review process for multisite trials; it's not as important if you have a single site and a single IRB, that's fine, but what we run into with trials is that we have, for example, as I said, theA4 trial has over 60 sites, well, each site has an IRB. With a single IRB there'll be a single IRB of record. There can be some small changes and there can be some local input but there'll be a main IRB that'll review the protocol and we really hope that that will streamline getting the studies up and running, for example, if there have to be changes in the study there'll be a main IRB of record. That's going to take place this September so all applications that are for multisite clinical trials coming to the NIH after September 2017 will have to propose a single IRB. So we think that's actually going to be very, very impactful.

Another thing that will be happening some time in 2018, we're still working on it, is, the NIH is going to require a trial specific funding opportunity announcement for clinical trials. And what that means is instead of having an investigator just respond and send in applications as they normally do, we're going to have specific funding opportunity announcements with specific parts of the application that they have to talk about, things like rationale, design, the operational analysis plan, and so the reviewers will be able to look at things like, are the sample sizes adequate, are the recruitment plans well thought out, so those will actually be criteria. So that's coming down the road in 2018 but will also have, I think, a big impact in making sure that when we get studies in, that people have really thought about how they're going to recruit and retain participants. Because I think sometimes that falls by the wayside; people—especially if they are not well experienced—they don't realize how hard it is to actually reach out and recruit and retain individuals.

Another thing that the NIA specifically is doing, is, we have had a clinical trial infrastructure for a very long time, actually since 1991, but we've realized that we need to actually make that more efficient. And so earlier this year, we had a call for applications for what we're calling the Alzheimer's Clinical Trials Consortium, or the ACTC, those applications were actually just reviewed in May and we will be making a funding decision on those after our NIA council second level review in September. And the purpose of this, really, is to establish an Alzheimer's and related disease Clinical Trials Consortium that will run trials focused on interventions that will prevent, delay, or treat symptoms of AD and related dementias. It will include multiple clinical trial sites and trial coordination management infrastructure, and specifically, that was a big problem, there wasn't dedicated personnel at sites to run studies so we wanted to make sure that every site in the ACTC will have dedicated personnel. They will be able to conduct trials from Phases 1 to 3 of both pharma- and non-pharmacologic interventions for both the cognitive and neuropsychiatric symptoms, and we really see this across the spectrum of disease from pre-symptomatic to more severe stages. I think it's important, I didn't mention that earlier, while there's a heavy emphasis on prevention of course, we are still looking at ways to improve the lives of people going forward to slow progression and then to treat symptoms, like the neuropsychiatric symptoms.

And so this really, we hope, will be a state of the art clinical infrastructure. And one of the things that it has to include is a recruitment unit, and this will be responsible for developing and implementing cutting edge participant recruitment and retention strategies, in particular,

strategies focused on improving participation of diverse populations. Because as I noted that has been an area not just again for Alzheimer's disease but I think across the board for clinical research, that we need to make sure that we are reaching all levels of the community and we need to get people in from different backgrounds particularly underserved backgrounds, minority populations, rural populations.

So really what I want to end on is, how are we moving forward to implement this national recruitment strategy?

As I said, NIA is leading these activities with substantial community involvement and coordination. So there was an initial meeting at the Alzheimer international conference last year in 2016, and then following that in December of 2016, we brought together a number of stakeholders, both from the public sector and private sector and government to really talk about ideas, how can we move forward on a national strategy, because NIH can't do it alone, industry can't do it alone, and our foundation partners can't do it alone, it really is critical that we all come together and leverage resources. And so as a result of those discussions, we convened a steering committee to form a framework for a national strategy for Alzheimer's and related dementias. And the steering committee is made up of volunteers from the AD community assisting NIA in several key areas, and there are three main areas: one focused on the national efforts, how do we have a national campaign, and that's being led by Dr. Jason Karlawish; recruiting and retaining local and diverse participants, that's being led by Dr. Laura Baker[3]; and then capacity building, how do we have, sort of what I talked about with the ACTC, we have to have onsite personnel, how do we build the capacity of the sites to see large numbers of participants even if they're a good site, do they have the staffing levels they need, can they actually do this efficiently, and that's being led by Pierre Tariot.

We had our recent face-to-face meeting of the working groups that was held in April. The groups are now working on the strategies, finalizing them, we're hoping to have that done by the end of the summer, and releasing that to the public for feedback, so we're going to get public input, and then, ultimately we hope to begin implementation in 2018.

So I want to just wrap us this part, and hopefully people have a lot of questions, if you would like more information about what the NIA's efforts are, the NIH, there is a website that I'm going to give to you, it's the Alzheimer's Disease Education and Referral Center, ADEAR, and it's www.nia.nih.gov/alzheimers. We have information for researchers, people who are interested in participating in clinical research not just trials, as well as caregivers and patients. I think I'll stop there and open it up for questions.

George Vradenburg: Thank you very much, Dr. Ryan. I appreciate it. I've just got one comment; I've got a couple of questions and then we'll get to the questions that are coming in. The comment I make is the one that you have emphasized and that is the importance of recruiting communities of color into clinical trials. The striking statistic that has stuck in my mind is that the majority of Americans with Alzheimer's related dementias in 2030 are going to be either African-American or Latino. That says that 50 percent of those with the disease within the next 13, 14, 15 years are going to be what we call minorities and yet the participation of African-Americans and Latinos in

[3] Dr. Laura Baker was the guest on the November 2016 Alzheimer's Talks to discuss the EXERT exercise study.

the current clinical trials is less than five percent. So we are developing medicines that hopefully will work in all segments of society but only testing them largely on white Americans. And that just is a danger, a risk, that the medicines that we develop will skew to the particular characteristics of the white population since blacks are twice as likely or more to have this disease at the same age, Latinos 1.5 times as likely as non-Latino whites. There is something different in the African-American and Latino communities that we need to assure that we are taking account of, as we develop innovative medicines. So I would, in particular, applaud Dr. Ryan's comment and emphasis on the need to build into our recruitment systems, systems that are intentionally aimed at minority communities.

So with that said, I've got a couple of questions. Let me ask you, Dr. Ryan, could you identify why it takes 700,000 people to show up and put their hands up for a clinical trial, in order to get 70,000 participants?

Dr. Ryan: Sure, let me give you an example, the two examples that I gave. One is the A4 trial, so if we look at the criteria, who needs to get into the A4 trial, you have to have a certain level and be cognitively normal, so you go through a cognitive assessment. And then you also have to have high enough levels of amyloid, on a PET scan, to actually get into the trial, so large numbers, ten times the number you need, have to be screened, because a number of people will what we call screen fail, they won't actually be appropriate for that particular study; it doesn't mean they won't be appropriate for other studies but maybe not that particular one like the A4 trial. So what the A4 trial did, it had another arm, as I was talking about, it had a natural history arm, to see what happens to individuals who don't have high levels of amyloid but we want to look at them over the same amount of time to see what the changes are and how it might look different, moving forward with the cognitive assessments. So there was an arm that was available to people.

But that's why because depending on the criteria for the particular study, we may need a large number to screen because we'll have a number of people who will, like I said, we call it, screen fail for that particular trial.

George Vradenburg: You mentioned the A4 study, and talked about that. When did it start recruiting individuals into that trial?

Dr. Ryan: I believe A4 started recruiting in 2014, early 2014 if I'm not mistaken. So it's been a long time coming, we're at 2017 now and of course recruitment is going well but it wasn't as fast as we wanted, so they are about finished enrollment now, which is tremendous, but, yes, the screening took a while. We're talking about 60-plus sites in the U.S. and internationally.

George Vradenburg: So it's taken three years to recruit participants into the clinical trial. And how long is a participant in that trial, in order to test the medicine involved?

Dr. Ryan: They vary for different studies but for the A4, they have been on the drug, and of course they are going to be followed, for 72 weeks. There will be some other things coming out regarding A4 but yes, it's a long time. You've got to get the people in, and then you've got to follow them.

George Vradenburg: So that's about a year and a half, so from the time the first participant started, in 2014, till the time the last participant started in 2017. Until the last participant in that trial is completed, it's another 72 weeks, so you're talking probably end of 2018. Start the trial in 2014, start recruiting in 2014, and the actual trial of the drug is completed in 2018.

Dr. Ryan: Right.

George Vradenburg: And then there's a period of analysis.

Dr. Ryan: Right and usually they try to get those, the primary endpoints soonest but that will be a few months, before there are results.

George Vradenburg: I'm just emphasizing to those who are listening how long these trials are and this is a trial in, as you said, persons who are cognitively normal but with a significant amyloid burden in their brains.

Dr. Ryan: Right, which puts them at a potentially higher risk of going on to develop Alzheimer's dementia.

George Vradenburg: As I understand it, there are now potential trials of drugs at even earlier stages of the disease, that is, at even lesser burdens of amyloid, which suggests that it may be even harder to find these people.

Dr. Ryan: Right, exactly. Although we did have, as I talked about screen fails, there were a number of people who were very interested in A4 but screen failed because they didn't have high enough levels of amyloid, so we do think there's interest, but you're right, it's going to add another layer if we go earlier.

George Vradenburg: You mentioned the phrase, just for the purposes of making sure everyone's on an equal information plane, the words secondary prevention. Could you describe what secondary prevention is?

Dr. Ryan: Secondary prevention really means, we're looking at individuals who are at a higher risk for a disease, they don't have the disease but they're at higher risk for it. In the A4 trial, it was high levels of amyloid on PET scans which have been found to be a risk factor; in the case of the Generation study, having two copies of the E4 allele, it doesn't mean you're going to get Alzheimer's but puts you at higher risk for it so you're in a high risk category.

Whereas when we talk about primary prevention, what we're really talking about is a population at large, not looking at who has definite risk factors, so it's a bit different; we're really talking about people who are at higher risk to go on to develop the disease.

George Vradenburg: So we've got a question here: how do we sign up for trials?

Dr. Ryan: That is a great question. I would say there are a couple of options and they're not always easy to navigate, quite honestly. So the federal government runs something called clinicaltrials.gov. You can put in a type of disease or a type of trial and look at what's available. Alternatively, and this may be easier, if you're looking specifically for Alzheimer's and related

dementias, I think there's two ways to go. The Alzheimer's Association has something called TrialMatch, which, they're really trying to match participants with ongoing clinical research studies. And then the NIA through the ADEAR website, we have a listing not just of NIA trials but we also have a listing of trials by pharmaceutical companies and anything that's listed in clinicaltrials.gov. We've tried to pull out the ones for Alzheimer's and related dementia. So you can use both of those services. I would think those would be the best way to go. Then try to navigate clinicaltrials.gov, I mean, it is actually difficult, so I would recommend either of those two, TrialMatch or the ADEAR website.

George Vradenburg: So just a reminder to people, if you've got questions, put in star 3 on your phone, you'll get into a question queue and we'll get to your questions as we get you online. Here's a question from Larry Cowen online. Are cutbacks in research for Alzheimer's being proposed in the President's budget?

Dr. Ryan: From what we've heard so far, regarding the skinny budget the NIH as a whole would be getting a cut. We have been very, very fortunate at the NIA with Alzheimer's research to get increased funding the last two years, and we just got an initial $400 million, which is fantastic. We're not there yet, but it puts our funding for Alzheimer's disease now at almost a billion and a half dollars, so I think that's been very, very helpful. Obviously we would not like to see cuts but we're very thankful for what we've gotten so far.

George Vradenburg: Here's a question online from Shelley Moore. Does the steering committee that you're heading address study partner recruitment as well as participant recruitment?

Dr. Ryan: Yes, absolutely. As I mentioned, that's one of the potential barriers for Alzheimer's and related dementia studies, is the requirement of the study partner, so we have both the national team looking at that, and also the local diversity team led by Dr. Laura Baker; they are looking at that as well, yes.

George Vradenburg: A question about 2025. What do you think is the most significant pacing items to see whether we can get means of prevention and treatment by 2025?

Dr. Ryan: I think that we are very fortunate that even though there's a lot that we still don't understand about Alzheimer's in terms of its complexity, we are understanding more and more. We have a number of studies, I think, now, that we have things like amyloid PET scans and whatnot, we can actually try to screen participants so that we can find the right treatment for them.

Alzheimer's isn't going to be one thing and I don't think we're going to have all of the answers by 2025, but I do feel like we will have things that are helpful in some particular individuals so I do think we're going to get there. But we're going to need to have, most likely, combination therapies for individuals who have different risk profiles. My risk profile might look very different from yours, I might have cardiovascular disease or diabetes that puts me at risk; someone else might have two copies of APOE-4 allele. So there's going to be different combinations. I think the exciting thing is really, really using things like some new approaches, such as systems biology to looking for novel targets and networks as well as some of the things that have been brewing longer like the amyloid therapies. We are going to find combinations that work for individuals. So it's very exciting, but I do think understanding the complexities of this

disease is really going to help us target the right treatments, for the right individual, at the right time.

George Vradenburg: So that answer actually feeds into a question from Del Muzzillo from California. Why are we focused on a single medication when we know from heart disease and cancer that only a multi-faceted integrative approach, maybe including medication but maybe other things, will work?

Dr. Ryan: I think we're not solely focused on that, but if you look at the way other diseases have done it, we have to identify things that can work on particular disease targets but it is going to be a combination so I think people are looking at individual targets, but with the knowledge that we're going to be needing to use treatments for multiple targets, that we're going to have address at the individual level, so we are looking towards what we're going to call precision medicine.

Again, looking at different risk profiles, meaning I'll get a different combination of treatments from other people, so even though it looks like, yes, a lot of these studies right now are looking to see if there's an effect with a single intervention, we are looking at these therapies that will likely have to be used in combination and not just with other drugs, but as you point out, lifestyle interventions, exercise, cognitive training, actually social stimulation, diet, so these are all things that, you're right, we're going to be needing to do in combination.

George Vradenburg: What is the NIH view on whether or not one can delay or mitigate Alzheimer's through lifestyle interventions only?

Dr. Ryan: A lot of the observational studies and the animal literature has really said, well maybe we can do this, people who have healthy diets, have healthy lifestyles, they seem to delay when people have onset of the disease, but we don't actually have that in terms of the actual trials, good evidence from the trials themselves, although I'd say some of these large scale interventions are going on right now, and one I'll bring up is the EXERT study which is being run through the Alzheimer's Disease Cooperative Study and Wake Forest led by Dr. Laura Baker[4], looking at, can we intervene in individuals who don't have dementia yet, they have mild cognitive impairment, can we intervene to slow progression /delay dementia. So we're doing the large-scale studies now to actually see if the intervention can impact the disease. From smaller studies, it looks like there's some evidence that it's possible, but there's not great evidence right now that I can tell you, if you go out and exercise it's going to delay the onset of disease, we cannot tell you that, but living a healthy lifestyle does seem to help in terms of how you age over time and certainly I think these large studies like EXERT will give us more definitive answers.

George Vradenburg: Do you have a view, this is a sophisticated question, do you have a view as to whether or not there is a marker of disease which one could rely on, in assessing the effectiveness of a medicine, as opposed to trying to demonstrate clinical benefit?

Dr. Ryan: Well, that's actually something people are looking at as well. So we've talked about amyloid PET, for example, that's being used right now to see what, to get people into trials, people who are at higher risk, but also we want the potential to look at tau imaging, for example,

[4] Dr. Laura Baker was the guest on the November 2016 Alzheimer's Talks to discuss the EXERT exercise study.

can we actually use these brain scans or ultimately we'd like to have something more simple, you know, like we have for cholesterol and cardiovascular disease, can we actually look at who's at risk, look at if we can mitigate that risk like we do with cholesterol. We're not there yet, and FDA actually is very, very involved in this, they do want to see clinical outcomes right now but ultimately if there is something that can be shown that it actually tracks with disease progression and treatment response that would be very helpful and is something we are looking for, but unfortunately we're not there yet.

George Vradenburg: Question from Gene Pettinelli from Massachusetts. This is one that I'll be very curious as to how you answer. Which drug trial is showing the most promise?

Dr. Ryan: That is a hard question, actually, really, to answer because until we actually get the large studies done—many things have looked good in smaller studies, then we've gotten into larger ones, and it hasn't panned out as well—so I think, what I find very exciting is that while, amyloid is the furthest along, in terms of what the research has been doing, that there are other targets now that people are looking at; there are nerve growth factors, for example, that's one that's being supported by NIA, people may have seen it, it was in Time Magazine, Dr. Frank Longo's compound at Stanford, we're actually supporting the Phase 2 trial on that.

So I think there are a lot of exciting targets that are not just amyloid, that are very promising, but until we actually get through the large-scale studies we won't, unfortunately, know how promising they are.

George Vradenburg: Here's an interesting question from Antoinette. Is it possible for someone to have Alzheimer's disease for over 20 years?

Dr. Ryan: Well, that's interesting. If we mean clinical symptoms, that's pretty unusual, although we know, now, that Alzheimer's disease starts in the brain a decade or more before we actually have a clinical symptom. But people certainly have been known to live going on a decade or more with clinical symptoms, and actually, I can give a personal example here. My father's 94 and he has Alzheimer's or a mixed dementia, and it's been, probably, since he started showing memory impairment over eight years now, when the symptoms started mildly. He's in the moderate stage now, but he is still physically going strong. So people certainly can have the symptoms for over a decade. I haven't heard people having full-blown severe symptoms for 20 years but we know that the disease has already started in the brain in many people by that time.

George Vradenburg: I can give a response to this just from personal information. A colleague of ours, one of the founders of our organization, named Meryl Comer, has a husband who has had symptoms for 21 years. He was symptomatic at age 58, he's now 79. I agree, it is very unusual but there are cases where symptomatic Alzheimer's can last that long.

Dr. Ryan: George, as we have better care for people with the disease, we may be seeing that people will actually live longer because they are healthy in other aspects.

George Vradenburg: This is a hard way to put it, but he has very strong lungs and a very strong heart, and he's been able to continue to be alive for now 21 years.

Dr. Ryan: Yes.

George Vradenburg: So, we have someone on the line here, Michael Ellenbogen, from Pennsylvania. Michael, could you go ahead and ask Dr. Ryan your question?

Caller: Sure. First of all, I'd like to just add on, I just turned 20 years living with Alzheimer's disease, so I think I'm doing something right, but anyway, you had mentioned about ways of researching for clinical trials. There's one place that I found better than the one that you had mentioned, it's a place called Antidote. I think it makes it much easier to do searches.

Dr. Ryan: Fantastic.

Caller: Now, I have a question for you.

George Vradenburg: Just to add, Michael, the Antidote website is antidote.me.

Caller: Okay. I have a question for you. In reference to what you're trying to do right now, as far as to do research on how to improve clinical trials, are you looking or recommending telemedicine for study partners, such as being able to use videoconferencing for those folks?

Dr. Ryan: Actually that falls under technology, and yes, there are a number of efforts trying to utilize mobile and other technologies and that would be one way for the study partner, again, to actually be able to assess people in their living environments. So there are a number of efforts, yes, trying to tap into the technologies we have now to improve clinical trials.

Caller: Thank you.

George Vradenburg: Question online from Genny Matthews. Where can we find the national recruitment strategy committee deliberations?

Dr. Ryan: Well actually, we don't have the deliberations online, but we did publicly have had a public meeting, I believe at CTAD, which is the Clinical Trials in Alzheimer's Disease, last December, and we are going to have a public venue again once the document is ready and then that will also be made available online for people to look at. So right now the deliberations we don't have online, but the product for comment will be online as well, there will be actual public presentations on it as well.

George Vradenburg: You said roughly this fall?

Dr. Ryan: I think so, that's what we're shooting for, absolutely, George, this fall.

George Vradenburg: And we'll make that available on our website when the NIA posts it for comment, and you can obviously look at the NIA site as well, when it does get posted, and be able to make your comments. Got a question here from Jennifer online. Are there studies geared to rare forms of AD, specifically PCA [posterior cortical atrophy]?

Dr Ryan: You know, the related dementias have not, they are not as far along as the late onset Alzheimer's disease in terms of research, but there are a number of foundations and researchers focusing on other dementias. , I know we've been hearing of interest, and I'm not actually aware

of any particular trials although there may well be, if you did a search, as Michael said, at Antidote or TrialMatch to find one. But I know that the Alzheimer's disease related dementias are areas that are getting increased focus because they are rarer so there are fewer participants but I know that it is an up and coming area that people are looking at, including the NIH by the way.

George Vradenburg: A question here from Angelica. What examinations can we ask for, or do, to know if we have Alzheimer's?

Dr. Ryan: Well, Alzheimer's, again is not, there's not a single test, I wish there were, that we could give at this point. So what generally happens, and what people should do, if they're concerned about it, they should talk with their primary care doctors is who can refer for assessments, like cognitive assessment.

Primary care physicians, as part of Medicare, are also supposed to ask in the annual wellness visit about cognition, certainly if you have cognitive complaints then there can be a referral to a specialist which would end up being somebody like a neuropsychologist who then would be doing further tests and ultimately the cognitive assessment plus some other things, like if there's a concern, there could be a PET scan involved, an amyloid PET scan, so there are a series of triggers, if you will, for advanced assessment. If you have concerns, I would absolutely suggest talking to your primary care physician and then of course, they could then refer to a neurologist, neuropsychologist, for further assessment, but that's where you should definitely start, ask, if you're having worries about cognition, that's where I would go.

George Vradenburg: A question here from Carla Danesi from East Rochester. Carla, would you ask your question please?

Caller: Hi, George. You are all my heroes. Hi, Dr. Ryan. I just wanted to put this on your radar: J147. They are completing toxicology as we speak and they've done very, very well, he's completing a couple of assays and then he's going to be ready to go on to human trials. Now this is the only compound that has shown in mouse models to reverse symptoms, so it's huge, it's bigger than Aricept, it's supposed to fare better than Aricept. Of course the way we'll know for sure is once it gets to human trials, so I want it on the radar for everybody to look out because it's coming. And I've studied this for 20 years myself, as a caregiver of a mom with severe Alzheimer's who's still alive by the way who's doing very well after 20 years. So, just keep J147 and Dr. Schubert on your radar please, because it's up and coming, and it'd be awesome for prevention as well. So, prevention, mild-moderate, and severe treatment as well, coming up.

Dr. Ryan: Thank you.

Caller: You're welcome, thank you.

George Vradenburg: I've got a question here that actually relates, potentially, to that, and that is, what is the current thinking, Dr. Ryan, about stem cell therapies?

Dr. Ryan: That's another area that people have been very interested in, and has been further along in other disease areas, so I think it's up and coming but the research is still at a very early preclinical—I shouldn't say preclinical in terms of symptoms but—in animal studies, so I think it's up and coming but not advanced yet in terms of human studies.

George Vradenburg: Question here from Dr. Janice Moore from Georgia. How close are we to finding a cure?

Dr. Ryan: I think that goes back to what I was talking about earlier, that we're likely to have a need for multiple therapeutics, against different disease targets whether it be amyloid, tau, looking at insulin resistance, some of the cardiovascular, looking at lifestyle, so I think we are, we have a number of studies people have heard about like A4 that are in late stages to look at certain aspects of the disease, and we're very hopeful that we'll have a positive result in some of those, but we're going to need more than that. So all these other studies that are looking at different targets, like I said, nerve growth factors, oxidative stress, inflammation, those are all areas that we're also targeting and that we're likely to need multiple therapies that will be unique to the individual based on their risk profile, so I think we're going to have hopefully things that will be successful but we're going to need multiple things to actually attack and defeat this disease.

George Vradenburg: With that assumption, let me try the question again. So, how far are we from a cure? Sounds like it's a long way away.

Dr. Ryan: Well, I don't know, George, we have, as you've said, we have a number of studies that will be finishing in 2018 and we're hopeful that we'll have a positive result for some of the late stage studies, but they won't be the end of it all. Even if we have a positive result, we're going to need multiple therapies, so I hope that we have some things that are ready by the goal of 2025, we're certainly working on that, and there are trials that will be finishing up, some of these late stage trials that we just talked about. But we're likely to need other things in the arsenal as we're moving forward. So it won't be the end, but we're hopeful that some of these late stage studies will be positive, that are ending around 2020.

George Vradenburg: Dr. Moore presses the question differently: How soon will there be a medicine that will slow down the disease?

Dr. Ryan: I'll go back to A4. So if A4 is successful, and it's finished roughly in 2018, and then it's in the FDA's hands, but in theory you could have something, a year or so after that, depending on the FDA review and I can't speak for the FDA, but I would imagine that the trials that are wrapping up now, these pivotal, these large Phase 3 trials, if they are successful, there could be something by the time of the target of the national plan of 2025, so I do think it's possible. I know, I think the field knows, that we're going to need more than just anti-amyloid therapy, for example, even if successful.

George Vradenburg: Just a couple more here and then we'll run out of time. From Kristina Madarang: What's the latest on nilotinib for Alzheimer's disease[5]? This is a cancer drug.

Dr. Ryan: I'm actually not that familiar . . . there are a number of different cancer drugs that are being considered, but I can't actually, unfortunately, give you an answer on that because I am not sure.

[5] Learn more about nilotinib, in the Alzheimer's Talks with Dr. Scott Turner.

George Vradenburg: Okay. And last question here today from Ashley Peterson in Tampa. Ashley, would you please go ahead and ask your question?

Caller: Hi, I was just curious to know, when researchers look at PET positive images, what exactly are they looking for? And this question comes about because I recently had a patient who was independently tested and was found PET positive by a neurologist but then was not accepted into one of the studies, as the PET scan came back negative. I wasn't sure if that was because the researchers are looking for a certain level of beta amyloid in the CSF [cerebrospinal fluid] or in the PET scans or if it was just a false positive on his first scan.

Dr. Ryan: Now, generally speaking it's the level of amyloid, so in A4 there is specific level of amyloid that has to be reached. There are some people that are technically still showing amyloid on scans but wouldn't be eligible for A4 because they didn't reach a high enough level and so that's likely what would be the case, they would have signs of amyloid but not at a high enough level that they would qualify for a particular study, would be my guess.

George Vradenburg: Great, thank you.

Well, thank you, Dr. Ryan, thank you for being here this afternoon, thank you for what you do every day, to try and get at this darn disease. Sorry we couldn't get to everybody's questions but thank you very much for participating on the call today. If you've not already joined UsAgainstAlzheimers, please go to http://www.usagainstalzheimers.org/ and sign up. We'll send you a recap of this call, invitations to future calls, important updates, and simple ways that you can get involved and engaged as we find that as the policy agenda here ramps up on the health care side and currently respect to next year's budget which will be very challenging. We're going to be calling on all of you to participate in making your voice heard in Washington and continue the positive results we've had in the past, as Dr. Ryan's indicated, in increasing the amount of money that's being invested in Alzheimer's research through the NIH. The President's budget does contemplate significant cutbacks.

Thank you to everyone on the phone or online for participating in this Alzheimer's Talks. In a couple weeks we will have a copy of the recording and a transcript on our website for you to share with your friends.

Please stay on the phone to leave us a message. We are particularly interested in your feedback on this call and ideas for upcoming calls. Thank you for joining us today and have a good afternoon.