

**Alzheimer's Talks
with Dr. Howard Fillit
May 25, 2017**

Note: This transcript has been edited for content and clarity

Welcome to [Alzheimer's Talks](#), a free monthly teleconference presented by [UsAgainstAlzheimer's](#).

My name is [George Vradenburg](#). I'm [Chairman and Co-Founder of UsAgainstAlzheimer's](#) and I want to thank you so much for joining us today to hear about this interesting new analysis called "[Single Endpoint for New Drug Approvals for Alzheimer's Disease](#)" by a number of authors associated with our network, [ResearchersAgainstAlzheimer's](#). ResearchersAgainstAlzheimer's is a global coalition of Alzheimer's researchers extending from Japan to the United States and Canada to Europe, that advocate for research funding and research-friendly policy reform to prevent and treat Alzheimer's by 2025.

Just a quick report from Washington: This has been a busy month or two in Washington, what with investigations into collusion with Russia, the firing of FBI Director Comey, investigations into former National Security Director Flynn, but beneath all of that, there is a very important development in terms of commitment of the government, on a bipartisan basis, to Alzheimer's research. [The United States Congress passed a budget by overwhelming margins, both Republican and Democrat, that would increase NIH spending in this fiscal year](#), which started last October 1 and ends on September 30 of this year, by \$2 billion, and in that, they asymmetrically, that is, out of proportion to increases in other areas, increased the investment in Alzheimer's research from \$1 billion a year to \$1.4 billion a year. Now just to place that in some context, when UsAgainstAlzheimer's was formed back in 2010, the level of annual funding was in the low \$400 million every year. Now, we're at \$1.4 billion. So there has been a bipartisan commitment, both to NIH generally as well as to increasing investments in Alzheimer's in recent years, in particular. So that is, in a sense, good news.

With that said, the [President's budget proposal for 2018](#) contemplates a very significant increase in defense spending and a commensurate very significant decrease in domestic discretionary spending, and an \$8 billion reduction in funding for NIH, a \$750 million decrease in funding for the National Institute on Aging—which has the lead for Alzheimer's research.

So we are, as an advocacy organization, [strongly resisting those massive cuts at NIH and in Alzheimer's research](#), and we will be urging all of you as well as all of the individuals in the UsAgainstAlzheimer's community to talk to their congressperson and their senators and tell them that we need to increase research funding on behalf of the millions of Americans who have Alzheimer's.

Today, we are honored to have [Dr. Howard Fillit](#) as our guest. He is Founding Executive Director and Chief Science Officer at the [Alzheimer's Drug Discovery Foundation](#), a leading Alzheimer's research investor and leader, and a founding member of our ResearchersAgainstAlzheimer's network. He is also a clinical professor of geriatric medicine and palliative care, medicine, and neuroscience at the [Mount Sinai School of Medicine](#), and in addition to all the above he has a private practice in geriatric medicine, and obviously, no hobbies. He co-authored this brand new analysis on regulatory endpoints for Alzheimer's and so, we are very grateful for his work generally, his work as a physician with individuals, his work at the Alzheimer's Drug Discovery Foundation, and grateful for his time today.

Just as a reminder, if you have a question during the call, please press *3 on your phone. By pressing *3 you will be placed into the question queue. Please have your question ready to share briefly with a member of our staff. If you are listening to us online, you can simply type your question in the box, and we will get to as many questions as possible, as soon as Dr. Fillit has completed his initial

remarks. Please note that Dr. Fillit, like all our guests, is not able to answer personal medical questions on this call.

Thank you so much for joining us today, Howard. The microphone is yours.

Dr. Fillit: Thank you George, and hello, everybody. I do like to play tennis occasionally George, because I know that exercise is good for my brain! But thank you very much for that kind introduction and hello, everybody.

So let me start off by why what we're talking about today is important. It takes roughly twelve to fifteen years to develop a drug, estimates are now that it costs upwards of around \$2 billion to develop a drug. Most of these programs that enter into the Phase 1 time, the early phase of drug development and Phase I of an FDA approval process, about ninety percent of those will fail. In our field, in Alzheimer's disease, since 2003, we've basically had 100 percent failure rate, a couple hundred trials have been done. The thing is, we really need to work with the FDA to develop standards that are reasonable for our populations, for people with Alzheimer's disease, to promote safety, which is the primary mission of the FDA, and to demonstrate efficacy of the drugs that we're developing. So spending all that money and time and patient effort and patients being involved in these trials, and coming to that final day, when the FDA committees and the FDA itself have to decide whether or not to release a drug to the market based on the studies that are being done—you can imagine how important that decision is.

Now, in our field, as opposed to cancer, diabetes, and hypertension, where we've had drugs for 70, 80 years, and we've had drug approvals for 30, 40 years, in our field, we're relatively newcomers in terms of research. I remember doing one of the first clinical trials back in the early '80s. In those days, we were just getting started and doing clinical trials and we really didn't know how to do clinical trials. We were learning about the biology, we were learning about the science, we were starting to translate the science and recruiting patients into trials and trying to get drugs approved. And in the '90s, the standards for drug approvals were developed based on technology and understanding of the disease that was available at the time. At the time, we were basically studying people with dementia from Alzheimer's disease, or what we thought was from Alzheimer's disease, so dementia, being a description of the patient who is having memory problems and other kinds of cognitive impairments that lead to functional impairments, things like not being able to pay checks or manage medications, which we might call a phase of mild dementia, having some problems with planning trips and things like that, and moving into more serious deficits in a moderate stage of dementia, like having trouble dressing yourself, and then going into the severe stages where people really have to be fed and they're incontinent.

So we have these three stages—of mild, moderate, and severe dementia. And the guidelines for developing a drug—clinical trials were done in the different stages. Some of the first drugs were developed for mild and moderate dementia, and then some of the later drugs like memantine were developed for moderate to severe dementia, the cholinesterase inhibitors that were proved in the '90s, were first developed for mild to moderate dementia, ultimately got approval for mild, moderate, and severe dementia.

Now in those days, people were recruited into trials mostly based, or almost completely based, on their clinical definition of the disease. Brain scans were done to rule out strokes and blood tests were done to rule out other diseases like B12 deficiency but basically, people were being enrolled in trials based on the current technology which was their clinical status, which was essentially cognition. We had measures of ways to objectively measure cognition, things like memory and so on, and function—function as I mentioned being the ability to tie your shoes, which is a little more subjective but still measurable.

And at the time, there was consensus in the field, I think, and of course, the people in industry and academia and the FDA, and also the NIA, National Institute on Aging, and foundations like the Alzheimer's Association, all talking to each other at the time, coming to consensus about: what do we

need to show, to show that a drug is effective in Alzheimer's disease, because Alzheimer's disease is a disease of the human mind. It's not like diabetes, where we can measure glucose, and if the drug works, we know that that's a good thing because it's reducing these high levels of glucose. And in those days, it was kind of hard to do that and so a standard came up, which kind of said something like this: we're going to be measuring cognition and we're going to be measuring function, and I think the consensus was, well, sometimes you could show a benefit on a specific neuropsychological test, which was the way we measured cognition, but that might not be clinically meaningful. So let's say you measured 100 cognitive tests and you found two or three that were positive. Could that really be showing the benefit of a drug? And the answer was, probably not. Because if you did a lot of cognitive tests, you might be able to find some benefit but we wanted to make sure that any benefit that was seen on these cognitive tests was associated with an improvement of function. And the idea was that that combination of cognition and function meant that the improvements in cognition were good enough to improve function and therefore were clinically meaningful.

So that's sort of what we call a co-primary endpoint of cognition and function came about. We wanted to show that drugs were clinically meaningful. And at the time, in mild to moderate to severe dementia, there were enough functional impairments that we could say that a drug was actually improving function, in some way, and that put the drugs that were proved, in those days, prior to 2003, the cholinesterase inhibitors and drugs like memantine, the NMDA antagonists, that's what they were able to do. They were able to show that they improved cognition and function.

Then what happened? Well, the field evolved. A concept called mild cognitive impairment was recognized. This was recognized as being sort of what we call a prodromal state, a state that happened pre-dementia, that was characterized only by memory loss, and people really, in this MCI or mild cognitive impairment state, really didn't have much functional impairment at all. They just had memory loss. It was severe enough to not be thought of as normal cognitive aging, it was somewhat disruptive in people's lives; husband was asking wife 10, 15 times a day the same question, perhaps. But if you met that person in a restaurant and they were your friend, you might not know that they were suffering from Alzheimer's disease at all. So that was one thing. And we started thinking about doing clinical trials in MCI because we thought that by doing clinical trials, in this earlier stage, we might have a better chance of success.

And the other thing that happened that advanced our field was that (and if you're hearing an ambulance in the background, it's because I'm in New York City on 57th Street and I apologize) the other thing that happened is we started developing biomarkers. Biomarkers are really important for drug development and also for the FDA, because they tell us something about how a drug affects a disease. So as I mentioned earlier, in diabetes, we want to look at glucose, and drugs that lower glucose or hemoglobin a1c, they have a better chance of approval because we know that that biomarker, or in the case of—to use a technical term—that surrogate marker, which is the biomarker that's recognized by the FDA as being relevant to the disease and could be the measure of a drug's efficacy. Blood pressure would be another biomarker for hypertension, for example, as one that not only recognizes the importance of the disease and represents the disease but could also be used in getting hypertension drug approval. We didn't have any biomarkers in Alzheimer's disease; but now we do.

And our foundation, the Alzheimer's Drug Discovery Foundation, and the National Institute on Aging and others, we funded many biomarkers and today we have pretty good biomarkers. We have all kinds of neuroimaging biomarkers, like we can see the amyloid in the brain of people with Alzheimer's disease, we can make the diagnosis and we can use these biomarkers like brain amyloid on PET scanning to monitor the course of therapy during a clinical trial. And we can use these biomarkers to enroll people into Alzheimer's trials. And so, what's happened most recently, for example, is that Biogen, and to some degree, Merck, did an amazing thing. We've had 450 trials in our field—and for the first time, everyone who enrolled in a clinical trial got a PET amyloid scan and that meant that everyone who enrolled in the Biogen trial actually had Alzheimer's disease. And the critical advance of that was, before that up to 35 percent of people who were enrolled in trials, turns out didn't have Alzheimer's disease when we went back and looked at their scans. So the trials that we've done in

history prior to this recent Biogen study, for example, they were not really high-quality trials. It's nothing to do with the investigators or the companies or anything, we just didn't have the technology to really do these sophisticated trials. We've learned, from our research, how to do modern trials now. We can enroll people that we know have positive amyloid scans which means they have Alzheimer's disease. Then we can use that scan over time to monitor therapy.

So, for example, again in the Biogen trial there was a dose-related decrease in the PET amyloid signal over one year so that at the highest dose at one year about 75 percent of the amyloid in the brain was removed—the signal was reduced. That was a pretty amazing finding and supported the fact that the drug worked in the sense that it did what it was supposed to do. These were anti-amyloid drugs—they removed amyloid from the brain. We still don't know whether that's going to result in a cognitive improvement, improvement in patient conditions, but that was a major advance that just happened in the last few years.

So let's go back now and think about the old FDA standard or what was generally a consensus for what would be an approvable drug. It used to be for mild to moderate to severe dementia where you had to show cognition and function and if you did that, then you had a drug that was thought to be clinically meaningful. Now, fast-forward to modern day, we're doing clinical trials in much earlier patients who have what we call MCI, they don't have much functional impairment so can't really show in any reasonable way, a functional improvement by a drug. In a clinical trial, that's not to say that the drug isn't clinically meaningful because improving patients' lives with MCI is important. But also slowing down the process of MCI going to dementia is really important. And finally we have all these biomarkers, and when I say all these biomarkers I mean not just PET amyloid scanning but we can do what's called MRI volumetrics and look at the brain's size and see that the shrinkage is slowing down. We can look at spinal fluids and look at things like that, not only amyloid but a molecule called tau in the spinal fluid to see if neurodegeneration is slowing down, and we can even look at brain function by doing what's called FDG, fluorodeoxyglucose PET scans that actually look at brain function and those are just a few of the biomarkers that we have today.

So what we proposed here and what I think our field in general has come to a consensus about is that we need a change in the way we think of what is the clinically meaningful drug and what should be an approvable drug in our field. I think to summarize, what's really in our report, what we think is meaningful is a drug that affects cognition on some agreed-upon or presented battery of cognitive tests, so you're not just doing one out of a hundred tests and showing cognition, but you're looking at a clinically meaningful battery of cognitive tests, don't necessarily have to have function because function's hard to measure and show change in a reasonable clinical trial. And combine that, what we call primary clinical endpoint of cognition, which is a *sine qua non* of Alzheimer's disease, with some of these biomarkers to show that there's a reasonable way to show that the drug is actually working and hitting its target or having some biological effect on a patient. And that should be pretty much enough to get a drug to market, assuming of course that it's safe. And of course that's the ultimate goal here, of regulation, let's say, is the safety of the public, which is the FDA's mission but also to make sure that drugs that come to market are clinically meaningful. And that, as I mentioned before, with diabetes and hypertension, is where we ultimately want to go as we're developing exciting new therapies. There are over a hundred drugs in clinical trials now that are really exciting, so the times have changed and the field has changed so much now, that it's a really exciting time in our field in terms of the number of new drugs that are being developed, not just on amyloids but on tau and so many other endpoints.

The problem is this: a Phase 3 program, one Phase 3 clinical trial in our field on a disease modifying drug, costs about \$300 to 400 million, and a complete drug development program in our field could cost anywhere from \$1 billion to \$2 billion or even more. Somebody's got to take that risk and basically it's going to be big pharma; they're the only kind of groups that really have the kind of resources and so on to take that risk. Somebody's got to be willing to take that risk of \$1 billion to \$2 billion on a drug and do the human experiment that's necessary for this human disease of the human mind; it's the only way we're going to get there. And have some reasonable scientific structure, let's say, or paradigm, to work with, to know what success is going to look like.

And if we raise that bar too high, or base that bar on older standards, we don't incorporate the new knowledge that we have about biomarkers, the fact that cognition does correlate with function but that cognition alone might be the only clinical primary endpoint in an MCI trial, for example, where many of the studies are being done. If we don't create realistic expectations for the clinical meaningfulness of a drug especially at the FDA, which is the last step in risks that we all have to take in this, then I think it can reduce investment. It can reduce the amount of money that's going to come into our field. We're going to need 10s of billions of dollars to test all these new drugs, through Phase 1, Phase 2, Phase 3 stages. We're going to need a lot of experiments and I think that to take that kind of risk we really have to have realistic expectations.

And finally to put those expectations of what a clinically meaningful drug looks like, and what an approvable drug looks like, in line with other disease states as we say in our report, we want to be like everybody else. We want to have a single primary clinical endpoint, that's clinically meaningful, reasonably measurable, combine that with some biomarkers to show that there's a rational way that the drug works, and get those drugs out to people that are suffering this horrible disease.

And with that, I think I'll be happy to take some questions and close my remarks.

George Vradenburg: Thank you very much, Howard. I have got a question just to start this off. Howard, would you characterize the change that this report suggests as lowering the standards for the approval of drugs, as modernizing the standard for the approval of drugs, or some other verb?

Dr. Fillit: Well, I think it's definitely not lowering the standards. I think it's making the standards modernized, absolutely, because what we're proposing here, really, is having the standards—and they're not standards in the sense that it's X, Y, Z; I don't think the FDA committees work like that, they're going to be looking at the full body of the dossier of information that they're being presented with to make a decision about an approval so, standards is a little bit of a heavy word, I think here, but just generally guidelines and how we look, as a field—governments, industry, philanthropy, FDA, and when I say government I mean NIA and academics, how we all, in the field look at what is a clinically meaningful drug. And I think as I mentioned, with the advent of biomarkers, and the incorporation of these biomarkers into trials, and the movement of these trials into earlier patients who basically have no functional impairment, clearly we need to modernize our standards so that we're working within the clinical context of the kind of patients that we're testing and hoping to treat, namely people with MCI, and the kind of technology we have today that we didn't have 20 years ago in terms of biomarkers to be able to measure the progression of the disease in a clinically meaningful way.

George Vradenburg: There are a couple of questions here online, from Chrissy Wendell and Stephanie Bertels, which are general questions. How close are we to being able to prevent Alzheimer's? What do you see as the timeline, given the drugs in the pipeline, for a potential means of preventing the disease or preventing the symptoms of the disease?

Dr. Fillit: Well, I'd like to nuance my answer to that in a couple of ways. First of all, prevention often involves public health and epidemiology and we've come a long way in learning that, the sound bite being, what's good for your heart is good for your brain, and that seems fairly evident now. Some recent cohort studies have shown that the incidence, the number of new cases per year in various age groups is declining, and we attribute this to the improvement in public health—more exercise, better diets, better management of hypertension and diabetes and other risk factors. So in terms of primary prevention through public health, through lifestyle, through better diets, through better management of diabetes and hypertension and other risk factors, I think there's a recognition that we're probably already making an impact.

In terms of drugs, we could look at using drugs for prevention, again primary, secondary prevention, the way I'd like to make the analogy, and this might be arguable but I think it's a reasonable way to illustrate what we're talking about here, is that the statins were initially developed in clinical trials for people who already had a heart attack, to see if you could prevent the second heart attack. So that

would be what I would call secondary prevention. In other words, these are people that already have the disease and we're trying to prevent some of the complications of the disease, in terms of the secondary effects, the second heart attack. And statins clearly showed that they could prevent the second heart attack. And then after we showed that, we went and did primary prevention, where we started giving statins to people that had high cholesterol but hadn't had that first heart attack.

Now to analogize that to Alzheimer's disease where you have these different forms, you have what we call normal cognitive aging, you have MCI where people just have memory problems, and you have dementia where people are really start to suffer mild, moderate, and then severe dementia. So one could think of prevention as trying to treat people with MCI, they're kind of like the people in my mind, just to make an analogy, the people who've had their first heart attack. People who've had the first heart attack, you prevent the second one, they're back at work. Now I'm not saying the people with MCI are necessarily going to go back to work but they have quality of life and very little functional impairment. So if we can show the way we're currently doing in a lot of clinical trials, testing people with MCI and seeing if we can delay the progression to mild dementia by one, two, three, four, five years in an elderly population, an improved quality of life during that period, to me, that's prevention. That's slowing the rate of progression but it's also prevention to an endpoint of mild dementia where people really start suffering. Now it's a continuum, it's not a dichotomous outcome, but it is a form of prevention.

The other form of prevention would be taking normal people, that, let's say have positive brain scans, positive PET amyloid scans, and we know from these amyloid scans that the disease starts developing 10, 20, 30 years before people become symptomatic, just like we know now people start getting atherosclerosis in their teens and twenties but they don't get their heart attack until they're 70, same thing with the PET amyloid scans, we know that people start developing amyloid in their brain and therefore Alzheimer's disease in midlife. And so some studies are going on now which might be thought of also as primary prevention in which we're finding these people that have either minimal or no cognitive impairment in their fifties and sixties let's say who have positive amyloid scans and seeing what drugs we're currently testing, the anti-amyloid drugs, whether by doing that we can slow the progression of these very mild symptoms and even progression to mild cognitive impairment. So, that I think is an achievable goal. The studies are ongoing; they're going to report out in the next few years and I think we're all very excited to hear the results of those studies in the next two, three, four years.

George Vradenburg: So we have a question online from Donald Connor. He asks: one of the original problems, I take it, justifying the cognitive plus functional outcomes, co-primary outcomes, was not the number of tests but that a statistical difference on the cognitive test can be clinically meaningless. How do you address the clinically meaningful effect size if you are going to have a single cognitive primary endpoint?

Dr. Fillit: Well, I think that's a great question and a really important one. It's somewhat of a technical one, I would say, in some ways, but I think it's a really important question. One way to possibly answer that is we're not just talking about one test, we're probably talking about a composite of tests. We have sort of standardized testing in various different ways. We have the ADAS-cog and the NTB, these are obviously acronyms for various tests. So, I think the important thing in answering the question is, that the meaningfulness in cognition comes from an improvement on multiple aspects of cognitive function. So if it's just memory, let's say, and there's no other cognitive improvement, would that be as clinically meaningful as a composite of cognitive tests that showed improvement in various forms of executive function and memory and the various kinds of memory that can be tested and so on. And I'm not a statistician, but I think that estimating effect size is, we're knowledgeable enough about the parameters of these various tests at this point that we can model and do the power analyses in a meaningful way to determine how the composites on these should move to get a clinically meaningful response. I also think that in some ways, the p-value, although we think of the p-value as .05 . . . the tyranny of the p-value I think is affecting a lot of our clinical trials and this has been written up in various leading journals recently. We're so dependent on the tyranny of the p-value to get all of our work done these days in the clinic, and I think we need to think a little more broadly

about looking at the results of our trials in a broader way. But I agree, I think the question is a very important one, I think the answer is getting at composites of cognition that look at global cognition and not just one memory test.

George Vradenburg: This question is coming from me. Do you think we need some new scales? Are the existing scales, which were initially designed for later stages of the disease adequate for testing cognitive clinical meaningfulness in earlier stages of the disease?

Dr. Fillit: Well, I know the National Institute on Aging through its various centers has fostered the development of new scales, new forms of the standardized scales and these have been developed for mild cognitive impairment and even some of the earlier stages so I think that's happening, George, and they are being targeted for the kind of cognitive symptoms and deficits that occur in the earlier stages of the clinical progression of the disease, so that's absolutely necessary and actually has been done, and is continuing to be done.

George Vradenburg: The FDA is likely to be charged by PDUFA-VI, this new set of instructions based on legislation to, increasingly through the next three to four years, find mechanisms and means by which patient input into these decisions is more rigorous and more statistically significant and subtle. In your view, is there value in trying to reconceptualize these clinical scales based upon understanding from patients or from caregivers, what they regard as clinically meaningful, as opposed to what academics derive as clinically meaningful?

Dr. Fillit: Well, it's not just academics, I think. The problem, I think, that we've had to grapple with for 30, 40 years now, is that even though we're all terrified of losing our cognition and we think of Alzheimer's disease as a nightmare, cognition is not generally or historically been thought of as a medical outcome. So if you have a change in blood pressure, if you have a heart attack, if you have a stroke, if you have cancer, these are clearly seen as "Oh my god, this is terrible," and they are. You have a real medical outcome, you have a cancer and we're going to get rid of it. But cognition, like trying to create a view directly of how cognition affects quality of life, is a little more difficult.

But think of this. Let's say you're 65 or 70 or even 75 and you're still working, and now you can't work any more. That has a huge societal impact as the population ages—not just for the society but for individuals. Imagine someone who has been working for 50 years, and I have many patients like this, and suddenly they need to retire. And they love their work and they probably could have worked till their days end. But now they have cognitive impairment which, for the layperson, for many people, it's a very subjective thing even though we can measure it objectively. So, it's a little hard for people to get their arms around it. I have patients come in, and the wife will say, "My husband's had a change in personality, he's lost emotional control, he's getting angry, he keeps repeating things, he had to quit work, and I'm very depressed, [speaking for the wife] and now I have to be a caregiver." Is that clinically meaningful? Absolutely. Alzheimer's disease is the biggest threat to disability in old age. It's a cause of depression in caregivers and caregiver stress and caregiver burden. It changes people's lives so dramatically and I think we need more of that patient voice as an outcome because right now, and I can say this, there are many countries in the world, the United States included, that does not recognize caregiver outcomes as being really part of the most important aspects of the efficacy of a drug. We've done work on this to show that even the modestly effective cholinesterase inhibitors and NMDA antagonists that are currently on the market, not only improve the lives and the functions of people with Alzheimer's disease, but improve the lives and functions of their caregivers, make their care easier to do, improve pharmaco-economic outcomes in many ways, preventing perhaps hospitalizations and unnecessary types of things like that. So I think having the patient voice there is very important for the reasons that I just said. Alzheimer's disease really changes people's lives. Those are clinically meaningful outcomes and we need to hear more from patients about how that's happening and how drugs change caregiver outcomes, for example.

George Vradenburg: I have one other question here. You just described a scenario in which someone's memory impairment caused them to lose their job, caused them to change their mood, caused disruption in a caregiver's life. Those sound like functional outcomes. Is the distinction

between a cognitive and functional impairment blurred or increasingly—I'm not going to say irrelevant, but—increasingly confusing?

Dr. Fillit: Well, cognition and function are intimately related. If you don't have cognition you can't function. The thing is, certain functions, like the ability to tie your shoes can be caused by things other than loss of cognition; let's say you had a stroke and you got paralyzed. The ability to take transportation might be impaired by somebody having arthritis, and not being confused so they can't figure out how to get to the bus. So, there are different measures of daily life, basically, but there's no doubt that loss of cognition in a very sort of linear way is associated with loss of function. They're both important. All we're saying in our report is that to get a drug approved, to show its clinical meaningfulness, we only need to measure we think as a primary endpoint a composite cognition as for the reasons I mentioned, but also because there is this fairly linear relationship between loss of cognition and loss of function, so cognition actually, in Alzheimer's disease, does become somewhat of a proxy for loss of function. I don't think there's any confusion about that in our field. It's very clear.

And there are other ways, different ways of measuring function and so on. Function is very important and actually through function that I mentioned in my vignettes there, it's actually . . . cognition acts through impairments and function to affect daily life and when we're trying to plan, as clinicians—I'm a geriatrician—when I'm trying to help a family plan, for example, their home care needs, I'll do a cognitive assessment but I'll also do a functional assessment because if the patient needs help with bathing, I have to get somebody in there to help them with bathing. So measuring function is very important in clinical care. But it's not the critical piece that we used to think it was in showing efficacy of a drug.

George Vradenburg: Got a question online here from Kathy Siggins: My late husband took part in a protocol for Cognex in the 1990s at NIH. He went through a battery of tests to eliminate other causes. They didn't do a PET scan because they confirmed a stroke. What is the danger of having a PET scan?

Dr. Fillit: I would say PET scans are very, very safe. They're done all the time, they've been done for many years, they've been used in cancer for decades to see tumors and show tumor responsiveness to drugs. We take a very, very tiny amount of radiation, inject it into a person, it's a minuscule amount of radiation, and it passes through the body very quickly, in an hour or two, almost the entire injected dose comes out, it doesn't stay in the body, so I would be very comfortable saying that PET scans are very safe.

George Vradenburg: So maybe Ms. Siggins' experience is a legacy of the 1990s. Although I don't know if they had PET scans in the 1990s, so . . .

Dr. Fillit: Not the way we have them today. I mean, today, most radiology offices will have a PET scanner. The issue really was in the creation of these radiolabeled what we call ligands, they used to have to be made in a cyclotron. There wasn't a cyclotron on every corner; not that there is today, but the scale of commercial use is much different today than it was 30 years ago.

George Vradenburg: So, a question here from Denise, online, regarding prevention: Is there research being done on nutritional products such as B vitamins and coconut oil, plant based diets as a prevention measure, and if so, were might one find that research?

Dr. Fillit: Well, if I may say so, we have a wonderful website that I'm very proud of called Cognitive Vitality, all one word: cognitivevitality.org. I have three scientists working on that to do the kind of evaluations in a credible and understandable and evidence-based matter to evaluate the efficacy and safety and the evidence for things that you mentioned, supplements and diets and so on. Basically, in prevention, you have what we call the pyramid of evidence. At the top, we've always said that randomized control trials are the gold standard, but in prevention we rely a lot on what we call epidemiological studies and, let's say, biology to evaluate evidence because we can't put all of these supplements and other forms like diet into large clinical trials. That's being done now, it's very

expensive, and they're often complicated because people's lifestyles are very complicated and very different.

But just to give you an idea of how evidence can be misleading, I could prove to you that bread is bad for you—I'm being a little facetious here to make a point—but there was a front page story and big headlines that bread is bad for you, and when you read the evidence for that, it was shown in a study that the reason they concluded that bread is bad for you is because in this study, they found that 95 percent of all felonies were committed within 24 hours of eating bread.

So we need scientists to evaluate and explain evidence and that's what [Cognitive Vitality](#) does and I know the National Institute on Aging has a website evaluating these things and there are many websites out there, so there are places to go on the Internet. The other place to go might be to ask your doctor; hopefully they'll be up on the evidence.

George Vradenburg: There's a question that came in before the call, which is intriguing. Let's assume that one does a prevention trial and is able to demonstrate in a randomized control trial that there is a benefit to coconut oil or hemp oil or salmon or some other dietary intervention. The FDA would not approve a salmon diet. So why randomized control trials on these lifestyle interventions which are not necessarily tests to get regulatory approval?

Dr. Fillit: The thing is, we want to show that something works. Even though you're not going for regulatory approval, we still want to know whether an intervention like a diet actually works. As I said before, you can get evidence in mice, you can get evidence from epidemiology where you look for associations of that diet with disease, but perhaps the best way to show it is in a randomized trial and then, you see the thing is, people are making individual decisions but society has to make public health decisions. So for example, there was never a randomized trial of trying to prove that smoking causes lung cancer. And the reason is obvious. It couldn't ever be done.

So the recommendation for public health, that smoking causes lung cancer and heart disease and that people should stop smoking, was actually based primarily on biology and on epidemiology. So again we have to think, we have to explain to people the kind of evidence that's out there for these recommendations, because as an individual, I have the freedom to choose the kind of diet I want and I can look for evidence on our Cognitive Vitality website or wherever, but as a society the real danger is in making public health recommendations that aren't based on very, very strong evidence and that's why I think the real value of randomized trials is in informing public health recommendations.

George Vradenburg: Let us assume that one could do a trial that demonstrates that a combination of some natural elements has a positive effect and is incorporated in a food product. Does that product have to be cleared by the FDA and what is the standard for clearing a food product for general consumption?

Dr. Fillit: The FDA does have different standards for medical supplements, medical foods and supplements, and there are different regulatory standards or barriers for getting a label, basically, which is what a manufacturer can say about a medical food or supplement. So, supplements you see in your average store, you see them on the shelf, and the label there only has to be based, let's say, primarily on maybe biology and some epidemiology. In other words, B 12 might have a label, some B vitamin complex might have a label that says *IMPROVES BRAIN HEALTH* and there's many of these products out there that people take. But those products can never say they are indicated for Alzheimer's disease and to get that label, they basically have to be proven that they're safe and have some evidence that they improve the function of an organ or have some biology behind them.

Medical food has a higher standard because in that case you're taking a natural product or a medical food, and you really, to get a label that that medical food or natural product is good for a disease, then you do have to have, basically I would say randomized control data to get that label, that the medical food or natural product or even a supplement, if the supplement wanted a label for a disease—let's say to get a different kind of formulation of a B vitamin or ginkgo—that was good, to get the label that

it's good for treating Alzheimer's disease, then I would say you'd have to have enough evidence for the regulators to approve that label and usually that will come from some sort of randomized clinical trial.

George Vradenburg: Got a question here from Joyce Knapp online: What are the next steps towards reaching a consensus on a composite cognition endpoint and for convincing the FDA to change its guidance in this area?

Dr. Fillit: I think that's a good question and I have to say that in many ways we've certainly worked with the FDA, and what I like to say is that the people at the FDA are people too. They have mothers and fathers and wives and husbands who have Alzheimer's disease, and I think we're all in the same boat in terms of wanting to see drugs approved. I don't think there's a monolithic standard set in stone at the FDA for how we're going to approve drugs. The wisdom that I've heard from the people in the neurology program at the FDA is, show us a drug that works and is safe, and we'll approve it. And I think that's very true. I think the FDA has as much interest in getting a drug on the market for Alzheimer's disease as anyone else. The FDA also looks to industry and academia and foundations for guidance and to work together to come to this sort of consensus, and that's why our report is important because I think it kind of condenses into one report, I think, a lot of thinking that's gone on in the last several years about how this should change.

As we describe in our report, the Lilly decision to focus primarily on cognition hoping that an approval would be forthcoming on that, suspecting that the FDA would be amenable and probably in discussions which always happen between manufacturers, sponsors, and the FDA, there has to be a consensus, and so the FDA is not working in a void, behind high walls. There are conversations going on all the time about where fields are going and I think in our field there's an increasing recognition: Number one, that this is an epidemic, probably the most important epidemic of the 21st century; number two, that this is a horrible disease, not only for individuals but for our society, it could bankrupt Medicare if we don't get drugs on the market so there's a huge unmet need; and number three, as I mentioned earlier, the way we're doing clinical trials has changed dramatically with the advent of PET amyloid scans and spinal fluid tests and other neuroimaging technologies, biomarkers, and enrollment strategies, clinical trial design, better cognitive tests, and going into this MCI population which is early, which is very different than the populations that have been studied in the past. So I think that dialog here with the FDA has been very important and I think the bottom line of the whole conversation, which is everything that we do at the Alzheimer's Drug Discovery Foundation, what we need are good drugs. And if we find a good drug, if we discover a good drug, if a good drug works in a clinical trial, we'll know it. Everybody will know it, we'll see it. I don't think it will be that much of a hurdle unless it's a very marginal benefit and then the committees will have to make their decisions. But I think this is much more of a dialog than it is a mandate from anybody and I'm very hopeful that the modern state of our field will come across the line and we'll have safe and efficacious drugs for Alzheimer's Disease approved in the coming few years.

George Vradenburg: I hope your optimism is justified. It's certainly shared here at UsAgainstAlzheimer's. So thank you, Howard, thank you Dr. Fillit, for your time this afternoon. There were some questions that we couldn't get to today and I apologize for that but the time is running down. If you've not already joined UsAgainstAlzheimer's, by the way, please go to www.usagainstalzheimer.org and sign up. We'll send you a recap of this call, we'll send you invitations to future calls, and of course, we'll give you important updates and simple ways that you can get involved and really make a difference in the fight against this disease. I hope you'll join us.

Thank you to everyone on the phone and online for participating in this Alzheimer's Talks. In a couple of 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're particularly interested in your feedback on this call and ideas for upcoming calls. Thank you to Dr. Howard Fillit of the Alzheimer's Drug Discovery Foundation, thank you for joining us today, thanks to everyone on the call, and may you all have a good afternoon and a great Memorial Day weekend.

