



Alzheimer's or Dementia. What's the Difference?

Over 10 million people in the US have a neurodegenerative condition. Half of these people have Alzheimer's Disease making it the most common neurodegenerative condition in the US. Among the remaining, a large population suffer from frontotemporal dementia (FTD). However, FTD and Alzheimer's are very often misdiagnosed for each other and even the terms are used interchangeably. In reality, they are two different diseases that have varying effects on behavior. It is important to differentiate between the two so that patients and families can know what to expect and receive targeted therapies. Join us as we discuss FTD and Alzheimer's Disease, their similarities, differences, risk, diagnostic tests, progression stages, treatments and clinical trials with Dr. Murray Grossman and Dr. David Wolk from the University of Pennsylvania.

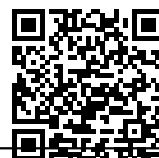
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Priya Menon: Good afternoon and welcome to Cure Talks. I am Priya Menon your host, and today we are discussing Alzheimer's and Dementia – What's the difference? With two very eminent guests from the University of Pennsylvania, Dr Murray Grossman, professor of neurology director, Penn FTD Center, and Dr David Wolk, associate professor of neurology, co-associate director, Alzheimer's Disease Score Center and Co Director of Penn Memory Center. Welcome to Cure Talks, Dr Grossman and Dr Wolk.

Dr Murray Grossman: Hi. Thanks for having us.

Priya: It is a pleasure. Dr Grossman. I also want to welcome Patricia White, who is on our caregivers panel today. Patricia has been caregiver to father diagnosed with frontotemporal dementia and mother diagnosed with Alzheimer's. She specializes in photo reminiscence therapy for people with cognitive challenges. Once again, a very warm welcome to all. We will be addressing questions from the audience towards the end of the discussion. You can send in your questions at priya@trialx.com or you can also post your questions in the comments section. So to get on with that discussion for today, Dr Wolk, the Alzheimer's Association International Conference was held last week and it would be great if you start off with a little bit about some of the breakthrough and promising research results that were presented, including the very exciting phase two results of the Biogen study of BAN2401, if you could talk a little bit about it.

Dr David Wolk: Yeah, sure, sure. Thanks for asking Priya. So yeah, I was at the meeting at Chicago little over a week ago and there were as usual a number of really exciting things to come out of the meeting as I think reflecting this incredible growth in the field right now and the excitement around research in this area. Before I get to the Biogen and Eisai study, I think there were a couple other interesting studies. One of them actually was presented by one of our colleagues here at Penn, Eliot Ness Rolla, who presented really important data showing that more aggressive blood pressure management in middle age and older adults seems to reduce the amount of brain vascular disease changes that's very common with aging and also reduces transition to more significant cognitive impairment suggesting that that one risk factor, maybe not necessarily related to Alzheimer's disease, but related to vascular disease maybe an important public health initiative for reducing cognitive impairment with aging. There were number of other really exciting studies with a variety of imaging markers that we're now able to better visualize more of the pathology of Alzheimer's disease in living subjects, which is quite exciting given that in the past really we only knew about some of this pathology through autopsy tissue specimens in individuals once they've passed away. But yeah, I think definitely the big news from the conference was the results of this phase two study that was from a drug that was developed by Eisai and then was bought out by Biogen called BAN2401. And what that drug is, it's an antibody that's given to people through infusion that binds to Beta-amyloid, which is the protein that builds up in the amyloid plaques of Alzheimer's disease and is thought to be a driver of the disease. And what the data showed was that one in a dose dependent fashion, there was very clear evidence that amyloid was



indeed being removed from the brains in these individuals. So people who had a scan that allows us to look at amyloid in the brain before drug treatment and then after with the highest dose of that drug, about 80% of them ended up no longer showing evidence of amyloid in the brain at least based on that scan. And that high dose group also showed some evidence of cognitive slowing, with regard to progression of Alzheimer's disease. And so, that was a compelling result. There were a couple things since it's a phase two trial that always gives you a pause. One is, while it was a very big phase two trial, it's still somewhat limited in size. There were some issues with the balancing of genetic risk in Alzheimer's disease between groups which could impact the results. But the bottom line is that this was yet another trial with a drug that is targeting amyloid in the brain and symptomatic patients that's at least pointing towards the idea that these kinds of interventions may slow down the course of the disease. And actually I think gives me a lot more hope for another trial that Biogen is doing that we participated in here with a different antibody that also targets amyloid called Aducanumab, which is in phase three trial. There's two phase three simultaneous trials going on that also showed very good clearance of amyloid from the brain and had preliminary data showing some benefit. So between this prior trial, with Aducanumab and now this newer trial, it seems like there's signal there that we actually are affecting the course of the disease, which obviously is very exciting to all of us.

Priya: Dr Wolk, was there some discussion on some of the side effects that was observed in the study?

Dr David Wolk: Yeah. So, the data was pretty limited as this was kind of a very last minute presentation because they had just been unblinded to the results of this study. And so there's much more to learn about this data set, but the most common side effect for the one that at least we think about the most in these antibody trials because we've actually done now several of them is something called amyloid related imaging abnormalities, which is some swelling in the brain. And, even, what are called micro hemorrhages or little tiny bleeds in the brain as well, which sounds obviously quite scary, although in most of the studies that had been done in these patients have been largely asymptomatic or get better when you stop the drug. The nice thing about this new drug relative to Aducanumab, which we're studying, is that the rates of these kinds of side effects were quite a bit lower than what we see with Aducanumab, more on the order of about 10% of patients versus more than a third of patients in our Aducanumab studies. that actually was also another very encouraging results from this study.

Priya: We have you been reading up and we know that Penn FTD center and Penn Memory Center is doing excellent work and neurodegenerative diseases areas with prevention studies, genetic profilings, counselling registries, Dr Grossman, it would be great if you could talk about research and trials on FTD that's going on at Penn right now.

Dr Murray Grossman: Sure, I'd be happy to talk about some of the FTD trials. FTD or frontotemporal dementia is much less common than Alzheimer's disease. Nevertheless, it's really important to learn about the results of trials and FTD because it can be directly relevant to Alzheimer's disease as well. Dr Wolk, my colleague mentioned Beta amyloid. It's one of the proteins that accumulates in the brains of individuals with Alzheimer's disease and can cause plaques. Another protein that can accumulate in the brain is called tau and this protein can become misfolded and can clog up brain cells in folks with Alzheimer's disease and that causes what are called tangles that you can see with a microscope when you look at the brains of patients with Alzheimer's disease. We study patients who have FTD or frontotemporal degeneration when there is just the tau protein alone that is accumulating in the brain. When this tau protein alone is accumulating in the brain, it causes a different kind of condition and this is called FTD and we are studying several disease modifying treatment trials to see if we can block the accumulation of the tau protein just the way Dr Wolk's trials are blocking the accumulation of the amyloid protein in folks with Alzheimer's disease. Like the strategy of using antibodies to try to capture amyloid in the trials for tau that we have for patients with FTD, one set of trials is using antibodies to try to capture the tau protein and try to reduce the negative side effects of this tau protein accumulation in the brain. So that's one kind of trial that we do with FTD. And this is focusing mostly on patients who have what's called sporadic disease.

This is disease that occurs for reasons that we are not really clear and we're trying to understand that as part of our research program. FTD has a large number of people where disease is inherited and this disease



is familial or inherited in FTD in about 15 to 20% of cases in our clinic. And so we are participating in some treatment trials that are targeting inherited forms of FTD as well. And these trials again are trying to manipulate the proteins that can accumulate in the blood and or can be too low in the blood or so that there is a change in brain functioning. And by virtue of trying to use antibodies to block the breakdown of proteins or to allow the small amounts of proteins to increase in their level so that there were healthy levels of these proteins, we can then try to treat individuals who have inherited forms of FTD. This is potentially very exciting because we are trying to target individuals who do not yet have any symptoms. And if we can find a treatment that's effective for individuals who have an inherited form of FTD and if we can prevent them from ever developing the disease, then we have the equivalent of a cure for dementia. So this is really exciting advance, I think, in the treatment of neurodegenerative conditions.

Priya: That's very exciting Dr Grossman, Dr. Wolk, I know you mentioned the studies on the lowering blood pressure, which reduces the risk of cognitive impairment and the use of biomarkers to study and use of antibodies. There is a study that I believe is going on, on Alzheimer's at Penn, which are some of these studies other than these that the patients or caregivers should be keeping track of?

Dr David Wolk: Yeah, sure. So I think one of the studies that I think is going to be a real inflection point in the field for a number of reasons, that I mentioned earlier is actually that Aducanumab study with an antibody. It's hard name to say by the way, but it's an antibody to Beta and as shown or amyloid Beta protein and has shown a clearance in the brain of amyloid. And the reason why I think that's such an important study is one, there's a lot of promise associated with it based on some of the earlier phase data as well as this new study. But another is that it would be a proof of the concept that amyloid drives the disease and that at least in symptomatic patients, if you stop amyloid production or remove amyloid, I should say from the brain, that that can slow down the course of the disease and that treatment at that point in of the disease is something that can be effective. And so I think it's going to be an important trial because there's a number of different drugs that have targeted amyloid in symptomatic patients in the past that haven't been successful and one possibility is that, stopping amyloid or reducing amyloid once you already have symptoms of the disease may not actually effectively change the course of the disease and I think because Aducanumab is so effective in reducing amyloid in the brain relative to some of the other drugs that have been tried, it will be really a significant test of that idea. And the reason why I keep saying symptomatic is because another set of trials that we're doing here at Penn that are quite exciting and somewhat akin to what Dr Grossman had mentioned earlier, is actually treating people in a presymptomatic or what we call a preclinical phase of Alzheimer's disease.

And so it's thought that the pathological changes, the things that proteins that are accumulating in the brain begin to do so maybe up to 15 years, if not longer before people have any symptoms of the disease whatsoever. And so one thought is that maybe one of the reasons some of the other trials in the past haven't been successful is because they're treating people too late, that the sort of cascade or a fire has already been started and you can't put it out at that point. And so this, these set of trials are actually giving people drugs that in the case of the three trials we're doing here, reduce amyloid in the brain either through a different antibody, one that, in one of the studies that was developed by Lilly called Solanezumab or pills that breakdown or inhibit enzymes that break down amyloid processing, which then stop or hold the sort of a deposition of amyloid in the brain. And there are three of these trials. One of them involves giving people who are normal in amyloid PET scan, which allows us to detect amyloid in the brain. And, if they have a positive amyloid scan and they're normal though, have no symptoms of the disease that we can detect we're then giving them this antibody and following them to see whether it slows down or prevents them from ever developing symptoms in the future or at least within the five years of the study. There are two other studies very similar to that that we're doing that involve looking for people who have high genetic risk of the disease related to a gene called the apolipoprotein E gene and in that study, those who are at higher risk kind of akin to what Dr Grossman mentioned earlier, are entering a trial and will also be given one of these drugs or these types of drugs to see if it can kind of prevent them from going on to developing symptoms.

Priya: Thank you, Dr. Wolk. I'll now get into some basics so that we address the topic of our discussion, bring out the difference between Alzheimer's and FTD. Dr Grossman, you mentioned that FTD is much less



in number when combined compared to Alzheimer's. But just to get to the most basic level, can you please explain in layman terms for our audience, what is neuro degeneration and what is dementia?

Dr Murray Grossman: Well, that's a great question. Neurodegeneration reflects the fact that there are misfolded proteins that are accumulating in our brains. All of our brain cells or neurons depend on functioning of proteins. And under some circumstances these proteins can become misfolded and when they become misfolded, they can no longer perform their essential function. And depending on where in the brain this process is occurring out, we'll see different kinds of symptoms. So if there are proteins accumulating in the that are misfolded and that are accumulating in the part of the brain that are important for language that will result in some difficulty with language functioning. If there are proteins that are becoming misfolded and accumulating in the memory part of the brain that will result in some difficulty with memory. If there are proteins that are accumulating in that are becoming misfolded and accumulating in parts the brain that are important for planning and organizing, then that cause some difficulty with dual tasking and executive functioning. So neurodegeneration is when misfolded proteins that accumulate in a particular part of the brain. And as these misfolded proteins accumulate, they cause difficulties with various kinds of symptoms. The symptoms worsen with time and this is due to the fact that the proteins continue to accumulate. It's unlike a stroke where there's just one sudden event that occurs, instead the misfolded proteins gradually accumulate and as they gradually accumulate, there's a worsening of the symptoms. And dementia refers to the progressive cognitive change that occurs as these misfolded proteins that accumulate in the brain. And there's the common misconception that dementia refers only to memory.

And the fact that memory is the first symptom that is evident in many of folks with Alzheimer's disease and Alzheimer's disease as Dr. Wolk mentioned is not the most common form of dementia, but there are other forms of dementia that can affect primarily language and we refer to these as progressive aphasia. Aphasia is a disorder of language and progressive means that the language is worsening and this is due to the fact that misfolded proteins are accumulating in language parts of the brain. There are also syndromes where there can be a difficulty with visual spatial functioning, where people have difficulty reaching for objects even though they're right in front of them on a table and have difficulties with other visually mediated tasks. This isn't a form of blindness, but this is instead difficulty being able to understand where objects and things are in space. There can also be conditions that affect our personality and our behavior. Now we refer to these as the behavioral variant of frontotemporal degeneration. And all of these are different forms of dementia. And the language problems can occur without memory difficulty. The visual spatial problems can occur without memory difficulty and the social problems can occur without memory difficulty. Over time certainly if one begins with a certain kind of problem, there can be additional involvement of other cognitive domains, so somebody who begins with a language problem, some of those folks can go on to develop some memory difficulty as well, and this is the progressive nature of of of dementia.

Priya: Thank you Dr Grossman, as I understand, that the accumulation of proteins in the frontotemporal lobes of the brain, it causes frontotemporal dementia.

Dr Murray Grossman: Correct, and the frontal and temporal parts of the brain are important for specific kinds of difficulties that we see in FTD. Half of the folks with FTD have a form of language difficulty that's called Progressive Aphasia and this is because the language parts of the brain are in the frontal and temporal parts of the brain. There are different forms of Progressive Aphasia and we've tried to be very careful about studying these different forms of progressive aphasia because each of these is a marker for a different kind of protein that is accumulating in a different part of the language network of the brain. So one kind of progressive aphasia can affect primarily difficulty in understanding the meanings of words and difficulty in understanding objects. We refer to this as a deficit in semantics or deficit in meaning, and this is related to disease that's accumulating in the temporal part of the language network of the brain. And the protein that accumulates in the temporal lobe is a protein that's called TDP. By comparison, another protein will accumulate in the frontal parts of the brain and cause very effortful and non fluent speech. And the protein that accumulates in the frontal part of the brain is the tau protein that I had mentioned earlier.

Priya: Yes. Dr Wolk, what are some of the initial presentations of Alzheimer's?

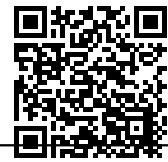


Dr David Wolk: Yeah. So I think, Dr Grossman laid out really nicely what you see in frontotemporal degeneration and I think that the theme that he mentions is this idea that where there is the pathology of the disease or that these proteins that build up in the disease that causes injury to the nerve cells or neurons, which are the sort of information carrying cells of the brain and that affects the cognitive function that subserved by the region that's affected. And so Alzheimer's disease, at least for one of the proteins that's really even more related to where there's injury in the brain than amyloid actually, the tangles that Dr Grossman alluded to earlier that are made up of this tau protein, they tend to begin in the part of the brain that's involved in memory, a part of the brain that some people know of which is called the hippocampus. But that's the part of the brain that is most important for holding onto memories and experiences in your life. And that's what tends to be injured earliest in Alzheimer's disease. And so memory loss tends to be one of the leading features of the disease. And the kind of memory loss that people have is what some people will refer to as short term memory, where you'll have trouble remembering something from a conversation earlier in the day or perhaps aspects of a movie you saw the day before, or, plans that you have for later in the day. The problem is as we're moving to trying to detect the disease as early as possible, a lot of those kinds of memory symptoms are things that normal, older adults have all the time and actually even young adults have to some extent as well. And so one of the things that our group in the memory center and others are working on as to how to differentiate when those memory symptoms reflect something more serious versus when they're just part of normal aging. The other thing I guess I would say that we've learned quite a bit about with Alzheimer's disease, is that while we like to think of it as this sort of typical disease that tends to affect memory. And then maybe a little bit later, you have some language and visual spatial function issues and then maybe attention and your ability to organize your thinking are affected. Turns out that there's a lot more heterogeneity that while generally people start off with memory, sometimes they can start off with other symptoms as well or have a different balance of symptoms. And so, one of the real challenges in the field is to be able to correctly classify those people who have less than typical presentation of Alzheimer's disease and differentiate them from conditions like frontotemporal dementia and other forms of dementia as well. But again, the sort of typical courses of subtle to increasing amounts of memory loss over time as one of the most salient features.

Priya: Thank you Dr Wolk. Dr Grossman I know you mentioned progressive aphasia, what are some of the diagnostic tests that we use for FTD and what are some of the treatments that are followed?

Dr Murray Grossman: Well, the most important initial test is a clinical examination by an expert in the area. So trying to find someone who has experience with seeing patients who have progressive aphasia or FTD or we're very lucky at Penn because we have experts in memory and the various variations of memory, difficulty that can occur in Alzheimer's disease with Dr. Wolk, he and his colleagues. So being seen first by an experienced individual experience neurologist who has seen lots of individuals is a great way to begin the diagnostic process. Once a clinical evaluation has been performed, then the next step is to try to see whether there is a difficulty in a particular part of the brain that is associated with the kinds of difficulties that are being seen clinically and a widely available tool to do that is an MRI scan of the brain. And so the oftentimes an initial step will be getting an MRI scan to see if there's a correspondence between the clinical difficulties that are seen and looking to make sure that there are no injuries in the part of the brain that corresponds to the difficulties that the clinician is saying. What kinds of things can occur? Many things can mimic progressive aphasia or can mimic memory difficulty. For example, there could be a tumor in the brain, or there could be inflammation that is gradually slowing down functioning of the part of the brain, or there could be an infection that is compromising brain functioning. So an MRI scan will help rule out all of these various conditions that can mimic a neurodegenerative condition. And there are also some systemic conditions that can mimic dementia. And so there are some blood tests that are important to them to obtain to make sure that there's no systemic condition that could be mimicking dementia.

The next step after this involves being seen at a specialty center like the University of Pennsylvania where we would try to obtain specific studies that determine the particular kind of protein that is accumulating in the brain and is associated with the difficulties that patients are experiencing. Dr Wolk alluded to PET scans. There are many different kinds of PET scans and the kind of PET scan that he alluded to, which is a molecular PET scan that specifically takes a picture of the Beta amyloid protein that can accumulate in the



brain that is associated with Alzheimer's disease. We're very fortunate at Penn. We're also able to use a kind of PET scan that can make a picture of the tau protein that's accumulated in the brain. This is a research procedure that is not yet widely available and we're lucky that we can take advantage of that here at Penn.

Other ways that we try to measure the proteins that are accumulating in the brain and that are causing difficulties are through a lumbar puncture where we analyze the fluid that bathes the brain and the spinal cord. Our brains make half a liter of cerebral spinal fluid every day. We make lots and lots of this and that's used to act as a cushion between the brain and the inner surface of the skull. So when we're nodding our heads, we don't knock ourselves out. We take a small sample of this fluid and we can measure the levels of the proteins that we've been discussing, the tau protein, then the amyloid protein, and as our research progresses, we're able to look at these same proteins in blood tests as well. And so that work is not quite ready yet for the clinical use, but is certainly advancing. The value of determining the specific proteins that are accumulating in the brain is that this helps determine whether somebody's eligible for a treatment trial. The treatment trials that Dr Wolk and I have been discussing are disease modifying treatment trials where we are trying to target the specific kind of protein that is accumulating in the brain and clogging up the brain cells. and the only way that we can do that effectively is by knowing that the specific protein that is involved in the memory difficulty or the language difficulty or the social and behavioral difficulties that we see in our patients.

Priya: Thank you. Dr Grossman, Dr. Wolk, do you have anything to add to Dr Grossman's observations?

Dr David Wolk: I would just say, first of all, I think everything Dr Grossman said are things that we consider as well when we see patients with Alzheimer's and part, and because we're trying to differentiate Alzheimer's disease from some of the conditions that Dr Grossman is also trying to examine as well. I think another sort of diagnostic tool we have, particularly as we're seeing patients who have much more mild symptoms, something that we sometimes refer to as mild cognitive impairment is time that we follow patients over time and measure whether or not they're showing any evidence of progression in their condition. And that also is I think a useful tool that sometimes we don't have a definitive answer the first time we see a patient, but the evolution can help us as well.

Priya: So moving on I have a couple of studies that I found interesting in the media. So Dr. Wolk, I like to hear your comments on the recently published research, which is part of the human microbiome project that say that there's evidence of viruses and bacteria that causes Alzheimer's.

Dr David Wolk: Yeah. So this has been, I think, something that's captured a lot of attention that the argument is that the general sort of idea is that various infectious agents, things that we're all exposed to to some extent cause some sort of immune response and it's been argued by some that the amyloid beta protein that makes up those amyloid plaques we've been talking about that, that's actually involved in a beneficial way in the immune response which is an interesting idea because one of the things that has perplexed our field for a number of years is that we know this amyloid protein builds up in the brain in Alzheimer's disease. But one question is, well, what is its normal function outside of the disease? And so the argument is that more exposure to certain kinds of pathogens like viruses and bacteria cause this immune response, which then causes more of this amyloid beta protein to be produced. And then if enough of that occurs, it's a factor in the sort of overproduction of it which ultimately then leads to the disease process. And I would say, first of all, that this is a pretty novel way of thinking about the disease and I really welcome the idea for having more novel ideas and in trying to understand the disease as I think, really trying to understand the mechanisms of Alzheimer's disease is there, there are a number of things that we just don't know yet. And so thinking a little bit out of the box I think is a good thing for the field. And I will also say there's some genetic data for people at risk of Alzheimer's disease that's linked to genes that play a role in inflammation. And so it's pretty clear inflammation has some impact on the disease. And so I think from that perspective, this is a relevant and important hypothesis. On the other hand, I think there are a number of other things that seem to increase amyloid protein accumulation in the brain or reduce its clearance. And so, I think what remains unclear is this infection even a factor at all? So is this true? But b, even if it is a factor, it



may be one of many, many different factors that cause the accumulation of the amyloid beta protein and it's unclear how much that's influencing things, but I definitely think it's a line of research that's certainly worth following and I think we'll hear quite a bit more about it in the coming years.

Priya: Thank you Dr Wolk. Dr Grossman there were some reports on eye tests being able to detect early signs of FTD. Can you comment on this?

Dr Murray Grossman: Sure. The back of the eye or the retina is an extension of the brain and a colleague, Ben Kim and I decided that we would do a look at that retinal layers to see if there was any change in FTD compared to controls. And there is a something called Spectral Domain Optical Coherence Tomography. It's a kind of scan of the retina that takes about 90 seconds to do. So it's very, very quick and it's painless and it takes a picture of the different layers of the retina at the back of the eye. And what we found is that the outer layer of the retina is significantly thinner than it is in controls and this outer retina is highly correlated with the cognitive functioning of the patients who have this thinning of the retinal layer. And so we're very excited because this is a quick and easy test that seems to be very meaningful in terms of being able to diagnose FTD. Unfortunately FTD is a difficult condition to diagnose. There are no blood tests that are available with the most definite way to make the diagnosis of FTD is run by a direct examination of the brain at autopsy. And this is not something that we do often during life, we don't take a sample of the brain to look with a microscope to see if someone has FTD. So this retinal scan is something that is a very exciting and promising diagnostic tool.

Priya: Thank you Dr Grossman. I'll now hand over to Patricia for her questions from a caregiver's perspective. So over to you Pat.

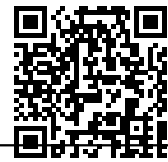
Patricia White: Thank you very much for having me today. I'd like to begin with just a little bit about my father who was an ordained united methodist minister in his prime at age 46 when he was diagnosed with organic brain disease, they called it back in 1960. His particular problem turned out to be the frontotemporal of course, problems with judgment and problems with inhibitions. And that meant that he was treated mostly with psychotropic drugs to control his behavior. And he was in and out of private and state run psychiatric hospitals for many years. My question for Dr Grossman, I think you answered it earlier, but saying that the name of the game is to block that tau protein, but are there any medications available now to delay the advancements of FTD?

Dr Murray Grossman: Right now there are unfortunately no medications that are available that will slow the progressive accumulation of these misfolded proteins that can affect the frontal part of the brain and can cause the difficulties with judgment and control of behaviors that you described in your father. There are now better symptomatic medications that are available that can help with management. So that there are fewer side effects and the treatment strategies seem to be more effective now than they were at the time when your father was first diagnosed with FTD.

Patricia: That's certainly certainly good news for others. My next questions are addressed to Dr. Wolk, my mother had a condition called atrial fibrillation and she was on a blood thinner for years before she developed dementia with Alzheimer's specifications. Is atrial fib another risk factor for developing dementia?

Dr David Wolk: Thanks Pat for asking the question. So atrial fibrillations, where there's a sort of funny rhythm in the heart that can cause the atria of the heart to get somewhat less that they have sort of less movement, which makes it more likely for clots to form in the heart, which can then cause strokes. And so untreated atrial fibrillation certainly if it causes strokes, can cause cognitive impairment, which ultimately can result in dementia because dementia can be caused by essentially any kind of brain injury that affects thinking to the point where people's function is impacted. That being said, treating atrial fibrillation on a blood thinner doesn't tend to be a significant risk factor for dementia and there's no particular link between atrial fibrillation and Alzheimer's disease.

Patricia: Thank you. My mother also had a condition called pernicious anemia causing her to need frequent



injections B12. My brother and I now both have this condition and we're getting the same injections and I also take a daily prescription of B12 in tablet form. I understand we may both be at higher risk of developing dementia due to this deficiency. Do you have any other recommendations?

Dr David Wolk: So I think one, I'm glad that it was discovered and you also knew that you had this and it can be treated, and it sounds like you're being treated the correct way. When Dr Grossman was sort of talking about the basic approach to how we diagnose patients with dementia and with cognitive impairment, one of the things that we do is we look for other causes of cognitive impairment that can be related to other medical conditions and one of them is actually having a low B12 level which can be associated with injury to the brain and to some extent to the spinal cord and can cause cognitive impairment. The reality is though that just like atrial fibrillation if B12 is treated, if you're given back B12 through injections or very high doses of oral B12, like what you're taking there really isn't a significant risk of developing dementia really, once you're doing what you're doing, you're actually allowing your B12 levels to be normal in your body and allowing B12 to do what it does to keep it from causing these cognitive symptoms. So I would say you're at no increased risk as long as you continue to treat 'em yourself appropriately for the B12 deficiency.

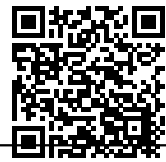
Patricia: That's good news. Thank you. I have a few other questions. What role does hearing loss play in causing dementia?

Dr David Wolk: Yeah, I think that's a fascinating question because I would say the answer is not completely clear and there are people who are studying the effects of sensory loss, visual and hearing and how that impacts the brain changes that occur with dementia and even with Alzheimer's disease, there's no doubt that having poor hearing or poor sight can impact your thinking because it causes you to be more distracted when you're trying to listen to what someone's saying. So if you're having trouble hearing what someone is saying, you're kind of focused on really trying to discern the words that they're saying as opposed to really thinking about it deeply in the way that we often do and that then impacts your ability to later remember that particular thing. And so in that sense it kind of exacerbates any issues that you're having with your thinking in the first place and actually it's one of the things that we often recommend for patients if they have changes in their vision or hearing. We really push them to try hearing aids or other things because that can lessen the degree of cognitive impairment that might be driven by something else in addition. But I think there also is some argument that there may be some sort of feedback between some degree of sensory deprivation with aging that can also in a more direct way results in and cognitive decline, but I would say that's an area of kind of fertile research right now.

Patricia: Thank you very much. Dr. Wolk and Dr Grossman.

Priya: Thank you Pat, Dr Wolk, Dr Grossman. We have quite a few questions that have come in. So I'll just read through them and I'll try, that'd not be a repeat of what you've already covered there. So Dr Grossman this is for you, what are some of the interventions for symptoms in advanced illness?

Dr Murray Grossman: So that's a terrific question and it's a very important one that we have to consider that as clinicians. We think of a two pronged approach, one approach involves medications and the second approach involves managing the environment. As far as medications are concerned, we look to see whether there is a medication that can help manage some of the symptoms that will help with the quality of life of folks who have advanced illness. The symptoms folks can have include hallucinations, for example, and can be very disturbed and upset. And we try to find a medication that can help manage this kind of a difficulty, people think will be quite distressing. As far as the behavioral management is concerned, managing the environment, we tried several strategies. We try to help with structuring the environment so that folks can feel more confident about and more confident in the reliability of their day to day activities, so there aren't going to be surprises and things that can be upsetting. We also tried to reduce provocative agents, if there are folks, for example, who have difficulties with inhibitory control, as we talked about earlier, some individuals with FTD can be quite disinhibited and can get very upset at seeing, for example, some ads in newspapers, we try to minimize exposure to these provocative agents that can be upsetting. So we try to pursue both a modest regimen of medications as well as managing the environment to see if we can help



ease the burden and optimize quality of life in folks with advanced illness.

Priya: Thank you. Dr Grossman is another one for FTD that says – one of the first steps in managing behavioral symptoms in FTD is identifying the problem. How can one keep track of symptoms?

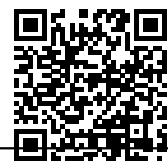
Dr Murray Grossman: Well, that's a great question as well. And Dr. Wolk addressed that also when he was discussing the fact that many of the things that we see in neurodegenerative conditions like FTD or Alzheimer's disease really can occur in folks who have a healthy aging. And the trick is trying to figure out at what point these subtle things that we see all the time start becoming more challenging and worrisome. And this can be difficult because these are very, very subtle things that we're trying to look at. Word finding difficulties, extraordinarily common as we get older and an exaggeration of word finding difficulty can become aphasia. There can be some personality quirks that we may develop as we get older. and an exaggeration of these can represent a behavioral variant of FTD. As far as memory is concern, a benign forgetfulness or senior moments can become exaggerated and can be some of the earliest features that can suggest that Alzheimer's disease may occur in the future. What I try to counsel folks that I see in clinic is to look for these kinds of changes that are occurring consistently and to the point where they're starting to interfere with normal everyday functioning and to keep a log of these unexpected or unusual behaviors so that you can monitor whether these are current consistently. And bringing these to into your doctor to discuss is the, I think the best way to manage some of the detection of early symptoms of FTD and neurodegenerative conditions.

Priya: Thank you Dr Grossman. The next question is can the doctors talk about deep brain stimulation and at what stage one must offer it? Dr. Wolk, would you like to take that?

Dr David Wolk: Sure. So deep brain stimulation which involves implanting an electrode in the brain to either stimulate a part of the brain or to kind of turn off a part of the brain that's overfunctioning, is something that's been used really in Parkinson's disease, which is a type of neurodegenerative condition that can be associated with cognitive impairment. But it's not the type of condition that we've been sort of talking about as much today. There's some other kinds of motor disorders that are also treated with deep brain stimulation. For Alzheimer's disease there's no approved treatment for deep brain stimulation. But it's interesting that the question came up because there has been some interest in using deep brain stimulation to stimulate the memory network in the brain and see if that could offer a benefit in patients with Alzheimer's disease. And we actually participated in a trial like that where a sort of part of the memory network of the electrode was implanted and was to try to turn on or enhance that network and it was a small trial largely for safety, although they were also looking at outcomes with regard to thinking and I must say the results were somewhat mixed. But there was some promise with it that there actually is a larger study that is going to occur in the relatively near future that will look at this to see more definitively whether or not it makes a difference. There've been a few other trials as well with different approaches to where to stimulate the brain. But right now this is really just purely a research tool that's being tested for clinical efficacy. Not something that we routinely would do as part of clinical care or practice.

Priya: Thank you Dr Wolk. The next question is my father had Alzheimer's, my mother had FTD. Are there tests that could give me an idea of my risk and is there a medicine or supplement that could promote brain health? Dr Grossman?

Dr Murray Grossman: So that's also a very great question to be asking, particularly with regard to FTD where there is a substantial risk for FTD being inherited. We find FTD is inherited in about 15 to 20% of the of the folks that we see in clinic and so we're oftentimes asked exactly this question. What we do, our first step is to take a detailed family history. If FTD is inherited, we see that it's inherited in a particular way so that there's somebody in every generation who's a direct relative has a form of FTD. So if a child is worried about FTD, they would see it in the mother or the father and perhaps in the mother's or the father's brothers and sisters, but there would also see it in, as if it's, for example, if the mother has FTD, would you then look to see if the mother's mother or father also has FTD. Then the pattern of inheritance – there should always be somebody who is a direct ancestor of the person who's concerned who has FTD. So doing a detailed



family history of that sort can determine whether someone is at risk for having FTD. If there is a history of FTD and a parent, but not in that parent's parents or, and not and that parents' brothers and sisters, the risk is in fact very low. So the first step to try to figure out about family history or the risk of inheritance is to study family history. If the family history is higher then what we do is we tend to refer to a genetic counselor and discuss the family risk in more detail and for some of the more common inherited causes of FTD, we can do a blood test to try to see whether in fact is inherited, we're able to identify the specific change in the genetic code that is associated with FTD.

Priya: Thank you. Dr Grossman, Dr Wolk, would you like to comment on that from an Alzheimer's perspective?

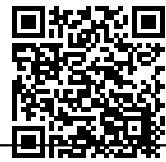
Dr David Wolk: Yeah, sure. So I think Alzheimer's is a little bit different. There certainly are genetic risks and I mentioned the gene that is probably the biggest risk factor for Alzheimer's disease called the apolipoprotein E gene, what's called the E4 variant of that gene is associated with a couple fold increased risk of the disease, we all have two copies of it and actually if you have two apoE4 genes, which is actually quite uncommon, you have a, maybe even five to 10 times increased risk of the disease. However, age is by far the biggest risk factor and towards really any of the genetic risk and the other risk factors that are things that can contribute to the likelihood of developing the disease actually include a lot of cerebrovascular risk factors and cardiovascular risk factors. So high blood pressure, high cholesterol and obesity and diabetes. And so all those things are contributors. I think we, as a field are not quite where they are in cardiology where we can have a risk score that we could give someone. But I think we're very close to getting to that point. And there are some calculators out there for determining your risk. With regard to genetics, there are places that if people want to get genetic testing like 23andme, they can and they will get returned a believe results. I might suggest that that would be better to be through a conversation with your physician. And as a final point, there are as I mentioned, these preclinical trials in people who don't have symptoms but may have risks where they would do some of the testing as part of a study and I think if someone is concerned and have some, has a history or family history, then that might be an opportunity for them in a more controlled environment to determine their risk to some extent as well as an opportunity to try to intervene if that's something they want to be kind of aggressive about at that point.

Priya: Well our next question is what is the best method/activity to maintain brain health if there is one? Dr Grossman and then Dr Wolk.

Dr Murray Grossman: Well, I think that there is now a very good evidence in the medical literature to suggest that physical exercise and mental exercise or both are very important to being able to maintain brain health. There is a concept that's called cognitive reserve and the cognitive reserve concept is that we can enhance our healthy living and maintain our brain health by having a high education, high occupational payment and engaging in significant midlife activities. And so all of these things when you speak to the fact that being active cognitively is very, very important. There's also good data to support the claim that a moderate amount of exercise on a weekly basis is really a good way to maintain brain health.

Dr David Wolk: Yeah. So I completely agree with everything Dr Grossman said. I mean, I think if anything, there's the strongest data for exercising your body is protecting your brain even more so than some of the data with brain games and things of that nature. I think some people might get caught up in some of these kinds of things that you see advertised about various brain games and things like luminosity and some of these other kinds of tools where to me it's still a little less clear about any specific brain game that's helpful. Other than, I would say more broadly to try to keep yourself mentally stimulated and doing things that you enjoy. So if it's crossword puzzles, you like, do crossword puzzles, if it's reading you like, do reading, but keeping it as engaged as possible I think is important and actually social engagement also maybe for the same reason is another thing that has been shown to seem to stave off the development of cognitive decline.

Priya: Thank you. Dr Grossman and Dr Wolk, we are actually at the end of our hour. Over 10 million people in the US have a neurodegenerative condition and half of these people have Alzheimer's disease, making it the most common neurodegenerative condition in the US. Among the remaining, a large population suffer



from frontotemporal dementia. However FTD and Alzheimer's are also misdiagnosed for each other and even the terms are used interchangeably. We have seen in the last one hour how they're different and how it is important to receive targeted therapies for the same. Dr Grossman and Dr. Wolk. Thank you very much for your time and for sharing all this information with us. Thank you Patricia participating and sharing your experience. We also thank the university of Pennsylvania and the audience. The talk will be available on curetalks.com. Please visit our website for details and upcoming talks. Thank you everyone. Have a great evening.

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