NWS HHS AOA 1

Moderator: Amy Wiatr
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Coordinator: Welcome and thank you for standing by. At this time, all participant lines are in a listen-only mode. During the question-and-answer session, you may press star 1 on your touchtone phone. Today's conference is being recorded. If you have any objections, you may disconnect at this time.

Now I'd like to turn the meeting over to Amy Wiatr. Ma'am, you may begin.

Amy Wiatr: Wonderful. Thank you so much. I'm Amy Wiatr-Rodriguez with the Administration on Aging within the Administration for Community Living and I'll be moderating today's webinar, Alzheimer's Disease and Other Dementias/Basic Refresher and Current Updates for the Aging Network on Symptoms, Diagnoses and Treatments, which is the first in a three-part series.

This webinar series came about through discussions within AoA and our AoA-funded programs such as The Alzheimer's Disease Supportive Services Program, Older Americans Act Title III-E, National Family Caregiver Support Program, National Alzheimer's Call Center and Elder Care Locator.

And how could we collaborate better with our colleagues at the National Institute on Aging and their funded programs such as Alzheimer's Disease Research Centers and the Alzheimer's Disease Education and Referral, or ADEAR, Center? We are so pleased that some of the participants in those discussions are presenting on today's call and others will be presenting on future webinars.

Before I introduce our speakers, we have a few housekeeping announcements. If you have not done so, please use the link included in your email confirmation to get onto WebEx so that you cannot only follow along with the slides as we go through them, but also ask your questions when you have them through chat.

If you don't have access to the link we emailed you, you can also go to www.webex.com, click on the Attend a Meeting button at the top of the page and then enter the meeting number which is 661443986. If you have any problems with getting into WebEx, please call WebEx technical support at 1-866-569-3239. That's 1-866-569-3239.

As the operator mentioned, all participants are in listen-only mode. However, we welcome your questions throughout the course of this webinar. There are two ways that you can ask your questions. One is through the WebEx - or through the Web using the Chat function in WebEx. You can enter your questions and we will sort through them and answer them as best we can when we take breaks for questions after each presenter.

Secondly, when after the presenters wrap up, we will offer you a chance to ask your questions through the audio line. When that time comes, the operator will give you instructions as to how to queue up to ask your questions.

If there are any questions we can't answer during the course of this webinar, we will follow up to be sure that we get those questions answered. Or if you think of any questions after the webinar, you can also email them to us at my email address, amy.wiatr@aoa.hhs.gov. Or you can also send your questions to any of the email addresses that are included in the PowerPoint slides that are the basis for this webinar.

As the operator mentioned, we are recording this webinar. We will post the recording, the slides and a transcript on the AoA Web site, which is www.aoa.gov, as soon as possible, likely by the end of next week.

Now I'd like to introduce our speakers today. We're very pleased to have all of them with us. They include Greg Case, Director of Supportive and Caregiver Services with the Administration on Aging, Administration for Community Living; Vicky Cahan, Director, Office of Communications and Public Liaison, NIA, the National Institute on Aging; Sandra Weintraub, Ph.D., Professor of Psychiatry and Behavioral Sciences, Cognitive Neurology and Alzheimer's Disease Center with Northwestern University Feinberg School of Medicine; Raj Shah, M.D., Assistant Professor, Family Medicine and with Rush Alzheimer's Disease Center and Laurie Ryan, Ph.D., Program Director, Alzheimer's Clinical Trials with NIA.

At this point, I'd like to turn it over to Greg Case with AoA, ACL to get us started. Greg?

Greg Case: Thanks Amy. As the first slide shows, my name is Greg Case and I'm Director of the Office of Supportive and Caregiver Services at the Administration on Aging of the Administration for Community Living.

This webinar kicks off a joint effort by multiple federal agencies to share resources to help ensure our health and long-term care systems continue to become more dementia-capable.

The Administration on Aging has been administering the Alzheimer's Disease and Supportive Services Program authorized by the Public Health Services Act for many years, and we are committed to supporting people with Alzheimer's Disease and related dementias as well as their caregivers.

As Director of the Office of Supportive and Caregiver Services, I oversee the Alzheimer's Disease Supportive Services grant program and work with AoA program staff and branch management officers to ensure this program provides the important supports and services intended under the law.

Efforts of this joint webinar series support the National Alzheimer's draft plan, including to strengthen state aging and public health workforces. The draft plan directs the US Department of Health and Human Services to coordinate with states to develop aging and public health work forces that are dementia-capable and culturally competent, and this webinar series is one piece of our effort to do so.

This work is important. Effectively serving populations with dementia and their family caregivers involves accommodating the needs of a population that in addition to memory loss, experiences a variety of physical, cognitive and behavioral symptoms resulting from both dementia and other medical conditions.

Dementia-capable programs are tailored to the unique needs of people with Alzheimer's or other dementias and their caregivers. For example, a dementia-capable information and assistance service would have a method to identify

people with possible dementia and may provide such recommendations as follow-up with a physician.

Again on behalf of AoA and the Administration for Community Living, thank you for attending this important webinar.

Thank you Amy.

Amy Wiatr: Wonderful. Thanks so much Greg.

And now I'd like to turn it over to Vicky Cahan with NIA.

Vicky Cahan: Thank you so much Amy and Greg, and good afternoon everyone. I also would like to welcome you to today's webinar. And we're excited to be partnering with AoA on this full series of programs to provide federal updates on Alzheimer's care, research and resources for the Aging Network.

NIA as many of you know is one of 27 institutes and centers at NIH, and we were established in 1974 as the nation began to recognize that indeed the population was growing older.

By our titles, we conduct and support research on aging, which includes working with many our sister institutes on diseases and conditions commonly related with age. We are designated as the lead institute at NIH for Alzheimer's disease research.

So along with training, research and (developing) future scientists for the study of health and aging, we are mandated by Congress to disseminate to the public and health professionals information on health and to report on research advances.

You will hear more later today and in the subsequent webinars about our Alzheimer's Disease Education and Referral Center, ADEAR - called ADEAR. Many of you may be familiar with it. Its Web site and clearinghouse activities are the federal government's primary source for information about Alzheimer's disease and about research to better understand and treat the disease, and along with AoA, on evidence-based approaches to care.

I'm very happy that Dr. Laurie Ryan from our own division of neuroscience can share with you the latest on treatments and the search for more effective intervention, and Drs. Shah and Weintraub are two excellent representatives from the NIA-funded Alzheimer's disease centers.

Some of you may work at or near one of these centers. There are 29 of them across the country and they are a critical part of the research infrastructure that we support.

As you know, this is a very special time in Alzheimer's disease research and care. As Greg mentioned, we at AoA - at NIA along with AoA have made significant progress in what we've learned about caring for people with Alzheimer's and in new understandings about the disease itself.

And these efforts have received renewed attention with the signing over a year ago of the National Alzheimer's Project Act. And in the year since that was signed, we've stepped up our collaborations with AoA and with other agencies with the public and private sector and we've worked on development of this national plan to address Alzheimer's disease which we'll be moving ahead to implement as soon as possible when the plan is finalized.

But we're not letting any grass grow under our feet, and in fact some of you may also be aware that next Monday and Tuesday, one of the first things mentioned in the draft plan includes the convening of a national research summit on Alzheimer's disease, "The Path to Treatment and Prevention."

And that's being held next week, and I want to invite you all to -- if you're not registered to attend in person -- to please join us at the summit through webcast on the NIH Web site. And that -- excuse me -- you can get to that through videocast.nih.gov.

So thank you again to all our friends and colleagues at AoA for organizing the webinar, and we encourage you to listen and ask questions and don't hesitate to follow up with us once the webinar has ended. Thanks a lot.

Amy Wiatr: Great. Thank you so much Vicky.

And now we're going to delve into our - the meat of our presentation here today. We're going to begin with Sandra Weintraub, Ph.D., with the Cognitive Neurology and Alzheimer's Disease Center at Northwestern University Feinberg School of Medicine. (Sandra)?

Dr. Sandra Weintraub: Thank you so much Amy and thank you for inviting me to participate in the first of this very important series. Our - I'd like to start with the first slide that announces that I have no financial relationships to disclose, and we can move on to the next.

So I'm going to start today's webinar with talking about what is dementia, how is dementia diagnosed and what are the different types of dementia. And before we swing to dementia, I just thought that I would talk a little bit about

our concepts of normal aging - normal cognitive aging and where dementia fits in that spectrum.

Next. So we see age-related cognitive change as a race against time. At the left of the arrow, we have a 35 years of age and on the right, 95 years of age, a nice, healthy lifespan after middle years.

And then the arrow on the left shows a change - index of change. So if I were to draw a parallel line to the top line, that would span 35 to 95 years. That would mean there would be very little change, but if I drew a line closer to the bottom, that means that I would be changing a lot.

And so this is the concept that's geared towards the individual person. Wherever you start in your younger years, how does time affect you in terms of cognitive aging?

Next. So we have this line here where these individuals that we call "super agers" who really don't change a lot. They're about as good as they were cognitively at the age of 90 as they were when they were 35.

Most of us, however, break away somewhere in the years in between that and join a group called the "normal agers." These are individuals who show a little bit of cognitive decline, but insufficient to cause any major impact on your daily living.

We've more recently learned that there are another group of individuals that fall under the rubric of mild cognitive impairment where they're showing more change than what's average for most people in their age cohort, but not enough to affect their daily living activities.

And then finally those who decline at even a sharper rate and cross that boundary and have so much change that their daily living activities are affected are said to have dementia.

Next. There's a very much emphasis now in all the Alzheimer's research centers and in most institutions involved with understanding cognitive aging on this pre-clinical state. And I think that perhaps Dr. Ryan may have a few words to say about that and also Dr. Shah.

Next. So what is dementia? Next. Dementia is a description of a condition. It's a clinical syndrome and it has many, many causes. And these are the features: initially the symptoms are unnoticed, what we call "insidious." There is a progressive decline in cognition and/or behavior from a prior level of functioning.

The decline can occur in anything that your brain does - memory, reasoning, language, perceptual processes and so on, although memory's the most common.

The thing that differentiates dementia from mild cognitive impairment or age-related change is that dementia interferes with customary activities and social relationships, causing dependence. And if the changes are mostly in behavior and personality, there's social alienation. And dementias are caused by brain disease.

Next please. So what are the causes of this very broad class of dementias? So we can split the onset of dementias into two categories. There are cognitive changes that are somewhat acute or what we call "sub-acute" over the course of days or weeks.

And there are a number of entities like metabolic disorders, vascular, infectious, epilepsy - lots of things that can give rise to what looks like a dementia syndrome but are potentially reversible.

The other class -- next please -- are cognitive changes that are gradual and progressive over months to years. And again there are several classes of disorders that can cause that kind of a change - and we have tumor, hydrocephalus, neurodegenerative brain diseases and vascular.

Under neurodegenerative brain disease, we've learned a huge amount about Alzheimer's disease over the past 35 years, but at the same time we've also learned that there are non-Alzheimer diseases that cause dementia like prion disease, frontotemporal lobar degeneration, Lewy body disease. And each of these diseases has a very different appearance when you're looking under a microscope at the brain after the patient has died.

Next slide please. So how do we diagnose dementia? Next slide. The evaluation for suspected dementia weighs very heavily on the clinical examination. Right now, we really don't have reliable biomarkers like a blood test or a brain scan or something that in the individual patient can say, "Yes. Alzheimer's is the cause of your dementia."

And so although we are hoping for this in the future, right now the clinical examination is the most important thing. The examination should be done by a clinician skilled in dementia, a behavioral neurologist, neuropsychologist, geriatrician, psychiatrist.

And here are the things that are very important to establish. Is there a change from the usual way of functioning? Has it interfered with customary daily

living activities and relationships? When did it start, slowly or rapidly? Has it progressed, stayed the same or gotten better?

Because there are some - as I said, you know, if somebody has undetected epilepsy -- not the kind where they might fall to the ground but epilepsy in their brain -- they may look for all the world like they're demented, but once the epilepsy is treated, they're going to get better.

What is the medical history? Are there any illnesses and disease that could give rise to cognitive deficits? And then, what is the psychiatric history? Is this somebody who has a lengthy, chronic psychiatric history and then is having a recurrence of that condition that's then causing them not to be able to remember or to think properly?

Next slide please. So the evaluation also includes brain imaging. And right now, MRI and CT scans are typically done to rule out all the other things that could cause dementia that are non-degenerative or stroke-related.

Brain - the MRI and CTs primarily look at brain structure. So has there been a stroke or more than one stroke, or is there a tumor that's mimicking a dementia syndrome?

Brain function can also be measured by positron emission tomography, and that looks at the way the brain is using oxygen. And so the positron emission tomography looks for patterns of brain dysfunction that are associated with different causes of dementia.

For example, in the frontotemporal lobar degenerations as the name suggests, the frontal and temporal lobes are not functioning as well as the other lobes, and you can see this with a PET scan.

The physician will also order a series of blood tests to exclude potentially reversible conditions, and then there's a neuropsychological examination. And the neuropsychological examination is playing a very important role because right now it is the only marker of the cognitive dysfunction, especially in somebody who was very high functioning in the past and who may be experiencing some mild decline.

Next slide please. It's very important for us also to collect information about activities of daily living, and this is - there are many such scales. This is an example of a scale that we developed at our center where we ask the caregivers to rate self-care, household care, shopping and money, employment, recreation, travel and communication activities on a scale of 0 -- meaning they're not having any problem and doing as well as they always have -- to 3, where they're no longer able to do the activity because of cognitive changes.

And so scales like this give us an estimate of how much the cognitive decline has interfered with daily living activities - mild, moderate or severe. We also use a number of tests that are - that allow us to stage the cognitive impairment.

So there are tests for patients, and I think most people are familiar with the mini-mental state examination. There's also a test called - it was actually I think the first examination of mental state for dementia, called the Blessed Dementia Scale. And Blessed has to do with the fact that Dr. Blessed created it. It's not a religious scale. And then the Montreal Cognitive Assessment.

And then there are other methods of rating the severity of the dementia by the observer or the clinician who's talking to the patient, talking to the family and then coming up with a rating, is this mild, moderate or severe. And the best

example of this is the Clinical Dementia Rating scale developed by John Morris and Wash U.

Next slide please. So how do you really know what's in the brain if you - all you can see is what you see in the doctor's office or your imaging scans? And so the definitive diagnosis of the disease causing the dementia, as you all probably know, still relies on postmortem brain autopsy. The brain autopsy shows the cell and the protein abnormalities that cause the brain cells to die and cause the dementia.

Next slide please. These are just some examples of what brain tissue taken from individuals who had these forms of dementias during their lifetimes, what is actually going on in their brains. So under the microscope, it looks very, very different.

You would not mistake the lower left picture that shows the plaques and tangles associated with a diagnosis of Alzheimer's disease from the photograph on the lower right that shows cortical Lewy body disease or the photograph above it that shows a tiny stroke in the brain. And I just have a photograph in the center that shows you what a normal brain should look like.

So each of these diseases are exquisitely distinctive under the microscope, although you could have a patient with Pick's disease under the microscope and a patient with cortical Lewy body disease under the microscope display similar clinical symptoms during their lifetime. And that's what makes things very difficult for us in terms of diagnosis.

Next slide please. So what are the different types of dementia, and that's what we call the "differential diagnosis." Next slide please. As I said, there is no one-to-one correspondence between the dementia symptoms and the

neuropathology at postmortem, but we have some pretty well-established correlations.

And so what we understand now is that if we look at what the earliest clinical symptoms were that a patient presented with, we're not going to have 100% predictive ability but we're going to come close to be able to say, "Well if memory's the primary symptom, Alzheimer's disease." Pathology is going to be most prominent, but not Lewy body disease necessarily. And I'm going to show this to you next in the next few slides.

Next please. So the diagnosis is based on the early clinical symptoms, and number one and probably the most common definitely in people over the age of 65 is dementia of the Alzheimer type. The initial symptoms in these individual is most often short-term memory loss -- forgetting conversations, repetitiveness -- and also they experience some reduced motivation, just seem to lose interest in things.

Later on as the disease progresses - and all of these diseases do. The pathology may start in a certain segment of the brain that controls memory, but then it moves. It moves and involves other areas and then causes other cognitive problems. At brain autopsy, 90% of individuals with this clinical dementia syndrome have AD neuropathology and 10% have something else.

Next. There are two major forms of what we call dementia of the frontotemporal lobar degeneration type, and that's kind of a big mouthful. And as I said, as we've been studying Alzheimer's disease, we've learned more and more about the FTLDs that tend to affect individuals a lot younger than 65, even in their 40s and 50s.

So one of the most prominent syndromes is primary progressive aphasia where the early symptoms are word finding deficits, but later on, patients will have more problems with language like reading and spelling errors.

Because the disease might spread into personality areas of the brain, they'll have behavioral changes and even short-term memory loss. At brain autopsy, 70% of these people have FTLD neuropathology, and I'm not really going to get into any of the details of that right now, but 30% have Alzheimer pathology.

Next slide please. The second major variant of the frontotemporal degenerations is called behavioral variant frontotemporal dementia. In these patients, because the disease doesn't start in the same part of the brain that controls memory or language but starts in their "personality centers," they have personality change - poor judgment, inappropriate emotions, odd food habits and later on they may also experience memory loss and they may also have motor symptoms like tremor.

At brain autopsy, 70% of these clinically diagnosed FTD patients have FTLD neuropathology, but 30% have something else, including Alzheimer's neuropathology.

Next slide please. Another major type of dementia is Lewy body dementia. In these individuals, again we have a very different clinical presentation. These patients have prominent visuospatial deficits, so they may have difficulty finding their clothes in the closet even though they're right in front of them.

They'll have early visual hallucinations, and the hallucinations are really interesting because they're not frightening and they know they're having

hallucinations. And this doesn't really cause any cognitive dissonance, and they're usually pleasant like little sheeps or lamb, or babies on the floor.

The symptoms fluctuate and they have motor symptoms that are Parkinson-like, like tremors or some rigidity. And brain autopsy in these individuals, 53% have cortical Lewy body disease, 26% have Alzheimer's neuropathology and 21% have something else.

Next slide please. Another very common form of dementia is called vascular dementia, and in these patients the symptoms can be very, very, very different and quite varied.

So we can have apahasia, we can have behavioral problems, executive function problems, motor symptoms. And typically the kinds of functions that are affected depend on where in the brain the stroke occurred. If the stroke occurred in the frontal lobe, you'll have executive function deficits, if in the occipital lobe, you'll have visual deficits.

And in vascular dementia, the syndrome is related or at least a higher for this syndrome comes in the form of chronic cardio and cerebrovascular risk factors like heart disease, hypertension, high cholesterol and there is progressive loss of function that is due to these multiple successive cerebrovascular events or what people are calling mini-strokes.

And then there is another - yet another cause of dementia called prion disease, or I think people know it more popularly as mad cow disease. And this disease is recognizable for its very rapid course. I mean, you can go from onset to death within months. I think maybe the longest I've heard of is one to two years. And there's also - some patients may also have a very severe sleep disorder.

And then there's a very characteristic jerking of the body, myoclonic jerks. It's a kind of thing - I'm sure everybody has gone to bed at night and then you kind of jump 5 feet in the air? Maybe not, but probably everybody's experienced that kind of a jerking reaction.

Next slide. The neuropsychological battery is conducted to show the profile of the cognitive strengths and weaknesses, and so that by defining this profile we can then say, "Well language is most impaired. Therefore, this person must have more of a chance of having FTLD pathology."

Next slide please. These are just a number of the tests that we use to evaluate cognitive functions. Each test is targeted at a different brain system - naming tests at language functions, drawing tests at the visuospatial functions, digit span, repeating numbers in the sequence that they are given to test attention.

The lower right-hand side shows a little test that we developed for memory where patients copy three designs and three words. We don't warn them that they're going to have to remember. We just take it away. And in number A2 you can see that an Alzheimer patient without any warning doesn't really remember very much.

We warn her that she's going to have to remember and then immediately after taking the paper away again, because she's trying really hard, she remembers all six. But after a delay -- even a brief delay of 5 minutes -- A4 shows forgetting of two of the words. And if you let it go any longer, she will forget all the information.

The Trail Making Test on the left is used very commonly to assess executive function, and then there are reasoning tests that ask patients to group items. So

in this example, there are four items. Tell me three items that have something in common. Well you'd pick 1, 3 and 4 because they're the same color. And I will ask you "Can you tell me another three that have something else in common?" And after thinking awhile, you might say "1, 2 and 4" because they all have straight lines.

Next slide. So to summarize, dementia, the early clinical symptoms -- neuropsychological, neurological, psychiatric -- tell which part of the brain is not working properly.

The postmortem brain autopsy tells what disease is attacking those parts of the brain in early stages. All of these diseases, no matter where they start or how they start, progress to eventually affect many brain regions and correspondingly all dementias progress to affect all cognitive and behavioral functions.

But the earliest symptoms are most helpful in predicting postmortem pathology and even more importantly, advising patients and caregivers on management. Because if you're dealing with someone who's got short-term memory deficit, their needs are going to be very different from somebody who can't come up with the rights words, but has no memory problem at all.

And on that note, I will end.

Amy Wiatr: Wonderful. Thank you so much Sandra.

Dr. Sandra Weintraub: You're welcome.

Amy Wiatr: And right now I think we're going to turn it over to Dr. Shah who is with Rush Alzheimer's Disease Center.

Dr. Raj Shah: Great. Thank you Amy and thank you Dr. Weintraub for presenting earlier. So what I thought I would do as part of the presentation of the three today is to reflect a little bit on all that information that was just learned in the presentation by Dr. Weintraub and to sort of prepare all of us for the information that will be presented by Dr. Ryan.

And so before I get started with the next slide, I would just like to show my disclosures that I've received research support from the NIH and the Illinois Department of Public Health, and then I've also received research support as a principle investigator for many clinical trials.

I serve on the board of directors for the local chapter of - the Greater Illinois Chapter of the Alzheimer's Association and I've also been on the advisory panels for two companies looking at new treatments for Alzheimer's disease.

So what I'd like to do in my talk is to really touch base a little bit on the diagnosing of dementia and then also on some risk factors. And how I thought maybe a useful way to approach this as many are you are actually providers of services to older adults, and maybe if I could frame it in a common scenario you may run into in your day-to-day lives, it may help in absorbing some of the information we're about to present or have presented.

So if you bear with me and think for a second about this case example -- maybe this has happened to you, maybe it's something that will happen to you -- but say that you're at work and a 75-year-old client comes in and mentions that he's concerned about memory loss.

He mentions he has a family history of Alzheimer's disease and has many brothers and sisters that have developed the disease, and he's really noticing

some changes in his abilities to think that he just doesn't feel comfortable about, but his spouse and his close friends really haven't noticed these thinking changes and how these changes may affect his day-to-day abilities.

And he asks you, "I mean, should I seek a cognitive evaluation? Should I get help?" and he's looking at you for information and how would you - may approach this. And maybe in the time I have, we'll go through some of the basic ways of providing information about the need for cognitive evaluation that you may be able to use in your day-to-day activities as professionals.

So what I'd like to do, like any good article or any good piece of information is, you really have to answer about six questions. You have to answer the who, the when, the why, the where, the what and the how.

And what I'd like to do is in Part 1 of my presentation is to really go through, you know, who should seek an evaluation, when should one seek an evaluation, why should we seek an evaluation early, where can one get an evaluation and what to expect to expect from evaluation and how an evaluation is conducted.

And then what I'd like to do as a segue to Dr. Ryan's talk is to say, you know, after an evaluation happens, what may someone expect a health provider to state after the diagnosis and what are the general properties of a treatment plan that would be put together by a health provider after an evaluation.

So let's start and go with the "who." Who should seek an evaluation? Well there's really two answers to this, and one is - I'll get back to when I answer the when question. But really people who should seek evaluations are persons who may have clinical risk factors for developing a dementia.

Now there's been a lot of work in trying to understand the risk factors for a dementia, but we don't have all of the answers, but we do have some ideas what might be factors.

And so on the next slide, what I present are some of the more common non-modifiable factors associated with dementia. These are factors we have we cannot change and may be associated with developing a dementia.

So the biggest one is that dementia is age-related. And so if I would test everybody that was 65 years of age in the country right now, about 2% to 4% would have Alzheimer's disease or dementia diagnosed.

When I progress further, if I tested everybody that was age 85 in the country, almost half of individuals could be diagnosed with a dementia through an evaluation.

Now that doesn't mean everybody is doomed to getting a dementia as they age. There are half of individuals over age 85 that have no memory problems and are functioning well, it's just that dementias and the diagnosis of dementia is more common as people get older. And as a geriatrician working at a center at Rush in our memory clinic, the average age of my patients are in their 80s, 82 to 85, the group that's most at risk for showing signs of dementia.

And then - so apart from age, another risk factor is family history. And what we find is individuals who have siblings that have Alzheimer's disease or dementia or a first-degree relative that has dementia is just more at risk for developing a dementia.

Now many family members ask me about this. They say, you know, "Dr. Shah, you've just diagnosed mom with having Alzheimer's disease. I'm 50, what's my risk of developing Alzheimer's disease?"

And we're still trying to work on finding all of the answers about the family history relationship with a dementia, but the risk we have to let people know is not so strong that somebody should feel that they're doomed to getting Alzheimer's disease if their sibling or their parents had the disease.

Again when I gave the example of the 2% to 4% having Alzheimer's disease, at age 65, if you're a person age 65 and have a family history, your risk instead of being about 2% to 4% is about as - double at about 4% to 8%. But that doesn't carry over until you're about 85. The family history dynamics change and their relationship with dementia.

And then the other factor that seems to be well-described as a risk factor for dementia is a protein genotype called apolipoprotein epsilon 4. It's a test that can be done to determine if somebody has - is a carrier of this epsilon 4 gene type, haplotype. And people who have E4 or two of them are at just more risk for developing dementia.

And so those are the non-modifiable risk factors that put people at risk for dementia. Now there are modifiable risk factors in the next slide that seem to be associated with dementia. The first one -- and Dr. Weintraub mentioned this -- is these cardiovascular disease risk factors.

We seem to find that depending on where you're at in your life course, having things like high blood pressure or diabetes or high cholesterol may play a role, especially in midlife, in predicting who may develop dementia later on, 20 to 30 years.

The relationships change a little bit when these conditions exist in very old individuals and their risk for dementia. But these are very common modifiable factors. We have treatments to help people with blood pressure and with diabetes and cholesterol, and we encourage people to stop smoking. And all of these things can play a role in maintaining cognitive health as people age.

We're also finding head trauma has a - as a risk factor for individuals in traumatic brain injury in the likelihood of developing a dementia. So one of our big suggestions for older adults, especially if they're involved in activities, is to wear things like their seatbelt or if they're going to ride a bicycle to make sure they have a helmet while they're riding a bicycle.

And then we - the information is coming out in prospective studies that lifestyle choices may make a difference in dementia, but these are still at a stage that's more exploratory and more work has to be done to really prove which lifestyle choices might prevent the development of a dementia.

And some of these things are - that might affect dementia are things like lack of physical activity, movement and daily activity, being more sedentary, having less cognitive activity, choosing a diet that might not have all the various nutrients we need to do well and low social engagement seems to be another factor. The more we socialize, the better we tend to do in maintaining our health and wellbeing.

So with the next slide, if we think about those as "who" as the risk factors for who may seek an evaluation, well the second phase is really "when." And what we tend to find in the United States is people wait too long to initially seek an evaluation.

And if that's one message we can get out, it's that if somebody's starting to experience cognitive problems that are bothering them, that are irritating them and preventing them from functioning at their peak and influencing their quality of life, they really should talk with a healthcare professional about their memory changes.

A lot of people will say, "Oh I'm just getting older. This is just something that happens to all older people and I shouldn't go and talk with or bother my physician or clinician in telling them about my memory loss. I can write more notes and cover."

But we really do encourage people to go early and really at the time when they start experiencing cognitive concerns that are really affecting their quality of life and function and when really things are starting to happen more frequently.

We all forget. Forgetting is part of natural human existence. A 2-year-old forgets, an 8-year-old forgets, an 11-year-old forgets. I forget at age 40 and my older client patients also forget at age 80. But really what becomes important is when the forgetting becomes more common and when it starts interfering with day-to-day function and wellbeing.

So that's the "when." Earlier is better, at least to start the discussion. And then the next slide is "why." Why should we go and seek an evaluation early? And part of the reason probably out of the three choices I provide is the peace of mind.

Usually a lot of individuals start noticing they're having troubles with their cognition. They start realizing it's affecting their day-to-day life, but they don't really know what's happening to them and they sometimes become fearful.

They sometimes think they're going crazy. It's something they've brought on themselves with the memory difficulties.

And when they actually go and talk with a health provider and go over their symptoms and get an evaluation and diagnosis, at least they know where they stand. And that's probably the first one is to know where in the trajectory people are at with their cognitive function.

And then if they do have some troubles with cognition, to really find if we can locate some treatable conditions that might help improve somebody's cognition, whether it be the cognition changes are due to medication side effects. Maybe there's a way to change the medications, or they might have a problem with their thyroid levels that might need readjustments. We can find conditions that can maybe help maintain people’s cognition if we see them earlier.

And so on the next slide, "where." Where can somebody go to seek an evaluation? Well I think in many ways, as trained in family medicine before going into geriatrics and now in dealing with Alzheimer's disease and dementia in particular, I really do think memory loss evaluations can start with primary healthcare providers.

It is a common symptom that has large public health issues, and a primary provider who knows the person for a long time can begin and initiate the evaluation. And sometimes the primary healthcare provider may need more help.

And where can somebody seek more help? They can look at their neurologist or a psychiatrist or a geriatrician with the aid and help of neuropsychologists to help in the evaluation process.

On the next slide, where can somebody get an evaluation? Well I think the starting point is in the - in their communities is to look for resources close by at private practices that might be in the area with healthcare providers - primary care healthcare providers.

And if they need more resources is to look at their community hospitals in the area. And then if they can't get resources there, to look at the multiple academic centers that are available throughout the United States, and some of them have a more specialized memory centers. And those might be the choices of where somebody can get an evaluation.

On the next slide, I wanted to just broach a little bit about "what," what to expect from an evaluation. And really people always ask me that about "How do I know I've got a good evaluation?"

And I think what it fundamentally comes down to is if the person who's going in with the memory concerns and had to really take that effort to go in and talk with somebody about these difficulties that they might fearful of, is that they walk out of the room after seeing their healthcare provider and feel they've been listened to, that somebody has taken the time to really explore what has been happening, to be able to look and to see if there might be underlying causes and to help develop a treatment plan.

So listening, or being felt that you've been hear is probably the most important quality metric that I find valuable when somebody is having problems with cognitive concerns and needs to see a healthcare provider.

And then I think what is really helpful is, you know, to expect that after an evaluation that there's a statement by the healthcare provider of where the

person with memory problems may fit on the spectrum of normal memory to mild cognitive impairment to dementia.

And then if a dementia's diagnosed, a statement about what may be the cause the for the dementia, whether it's dementia due to Alzheimer's disease, dementia due to vascular disease, dementia due to Lewy body disease, dementia due to vascular disease.

And so what we're really trying to do is -- again in the next slide -- is to really piece out where somebody may be on a spectrum of cognition between normal memory, mild cognitive impairment and dementia and give them a sense of where they fit on this spectrum.

And then the next slide is to show some of the difficulties that go into an evaluation and why you need to listen and take time to get a good story and a history to help somebody who might be having memory difficulties because the dementias themselves -- the Alzheimer's disease, Lewy body disease, frontotemporal dementia and the vascular dementia -- have distinct features but they also overlap quite a bit as Dr. Weintraub was mentioning.

And then there's other conditions that might also mimic and look and affect cognition, whether it be medication side effects, depression, chronic diseases, seizures, metabolic abnormalities, delirium or acute changes in memory or life stressors.

And really what we're trying to do is if we look at a dementia is really to be able to try to piece out what we think might be the primary reasons somebody has a dementia from a neurodegenerative standpoint, whether it's the Alzheimer's disease or vascular dementia or Lewy body disease or frontotemporal disease.

And so on the next slide, I again wanted to give a sense of, you know, a client might ask, "What should that evaluation look like? What should happen during the course of the evaluation?" And probably the biggest time spent is listening to the history, listening to what's happening with somebody's symptoms and reviewing their memory difficulties.

And that needs to be confirmed sometimes by another person, a person who knows the individual -- thinking's concerned -- well who can also provide input about what they've been noticing.

We also have to look for other things that might be affecting cognition, commonly depression which also happens in older adults quite frequently. And then we want to get a sense of the functional assessment of what somebody is doing and how the memory might be affecting their day-to-day lives.

There's also important needs to look at a medication review to make sure there might not be side effects of medications, the family history to get a sense of underlying risk for developing a dementia, getting to know the support network of somebody is very important so that we can develop better treatment plans and help them build support systems that could help in the future as they may progress with memory loss.

There will be pen-and-paper tests of thinking function that Dr. Weintraub described. There'll be a physical examination really to look at if there's signs of stroke or Parkinson's disease on the exam. There will be common blood tests that might be ordered like thyroid exams or vitamin B12 exams, and then brain imaging if necessary to rule out other conditions that might be affecting the memory.

And really when somebody goes through that entire experience, what the clinician is doing is trying to answer three questions and triaging people accordingly.

And the first question they're trying to ask is "Does this person have a chronic cognition problem?" So the two main pieces there are chronic and cognition. So if the entire evaluation goes forward and the person doesn't find that there's a cognition problem, they may have at this point in their stage normal cognitive function. And what individuals need to be advised at that stage is to maintain healthy choices, to maintain a healthy lifestyle choices that can help prevent things like stroke and cardiovascular disease that may affect their memory over a long period of time, and they need to be given an opening that right now today Ms. Jones I see that you have normal memory after I did this evaluation but I think, you know, if things change with your memory I would like you to come back and see me again so we can re-evaluate.

Now maybe somebody finds out that there is a cognition problem, but it's not chronic. It's not been lasting more than three to six months and there's an acute condition that might be causing the cognition problem. That would be delirium and there we would have to go through some more medical testing of exactly what's causing the condition of the cognition problem. Is it a medication and if it's the medication maybe the suggestion would be to stop the medication or change it to see if that helps the cognition. If it may be depression, the clinician may say we'll treat the depression first and let's see what happens but whatever we do in the treatment I want to see you back after we think the treatment has helped to see what your cognition is doing. Because a lot of people have an acute condition that is affecting their memory along with a chronic condition.

Now say somebody is defined as having a chronic cognition problem and the answer is yes. Then the clinician will have to try to answer, "Do I think this person has a Dementia. Do I feel that they have enough chronic cognition problems that it's affecting their day-to-day quality of life and impairing their social function?" And if the cognition problem is there, but it's not truly affecting the day-to-day life or interfering with social function it's what may be diagnosed as mild cognitive impairment and that I think Dr. Ryan will talk a little bit more about as far as some treatment options there.

And then if somebody is diagnosed with having a Dementia possibly the first question because it's most common in older adults might be to ask, "Do I think this individual has trouble with Dementia due to Alzheimer's Disease?" And if it's Alzheimer's Disease, then we start a treatment plan for Alzheimer's. If it's not Alzheimer's Disease, we think about more tailored treatment plans and diagnostic plans for the other neurodegenerative conditions that could cause a Dementia.

And really once -- in the next slide -- once somebody's made the diagnosis or made a statement of where somebody fits on the cognitive spectrum or if they have a Dementia what might be causing the Dementia, what we're really trying to do with a treatment plan is to build this pyramid. A pyramid that's based on education and social services with the medications we currently have available to help people that might be having memory difficulties.

And really the idea behind this pyramid and what it's trying to do is it's trying to help maintain cognition function for as long as possible, help reduce the behavioral changes we see with cognition, help maintain functionality and all of these things combined with help to reduce caregiver or support network burden.

And the way we have to do this on the next slide is really by forming a team -- a web -- that's going to help somebody as they have troubles with memory loss and the center is the person that's having the memory difficulties. And surrounding them are their caregivers and next to them are their healthcare service providers, and then there's community and social service providers for services that they need to access and maybe not now but in the future and legal services.

And the goal behind creating this dynamic web is that the person with memory loss will be supported throughout the experience and that we try to prevent some of these crises that can be really stressful and burdensome not only in the person developing memory loss, but also their health network.

And so in conclusion on the next slide what I wanted to leave with is that, you know, diagnosing cognitive disorders early will probably provide the most benefit because you'll have time to work with the network of services that are provided to older adults to build systems to help prevent crises.

And then I think the next thing is that diagnosis of individuals with cognitive concerns does require an integrated and team approach and it requires individuals that have face time with older adults to start recognizing symptoms and to help older adults seek services they may need in an evaluation and to prepare them for what an evaluation may look like. And then helping persons to know what to expect in a cognitive evaluation will make sure that they get the best health information possible for their needs. And with that I appreciate your time and effort and on the next slide I just left my contact information. Thank you again.

Amy Wiatr: Thank you so much Raj. That was wonderful. And now we're going to move on to Laurie Ryan, Ph.D. with the National Institute on Aging.

Dr. Laurie Ryan: Hi. Thank you all. I'm actually going to update you on where we are currently with Alzheimer's Disease clinical trials. So I'll talk a little bit about the current treatments we have available and then what we're looking at in research to develop even more effective treatments.

Okay. My next slide please is my financial disclosures and I am a Federal employee and I have no financial relationships to disclose outside of my government service. Next slide.

Okay. So current FDA-approved treatments for Alzheimer's Disease. We have two types of medications to treat the cognitive symptoms of aiding the memory problems and what not and these generally do provide temporary cognitive improvement and do slow decline in some patients with Alzheimer's Disease. They don't work for everybody and they only work for a limited period of time, but they do provide some benefit.

The current approved treatments, the two types. We have the cholinesterase inhibitors things like Aricept, Exelon, Razadyne, and then we have Memantine or Namenda which is the brand name. Next slide please.

Recently I'm sure it's made the news is that we've had a lot of our big phase three clinical trials which were really the gold standard for evaluating a treatment and a necessary step for FDA approval of a drug to treat illness. A number of them have actually failed. We've had things looking at some of the stating treatments Dimebon. The biggest one was one of the gamma secretase inhibitor, the LY450139 which was stopped due to toxic effects so adverse side effects and that's really the most common reason for things (fail). One is either that they aren't efficacious or they are very toxic.

So we've had a number of (unintelligible) in recent clinical trials have failed and it's pretty alarming because -- next slide please -- if new medications are found to prevent or delay or stop the progress of AD, it's estimated - this is from the Alzheimer's Association that the number of Americans will jump to about 13.5 million by 2050 given the aging of the population particularly the baby boom population and the costs for care are just going to skyrocket. They're high now, but the estimates are it might increase fivefold to $1.08 trillion a year which I think is a stark fact. It's about 25 times more than the 2010 budget was for the Department of Homeland Security. This information actually is from the Alzheimer's Disease Report from Pharma which is the industry trade organization so it's available on the web if people want to look at that.

So what we have currently in development you'll see on the next slide please is about 79 drugs or compounds that are in clinical development meaning they're being tested in humans right now and many more actually being tested in the animal phase. And there's 79 that are specific for Alzheimer's, 18 for cognitive disorders, 2 for just general Dementia not specific to AD, and then 5 looking at ways to diagnose. Next slide.

And the drug discovery development and approval process actually is actually a very long operation. It takes about 10 to 15 years on average for an experimental drug to travel, you know, go from the lab all the way to a U.S. approval. And if you'll look at that about only about 5 in 5000 compounds that actually get into animal testing make it to human testing and of those about only 1 is actually approved. So it's a pretty big and expensive operation.

Now the good news is that we have learned a lot more -- next slide please -- about Alzheimer's Disease and this improved understanding of the pathogens for the mechanisms of AD have led us to actually identify a number of

potential therapeutic targets. Many of these are being looked at right in the pre-clinical animal studies and a number more are being tested in human clinical trials and that's what I'm really going to focus on now is where we are with the human studies. Okay.

So as I'm going to talk about targets just to bring you back, you saw some of these slides from Dr. Weintraub showing what a plague and tangle looked like, but plague and tangles are really the hallmark of AD and AD plagues are made up of beta amyloid which is a protein in the brain and the neural fibrillary tangles are related to (unintelligible) protein and I'm going to talk a little bit more about that on the next couple of slides just to give you an idea - a brief overview. Okay next slide.

So we look at the beta amyloid plague. It's basically the amyloid precursor protein or APP basically is cut or (unintelligible) by enzymes in the brain and they produce fragments of beta amyloid and then these beta amyloid fragments come together and clump to form the plagues.

When we look at tau, neurons having -- next slide please -- neurons have an internal support structure that's made of both microtubules and a protein called tau helps to stabilize these. So changes in tau cause these microtubules to collapse and the tau protein to clump together to form the tangles. Next slide please.

And that's relevant when I want to talk about what are sort of the new avenues of the targets for Alzheimer's therapy. So at the top you'll see is to prevent the buildup of plague. So these are our anti-amyloid strategies to slow the buildup or to clear the plague out of the (unintelligible) plague from the brain.

The second one you'll see it to prevent basically these tangles from forming and that tau-focused strategies and then finally there's also we'd like to try strategies focusing on preventing self dysfunction and death. So preventing things like oxidated stress inflammation to increase protective molecules in the brain and to maintain viable connections between cells. And I'm actually going to talk about each one of these and where we are with the research on those therapeutic targets. Next slide please.

So this is just a graphic looking at sort of the amyloid targets and I just circled the ones that people are investigating right now. And I'm going to focus a little bit on the ones that are in the bottom right which are the immunotherapies. Next slide.

So what we can do with immunotherapy like in immunization for any disease is we basically in terms of -- excuse me -- Alzheimer's, we're looking at altering A beta or amyloid deposition by either (1) making the body have an immune response to A beta or by administering an antibody for A beta. And so one is active strategy where we have the body make it and the other one is a passive strategy where we actually give the antibody. Next slide please.

The very first immunization therapy was an active immunization therapy, the AN1792, and unfortunately the trial had to be halted because it actually caused encephalitis in about 6% of treated subjects. And it's not really important what it is, but basically we think it's a T cell response that actually causes severe adverse reaction. So there are a number of active immunization strategies in clinical trials that are trying to work around this so they're alternative and then we have the passive immunization strategies that don't initiate this type of response. So those two things are still being looked at currently. Next slide.

And the interesting thing about AN1792 is that they follow subjects even though the treatments were stopped about 4-1/2 years later and those in the active immunization actually did develop antibodies to A beta and the ones that had developed antibodies showed less decline in their activities of daily living which Dr. Weintraub talked about compared to the placebo treated patients. So there is a suggestion that if it hadn't had the very significant adverse effects on the brain that if we can get away - do away with that, we could actually see some improvement in the Alzheimer's Disease. Next slide please.

So passive immunization is another way that again does not have - doesn't have some of the same severe adverse effects that the active did. And one of the treatments that we're looking at -- at least the NIA-sponsored study is looking at -- is IVIG which is intravenous immunoglobulin. Sorry that's a mouthful. One of the brand names is Gammagard and that's sponsored by Baxter and that's basically a human blood product. So that was recently found to have antibodies to amyloid beta. The phase 2 trial was very small, had 24 patients, and it actually did show some improvement in cognition in subjects that had the passive treatment meaning immunization. There were no significant side effects so that was good.

Based on those results, there is a phase 3 study that's supported by the NIA through our very large Alzheimer's disease clinical trial consortium, the Alzheimer's Disease Cooperative Study or ADCS and Baxter. Now that trial is fully enrolled. It should be completed by the end of 2012 with reporting of results sometime in early 2013. So we should know fairly soon how this worked in treating mild to moderate Alzheimer's.

And you can see -- next slide please -- this is just showing that there are a number of other immunotherapies that are in different phases of clinical development for Alzheimer's Disease. Next slide.

Now that brings us to some other information that is becoming more and more clear to us is that the growing bodies of evidence suggest that the underlying pathology: the amyloid beta, the underlying pathology actually precedes the onset of clinically detectable Alzheimer's Disease. So before the clinical symptoms of mild cognitive impairment or Dementia appear by that a decade or more. So but we're thinking by the time someone comes to an office with clinical symptoms of Dementia that there is really massive neuron loss in the brain and widespread pathology. And the question really is then are we treating at least with certain therapies too late. Do we need to be treating in the pre-symptomatic phase. Next slide please.

So this is just a graphic from very recently the NIA and the Alzheimer's Association just published new criteria for Alzheimer's Disease and also research criteria for looking at this pre-symptomatic phase and that's where this actually - graphic comes from. But if you'll look, it kind of shows you the progression. We think that amyloid beta accumulation for example is one of the early changes that occurs in the brain, then followed by the tangle formation, dysfunction of synapses in the brain, neuron death that ultimately causes it to decline. Next slide please.

And then this is just another illustration that if you'll look at. So that pre-clinical phase is when a lot of these changes are occurring, but you don't see the cognitive changes until later in the process. And so the idea again is should we be trying to identify people earlier in the process. And we actually have ways now of measuring amyloid and tau through looking at the cerebral

spinal fluid and we can actually image using a PET scan technique called amyloid imaging.

You can see the buildup of amyloid in a human living brain so we actually have better ways now of measuring it. It's not ready for a doctor's diagnosis yet. It's not ready for prime time if you will for the clinic, but it is very helpful for research in helping us to identify can we predict based on some of these things who will later is at risk for developing full-blown Alzheimer's and then can we also intervene. Next slide please.

This figure many people have seen and used recently. It's showing through these biomarkers that I was talking about: the CSF and the brain imaging. It's not really important which ones are which, but just to notice that again we think there is this progression where (unintelligible) A betas in the red, beta amyloid -- those are interchangeable terms by the way that I'll be using -- changes occur first there followed by tau and neuronal injury, then changes in brain structure so we see shrinkage in the brain, then followed by memory changes, and ultimately activities of daily living changes. Next slide please.

So again are we testing the right drug at the right stage. That is really a big question. This is a wonderful commentary if anybody wants to read it by Reisa Sperling, Cliff Jack, and Paul Aisen really talking about this issue that we need to target our treatments to the right therapeutic target and at the right stage. Next slide.

So what these investigators suggest is that researchers need to start looking at targeting these selected therapies to specific stages of AD as we showed and to think about the disease in terms of primary, secondary, and tertiary prevention rather than lumping all of the disease modifying treatments together because again we may not see things work. If we're looking at

amyloid and it changes early for example if we're using an anti-amyloid treatment we may be - if we do it when someone's got mild to moderate Dementia, it may be too late to affect the change. That may need to happen earlier. Next slide.

And this is just the graphic from their paper showing primary prevention would be people have normal cognition and little or no pathology. The next one being secondary where people have the underlying pathology and you're trying to delay the onset of the clinical or symptoms of a cognitive impairment. And then finally the tertiary prevention and treatment where people have full-blown disease, but we're trying to prevent neuron loss and enhance a function of the neurons that are still remaining in the brain. So I think it's important to also know although I'm talking about pre-symptomatic as it being a target. We do not want to forget that people do have the full spectrum disease and that we're going to need therapies again for each of the stages. So I'm going to focus a lot on pre-symptomatic, but that is not the only thing obviously. Next slide.

Okay so implications. Again this is from the office of the paper. So that we're hoping that he advances in the pre-clinical detection. So being able to look at the underlying changes of Alzheimer's before the cognitive symptoms occur like with the amyloid imaging will help us to develop more effective treatments. And it's noted there by the authors that a lot of other therapeutic gains in things like cancer, cardiovascular disease, and what not involve treatments that are preventative. That you give like if you have high cholesterol, we give you a statin medication to prevent from having full-blown cardiovascular disease and a heart attack later.

And as I point out, it's possible that promising drugs particularly things like amyloid that we know occurs or we think occurs early in the disease process

may fail to affect the course later. So it will be interesting to see if the current amyloid treatments that we have that are being looked at in people with full-blown Alzheimer's whether or not they will have an effect. And if they don't, it may be that that treatment as we're talking about is too late. Next slide please.

So that brings me to where we are sort of in our thinking on pre-symptomatic treatments and there are a number of trials that are in development. Nothing's gone forward yet and these are all in development, but they have been presented before so it's okay to talk about them. Most of the investors have presented this in different forums. Next slide please. Okay.

The first one is the anti-amyloid treatment in asymptomatic AD or A4 trial. This is being planned by the Alzheimer's Disease Cooperative Study or ADCS that's NIA-sponsored. It's going to be using clinically normal or cognitively normal older adults who are showing - have signs of A beta accumulation on PET scan. So they have a high level of A beta that's on PET scanning. That's going to be the criteria. So we think they have the underlying disease, but they are cognitively normal. And if we treat those individuals with, you know, a biologically active compound like an anti-amyloid treatment for three years in a randomized double blind placebo control trial which is the gold standard to see if that impacts both the biomarkers, the imaging as I talked about, the cerebral spinal fluid -- we call those biomarkers -- underlying pathology of AD, and also looking at cognition. Okay next slide.

Again so it's looking at that first oval, the amyloid beta accumulation so you want to intervene early. Next slide.

The aims again I said are to determine whether decreasing amyloid burden will slow the rate of cognitive decline and the risk of progressing to MCI and

AD and also to look at the effective treatment on the later what we call the downstream markers. I talked about the ones that show up later in the stage like the tau pathology that comes after amyloid so there's a more downstream. Will it have an effect on preventing those changes as well. And ultimately too this trial will also help us to develop more sensitive outcome measures to look at future prevention trials. Next slide.

Another study that is in the planning stages is being done through the dominantly inherited Alzheimer's Network or DIAN. DIAN is actually looking at early onset Alzheimer's Disease, genetic mutation carriers. So there are some people and it's a very small portion of those with Alzheimer's. They think about 1% to 3% of Alzheimer's cases are caused by genetic mutation. These are people that if they have the genetic mutation, they're carriers, they will develop Alzheimer's Disease and usually it's before the age of 45 or even sometimes earlier. So these are people that we know are destined to get the disease if they're gene carriers.

And the DIAN network is run through Washington University in St. Louis and has sites in the U.S. and internationally because it's such a small population that we really need to have a whole network of sites so that there are enough people to actually learn more about this very devastating illness in the early onset and also to help us learn hopefully more about the late onset which is the most common version as you've heard of Alzheimer's. Okay next slide.

So the DIAN clinical trials are going to be looking at again treating pre-symptomatic, but gene mutation carriers and they're actually looking to do something a little different. They want to actually compare three drugs in three small trials together looking at changes on biomarkers and then if one or more is positive that would go into a longer trial to see if it has effects on cognitive functioning because the changes in cognition are much slower. So

we'd want to see first if it has an impact on the biomarkers and then to see if it has an effect on the cognition. Next slide.

The third trial that's in development is the Alzheimer's Prevention Initiative, API, and again this is going to be using individuals who are genetic mutation carriers cognitively normal. And the bulk of the individuals in this study would come from the largest early onset kindred which is in Columbia as well as some individuals from the U.S., but the largest portion is coming from Columbia. The Columbian kindred includes about 5000 people with a sufficient number of individuals who are pre-symptomatic gene carriers so they would be able to actually assess the treatment's effects on the biomarkers and the clinical end points within about two to five years. Next slide.

But for API, it would be a 24-month double blind randomized placebo control trial using the biomarkers that we talked about in cognitive end points. This will be a single drug. If after two years the treatment did not show positive effects on the biomarkers, the trial would be discontinued and then another drug would be looked at. But if the treatment provided to be positive on the biomarkers, they would continue the trial again to look at the cognitive functionings because again that's a much slower change. Next slide please.

Okay. So those are sort of the pre-symptomatic studies for Alzheimer's. Now I'm going to switch to the next target that we talked about earlier and targeting tau.

So as we said, tau seems to be - the tau protein is responsible for the tangles that we see in the brain and it's this hyperphosphorylation of tau that actually seems to lead to the development of the paired helical film -- I'm sorry -- within the neural fibrillary tangles. That's a hallmark of AD pathogenesis. Next slide.

Again so we're looking at the second oval then where we see tangle formation in this process. Next slide.

So although not ignored in the therapeutic target, tau really is not as well developed as amyloid has been and it's getting more attention now than it had and there's a number of types of compounds that look to do things like stabilize and microtubules. It's not really to know all of those. They're listed there if you're interested in finding out more, but the idea is really to affect tau and to prevent the formation of these tangles. Next slide.

And we talked about some other secondary pathways. If you look at this slide, this is just again a graphic showing the oxidation, apoptosis, inflammation, cell death. These are the other areas in addition to TAL and amyloid that are being looked at as treatments for AD. Next slide.

So we know that for example both chronic inflammation and oxidated stress are likely to contribute to degenerative processes and people are still looking at that although I have to say to date the treatments that have been looked at clinically including things like Vitamin E, the B vitamins, etcetera, have not shown effectiveness in human trials. And again it may be that we are simply -- we haven't found the right -- we're not even sure that these in the prior trials have actually hit the target. Are they doing what we think they're doing and also have we hit the right stage. So I think there's still some question marks there. Next slide.

Other things to look at are actually restorative strategies. So can we restore some of the functions to the neurons that have been damaged in an Alzheimer's brain for example. And one of the ways that people are looking at is looking at growth factors and they do seem to - growth factors do influence

neuronal survival and function and they seem to exhibit a broad activity against a number of different toxic mechanisms in the brain. And one of the ways that we can target the growth factors where we want to in the brain is using a gene delivery system. So a gene therapy. Next slide.

So Nerve Growth Factor, NGF, is one of the things that has been looked at. The hypotheses are really that NGF will protect the cholinergic neurons in the brain and the cholinergic system is really involved in things like memory and it's an area that is deteriorated in Alzheimer's Disease and why we see a lot of the cognitive dysfunction. But targeting the cholinergic system may actually benefit the patient. So you wouldn't be necessarily modifying the disease or delaying the disease process itself, but you'd be restoring function to improve quality of life in someone who already has Alzheimer's Disease.

And in fact the NIA is funding a gene therapy trial, AAV NGF, and it's actually being run through our ACDS or Alzheimer's Disease Cooperative Study. It's a phase 2 placebo control trial and it's looking to see if we can actually restore function to degenerating cholinergic neurons and does it have an effect on cognitive function in patients. Next slide.

And Dr. Shah talked a little bit in the part that I'm going to now shift from sort of tau, amyloid, and other protected strategies to talking about risk. You did hear a lot about what risk factors are a modifiable risk and I want to talk about some of the things that people are looking at to intervene on these modifiable risk factors. Next slide.

So you saw a number of these earlier. While age certainly is not really a modifiable risk factor other things are. Certainly blood pressure, cholesterol, diet, exercise. Those are all things that we can actually change because they're

not our genetic risk, they're not our age. But we can certainly have an impact and these may also impact the course of Alzheimer's Disease. Next slide.

The truth of diet and exercise, there have been a number of studies. Many of them are more observational studies and there are actually clinical trials going on too which I will talk about in a minute. But this particular study was a cohort study that looked at 1880 community dwelling older adults who did not have Dementia living in New York. It was actually a study that's done out of Columbia. And they look at how much someone adhered to a Mediterranean style diet and how much someone adhered to being physically active and they actually had a way to measure that. It was through a questionnaire of course. So again this is self report.

And what they did find though in this very large study was that the risk of AD was lower for both people that had higher adherence to a Mediterranean style diet and which is very high in things like olive oil and fish, omega 3, low in saturated fats and sweets. So it's not like the anti-Western diet that many of us do. And also those that were more likely to adhere to being physically active had a lower risk of AD and the thing is that both of these things contributed and contributed independently.

Again that's not a clinical trial saying that, you know, if I give you this amount of exercise to do that will delay your onset of Dementia or decrease your risk. But it is an indication that we may be able to affect some change in these modifiable risk factors that if not completely preventing disease may absolutely may help in terms of brain aging and may help us to, you know, another thing in our arsenal if you will to actually slow the progress of Alzheimer's. Next slide.

In terms of exercise again there are a number of clinical trials that are going now that are still being planned, but this one was done out of Australia and it was 170 community dwellings. So again it's a small study, older adults in Perth who are free of Dementia but they had subjective memory complaints or they had mild cognitive impairment and it was a randomized control trial to either 24 weeks of physical activity that the was the intervention or usual care. So people just went about their normal routines. And those that assessed the cognitive function were blinded to group membership. So obviously the subjects knew which group they were in and many of the investigators did, but those that were doing the assessment so as not to influence that were actually blinded to group membership.

And what the results showed was that there was modest improvement in cognition over 18 months and in fact the effective exercises apparent by six months and persisted at the 12 and 18-month assessments. And so I actually know that this group out of Australia is looking at a larger study now to see if this can be replicated in a much larger sample so. Anyway but again another study suggest that even if you have some memory complaints that you may be able to improve some of your functioning if you engage in exercise so. Next slide.

Another risk factor we know for sure is that people with diabetes are at much higher risk of developing Alzheimer's and so some folks and many investigators are trying to look at this diabetes, Alzheimer's and insulin treatment. And what the slide shows you next is actually a post-mortem study. So they looked at brains in individuals who had diabetes and who were being treated and it was 124 older adults both diabetic and then 124 non-diabetic and they basically found that of the diabetic patients those that were treated with both insulin and another oral diabetic agent had significantly fewer amyloid plagues. As much as 80% fewer than patients who either were not

taking - who were diabetic and took no insulin or other medications or those that only took one. So it suggests basically -- or the non-diabetic control -- so it suggested those that were taking the combination diabetic medication who had potentially had their diabetes controlled showed fewer plagues. So these medications may well have had an impact on Alzheimer's pathology. Next slide please.

So like as I said there are a number of researchers investigating this pathway to Alzheimer's and we have actually funded a number of small pilot trials. One and I'm going to talk more about this one in a minute is looking at intranasal insulin, giving that as a treatment, and what the effects are on cognition. That one is completed.

The other two are looking at other influence sensitizing agents. One is Pioglitzaone as well as exercise on individuals who have mild cognitive impairment and something called metabolic syndrome which involves an insulin resistance, high blood pressure, and other cardiovascular symptoms.

And another trial looking at Metformin which is a diabetic treatment effects on cognition and brain metabolism in those who are overweight or obese with MCI. Again looking if we can treat this potential disease pathway. Next slide please.

So the intranasal trial, it's based on the hypothesis that restoring normal insulin function in the brain may provide therapeutic benefit to those with AD. So the SNIFF-120 trial was a four-month randomized double blind trial of placebo versus two doses of intranasal insulin either 20 or 40 IUs. There were 104 patients and they had either Alzheimer's Disease or amnestic MCI and people with diabetes were excluded. So this was not a diabetic population.

The results show that the 20 IU doses of insulin actually had for delayed story recall -- so memory, delayed memory -- was significantly improved in those who had taken the 20 IUs compared to placebo and also their functional status was improved. These improvements persisted for two months after the treatment ended and in addition to the memory improvement they had an improved biomarker profile and also showing improvement in glucose metabolism showing a sign of better (runnel) function on FDG PET. That was in a subset of patients, but again this was a small study only 104 subjects. And actually Dr. Craft who was the lead researcher on this and our colleagues are actually planning to do a larger study in looking at this. But, you know, it's promising small study so we can't - again it's not the large phase 3 study that we need, but it is another indication that this is another pathway we may be able to use to treat Alzheimer's Disease.

So I want to go now to talk about another aspect of Alzheimer's that is sometimes neglected, but is important for treatment as well and that is the neuropsychiatric symptoms for Alzheimer's because this is again part of the whole spectrum of the disease.

The neuropsychiatric symptoms in AD are things like depression and apathy, sleep disturbance, anxiety, agitation, aggression, and even in psychosis. Next slide please.

And the prevalence of the symptoms is actually fairly high. It varies from about 60% of individuals in population-based studies so more in the community up to about 92% in clinical samples - those that are coming into the clinic to be seen. Next slide.

The symptoms are often multiple and simultaneous. You can have more than one. They contribute obviously to patient distress, but also to caregiver

distress and burden. They increase medical care and cost and often this is what precipitates someone being put into a nursing home. While you may be able to work around a memory problem, it's much more difficult if someone is wandering at night or they're agitated, if they're throwing things. So these are the symptoms that will get someone placed into a nursing home more likely than those - than the state of memory problem. And these symptoms tend to increase in prevalent severity as the disease progresses. And it's interesting that in individuals that have these neuropsychiatric symptoms, they seem to have a more rapid cognitive decline as well. Next slide please.

Amy Wiatr: Laurie, this is Amy. I just wanted to interrupt. I'm so sorry and let you know that unfortunately it looks like the Internet connection has been lost.

Dr. Laurie Ryan: Oh okay.

((Crosstalk))

Amy Wiatr: So for folks...

((Crosstalk))

Dr. Laurie Ryan: I was done anyway. (Unintelligible) the last couple of slides so.

Amy Wiatr: Right. They all will be posted.

Dr. Laurie Ryan: Okay.

Amy Wiatr: Again my apologies.

Dr. Laurie Ryan: No that's okay.

Amy Wiatr: And I just wanted to note too that we are coming to the end of our time...

((Crosstalk))

Amy Wiatr: ...right now.

Dr. Laurie Ryan: Yes.

Amy Wiatr: So, but if you want to kind of wrap up a little bit and we will do our best. And so sorry about that.

Dr. Laurie Ryan: Sure. Not a problem. So to wrap up about the neuropsychiatric symptoms of AD what you would have seen if you were on the webinar is that we really don't have any approved medications and that's much of what is used for standard psychiatric disorders and is off label. But some of these can have pretty significant side effects and one of the things people are looking at is non-pharmacologic interventions which really should be done first although they're much more labor intensive.

And finally what I wanted to end up with too is that in terms of AD treatment, we're probably going to be looking at down the road a combination of therapies for many people that, you know, depending on your own risk you may get a number of different treatments. It might be exercise plus an anti-amyloid, plus tau. So we're really going to be probably looking at a cocktail approach for AD. Okay.

Amy Wiatr: All right. Thank you so much Laurie. What I'm going to do is just finish up a little bit and I'm just going to be very abbreviated and note that we do have some information on some sources for more information on where you can

learn more information on Alzheimer's Disease and related stuff and to kind of plug the next two webinars that we have in our series. Hopefully we will be ironing out the errors that we had - the technical difficulties that we had on those coming up. But I'm not sure if our operator is there. I don't know if we're able to stay on the line a little bit and just see if we have any questions out there.

Coordinator: Yes thank you. If you would like to ask a question, please press star then 1. You will be prompted to record your first and last name. Please remember to unmute your phone. If you want to withdraw a question, you may press star 2. Once again to ask a question or make a comment, please press star then 1. One moment please.

Amy Wiatr: Wonderful. And again this is Amy. While we're waiting for any questions to queue up, I do just want to again remind you that we've got the webinar 2 in the series will be June 13. The same time 1:30 to 3:00 Eastern and that will be Online Tools and Resources to Assist Individuals with Dementia and Caregivers, talking about the National Alzheimer's Contact Center, Eldercare Locator, and ADEAR which is the Alzheimer's Disease Education and Referral Center.

Webinar 3 will be Thursday, July 12. Again the same time. And that will be talking about Connecting the Aging Network, Individuals with Dementia and Caregivers with Research Opportunities. And so I think that will be an especially interesting call for those of you that got to hear from Drs. Weintraub, ShaH, and Ryan about all the stuff that's going on research wise and how everything comes together to try to come up with some, you know, better treatments and interventions for people with Dementia and their caregivers. We'll pause and see with the operator. Do we have any questions?

Coordinator: Yes, we do have one question.

Amy Wiatr: Okay.

Coordinator: If you did queue up to ask a question, please check your mute button. Your line is open. Please go ahead.

Woman: Hi. Can you hear me?

Amy Wiatr: Yes.

Coordinator: Please go ahead.

Woman: Okay excellent. Thank you. Well I just have a question about environmental factors. Often when I'm out speaking about what Alzheimer's is and things like people are more interested in - people want to know is it only genetics? Can they control their environment to try and help with their risk factors. And I talk to them about healthy eating and their heart and things like that, but when it actually comes to I don't know do you live near a nuclear plant, you know, people ask me these things. I'm kind of lost at what to respond with. Is there - does anybody have guidance on that or am I completely off topic in asking that with this particular workshop?

Amy Wiatr: Who wants to take that?

Dr. Raj Shah: Maybe I can start...

Amy Wiatr: Sure.

Dr. Raj Shah: ...a little bit. So this is Raj Shah. So thank you for that question. It's actually very relevant to what we're discussing because it's what people are experiencing and asking about in the community. So I think we're understanding that Dementia and Dementia due to Alzheimer's Disease is the mix of genetics, lifestyle choices, environment, and they're all interacting to produce the disease.

We have some information about environment, but it's still not as strong as we'd hoped for it to be. You know, to my recollection there's - I mean a newer piece that came out recently that looked at sort of air pollution and its potential affect on risk for developing cognitive difficulties. I think there are some factors that people always ask about that have stayed about 30 years about aluminum and more than not we're not finding aluminum to be associated with the development of Alzheimer's Disease. But I do think it's an area we still need to do some more. Environment probably does play a factor and we just have to get better at delineating what some of those factors may be.

Amy Wiatr: Thank you so much.

((Crosstalk))

Amy Wiatr: Hopefully that helps to answer your question.

Woman: Yes thank you.

Coordinator: Once again if you would like to ask a question, please press star then 1.

Amy Wiatr: Do we have any other questions in the queue?

Coordinator: We have no questions at this time. It does take about 15 seconds for somebody to come up in the queue.

Amy Wiatr: Okay. I'll just while we're waiting to see if there are any other questions, I do realize that we're over time already. But as you can see, we had such wonderful speakers and so much information to share. I hope it was a good opportunity for you all. We are going to be posting the slides, a transcript, and the audio recording for this webinar. It will be on our AOA Web site within hopefully a week or so and it will be - you should also be receiving an email for those of you who registered. You should be receiving an email after this giving you the link, but it will be on the AOA Web site under the section of our Web site that is about Alzheimer's Disease.

So if you do have any questions or can't find it, or don't get that email you can also email me directly at Amy, that's A-M-Y, dot Wiatr, W-I-A-T-R @aoa.hhs.gov. Additionally if you have any other feedback that you'd like to share whether this webinar was helpful to you or if you have any suggestions for future webinar topics, we do want these webinars to be as useful to you as possible so we welcome your suggestions and your constructive criticism to help us do even better. I'll check one more time to see if we have any other questions.

Coordinator: Yes. At this time we have two questions.

Amy Wiatr: Okay.

Coordinator: Our next question is from (Cynthia).

(Cynthia): Yes, my question is concerning medications. Families have asked me when should they stop medicating with any of the anti-senility medications. I've

heard some different answers in the past. One of them being that as long as the patient's ambulatory to continue them on those medications if there's no other adverse effects. I'd like to have your thoughts on that please.

Dr. Raj Shah: This is Dr. Shah again. I guess I can field that. So it's an important question. We get asked about this in the clinic all the time, you know, from family members, you know, when they should stop or should they consider stopping the medication. And, you know, the struggle is is that most studies don't look at that. They don't look at, you know, if you can actually stop a medication or what the effects of stopping the medication are.

And so it becomes, you know, with imperfect information it does really become a conversation about what are we expecting from the medication, you know, what are we hoping for the quality of life of the individual that may be on the medication, what might be other alternatives to use the money that we're spending on the medications for other services. And we have to use, you know, sort of imperfect information to help (come) with the clinical judgment.

So I don't think there's an exact answer and I think the main thing is that it's an opening for a conversation and that's a lot of what we do in medicine is just having conversations with patients and their families to really at that point in time decide what is the best alternative for them.

(Cynthia): Thank you so much. I appreciate that answer.

Amy Wiatr: All right. And we'll take -- this is Amy -- we'll take one last question.

Coordinator: Our last question comes from (Suzanne).

(Suzanne): I wanted to say it was such a great webinar until we lost Internet service and I really learned a lot. But my question is is there or was there a study going on using aspirin as a possible potential delayer of Dementia or preventer?

Dr. Laurie Ryan: Hi, this is Dr. Ryan. Yes, I think I can answer it. There is currently a very large aspirin trial and it's looking primarily at cardiovascular outcomes, but as a secondary outcome they're also looking at the potential impact on cognitive functioning and risk of Dementia.

(Suzanne): Okay. Thank you.

Dr. Laurie Ryan: You're welcome.

Amy Wiatr: Wonderful. Well with that, I do want to wrap up today's webinar. I want to especially thank all of our wonderful speakers. Thank all of you who attended, and again apologies for the glitches there. And thank you to those of you who asked the questions just now. Again thank you. We look forward to having you with us in future webinars and with that we'll conclude today's webinar. Thank you.

Woman: Thanks.

Coordinator: Thank you for participating in today's conference. You may disconnect at this time.

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