In this lecture I'm going to talk about the development of the new diagnostic criteria for dementia, I’m going to also present some information about epidemiology risk factors, what constitute dementia workup, the use of biomarkers and treatments, some future treatments for Alzheimer's disease.

This is just to show that we had an old diagnostic criteria for dementia, it was DSM-IV and basically was based on the presence of a memory impairment plus some other area of the cognition impaired. For example language, executive functions, but one of the criticisms that we had with those criteria was that it was memory-centric so memory had to be impaired in order to diagnose dementia, but what we have learned over the time is that some people can meet criteria for dementia without having a memory impairment.

So that is why we have the new criteria for dementia, and it's basically similar to the DSM-IV. This new criteria was proposed by the National Institute on Aging and the Alzheimer's Association and they require the loss of intellectual abilities of sufficient severity to interfere with social and occupational functioning, and the criteria specifies that two domains, two cognitive domains must be impaired, not necessarily memory. One of the problems with these new criteria is that psychiatric symptoms can be considered a domain, so this means that if they have language problems and touch of depression by definition I am going to be - I am going to make criteria for dementia. So we are expecting the new criteria which are going to replace this one, so most likely within the next year or 2 years we will have new diagnostic criteria for dementia. But the most important thing is this issue of having two areas of the cognition impaired and we have used these criteria for the past 20 years in
our center and if you apply the traditional criteria, the memory based or the no memory based criteria in a population we miss 9% of the dementias. So that's why I think the criterias are moving in the right direction so they are moving away of this memory centric definition to a more flexible definition and I think that is what is going to end up in the next 2 or 3 years. But I wanted to let you know that the whole - something basic which is the concept of dementia is under a great deal of transformation now.

And I'm not going to talk here about the DSM-5, the DSM-5 uses a completely different approach, they use the approach of mild neurocognitive impairment and major neurocognitive impairment and that would be another big issue, but within the next 2 or 3 years what we are going to see is a big transformation in the definitions of dementia.

So this is the diagnostic criteria for Alzheimer's disease and basically for the diagnosis of Alzheimer's disease dementia must be present. The progression of symptoms must be gradual and they - so they stratify the certainty of the diagnosis as probable and possible. So probable is when Alzheimer's disease is there and nothing else would explain the cognitive problems. And possible is when we think that Alzheimer's disease is there and there is something else going on that can also affect cognition, for example it could be a person that has progressive cognitive problems and at one point has a stroke. So what you see here is the Alzheimer's disease causing the dementia and the vascular disease contributing. So by that case it can be classified as possible Alzheimer's disease.
The new criteria are bringing the biomarkers, CSF, PET, MRI, but they recommended the use of biomarkers for research purposes and in isolated clinical cases. So the biomarkers now in the definition of dementia are only required to use it in research and the research environment.

So in terms of the epidemiology of Alzheimer's disease and dementia we can say that 60 to 85% of the Alzheimer's disease is the cause of 60 to 80% of the dementias in people age 65 and older. Approximately 10% of the people aged 65 and older have Alzheimer's disease. Half of the population 85 and older may have Alzheimer's disease and the World Alzheimer's Report estimates that there are 35.6 million people living with Alzheimer's disease worldwide, and about 5 million in the United States and there is one new case of dementia diagnosed every 7 seconds worldwide and one every 68 seconds in the United States. And there will be approximately 115 million patients with Alzheimer's disease by 2030 worldwide and approximately 11 to 13 million in the United States. So if we don't find a cure, if we don't find something that can slow the conversion from normal to Alzheimer's disease this is going to have a tremendous impact on society and in the American system, and we are seeing that now.

And this is just to show you the prevalence, this is from the Cardiovascular Health Study, this was a large epidemiological study that was done here in Pittsburgh and as well as in Wake Forest, Johns Hopkins and UC Davis. We examined 3600 individuals in the four communities and we identified 770 dementia cases. And you can see that practically half of the population after age 85 met criteria for dementia. More women than men and that after age 85 that is the usual finding and the reason is that women live about 5 to 7 years more than men, so since age is the most important risk factor so
what we are detecting here is just basically the age effect. And just there are some studies that says after age 90 the dementia stops people, if you make it to age 90 then you are safe. What we are seeing now is after age 90 the incidence continues to progress and in this study here in Pittsburgh out of 1400 participants that we recruited in 1989 after - between age, today between age, those that survived and are age between 95 and 100 only 16 are cognitively healthy.

So these are when I talk structural lesions in Alzheimer's disease everything is at microscopic level. If you do an MRI or a CT scan you won't see anything, you will see just atrophy. The most important lesions are the deposition of amyloid proteins, senile plaques, neurofibrillary tangles, they amyloid, the position is outside the neurons and the tau proteins are being deposited into the neurons. So you have neurons are being destroyed basically from inside and from outside. There is synaptic degeneration, neuronal loss and 90% of the basal forebrain cholinergic neurons disappear and that's why - that's the medications that we have now for Alzheimer's disease are cholinesterase inhibitors because the cholinergic system is vulnerable to the disease. Half of the patients have cortical Lewy bodies and the Lewy bodies are the hallmark of Parkinson disease. So it's a marker, another marker of neurodegeneration. 30% of these patients have cortical TDP-43 and that is a protein that is linked to frontotemporal dementia. So basically every marker of neurodegeneration can be found in the brain of a patient with Alzheimer's disease. There are some other changes like free radical formation, inflammation, glutamate dysfunction, practically the neurotransmitter systems are affected but mainly at the end of the disease.
So this is just to show you the - how is the progression of Alzheimer's disease and what you can see in the upper part of the slide, what you see in blue is normal volume. And what you can see in gray is atrophy. And these are patients with I would say moderate Alzheimer's disease. And you can see the - so this is the - this is compared to normal people. You can see this is the temporal lobe, the parietal lobe and you can see how within a short period of time how the brain is shrinking. And this is the dorsolateral, prefrontal cortex, temporal cortex and parietal cortex and these are people with Alzheimer's disease, so the disease is there, it's progressing and you can see using these sophisticated techniques you can identify progression within a relatively short period of time. This is a neurofibrillary tangle, remember I mentioned before that these are the tau proteins and these are plaques, these are senile plaques, this is amyloid. Around the plaque normally we see inflammation, and that's why there were so many drug trials using antiinflammatories to prevent or to treat Alzheimer's disease. All of them were negative. But we have inflammation around the plaque and this is a Lewy body.

So what are the risk factors for Alzheimer's disease? I would say that the most important risk factor is age, and the older we are the greater the risk. The APOE-4 allele which is a genetic marker explains only 20% of the cases. And we call that probable risk factors. Something which is possible that was as I mentioned before women, but women can be explained by age. Cerebrovascular disease is a very hot topic now and we are doing many studies to understand the relationship between amyloid and cerebrovascular disease. A history of head trauma but within 10 years of the onset of symptoms. Family history of dementia, family history of Down's syndrome, but I would say of the possible risk factors cerebral vascular disease is the most important.
And then we have something that we call protective factors. And what we are detecting there is a lifestyle. For example moderate alcohol intake, and that has been found in many populations around the world. If you are in France 4 glasses of red wine per day is enough. So Mediterranean diet, if you live in the Bronx but if you live in Mediterranean countries your risk is exactly the same as in the United States. And one of the things that you see in all the Mediterranean countries that they eat very healthy but the salt intake is huge. So the hypertensive cardiomyopathy is very prevalent in those populations.

Physical activity, cognitive activity, but what you see here is a sort of a lifestyle. So if you go to - I mean when you drive around and you see all these, any park in Pittsburgh and you see old people in general they are walking 2 or 3 together, most likely they are having - because they talk so they have some cognitive activity, then they go to a restaurant. They read about healthy foods, so it's a whole lifestyle that is protective. It's not that this - that's why many studies are picking up this through wine or through diet, but it's a sort of a healthy lifestyle that is helping people to stay in good shape. It doesn't mean that you are going to be safe if you stop drinking wine, but at least this healthy lifestyle can delay the onset of Alzheimer's disease. Alzheimer's disease will be there, but it can be there later.

So this just another study that we did, this was done by one of our medical students. We tried just to - since age is the most important risk factor we correlate age with gray matter volume. And you can see here that age has no mercy with the brain. It's going to happen to me, it's going to happen to
everybody. You can see here that these are the heteromeral association areas in the parietal lobes, frontal lobes, temporal lobes, the primary sensory and motor areas and the cerebellum. So the age is affecting infratentorial, supratentorial areas, primary sensory and motor areas and heteromeral association areas. And that is what creates the vulnerability for the disease. So the gray matter is shrinking and it makes the brain vulnerable for the neurodegeneration.

So in addition to age we have hypertension for example, and for example hypertension is in red here. Those are the areas that affect this gray - this is gray matter volume affected by hypertension. Normally hypertension correlates with white matter lesions in the brain and what we see here is the projection of hypertension and white matter lesions in gray matter. And you can see in green is gray matter, especially in the frontal regions, and you can see hypertension affecting these posterior areas of the brain and in some places they overlap. You have this age effect and in addition to the age effect you have all these bad things that can happen as we age. And that's why hypertension and just you see here the example of hypertension because it's a risk factor for Alzheimer's disease. And we can talk more about this later.

Now the good news, and this is physical activity in the cardiovascular health study we measure physical activities in 1990-91, the relationship to gray matter volume in 1998-99 and what we found is that people that walk 72 blocks or more per week had better volumes in the prefrontal cortex, this is the prefrontal cortex, temporal lobes and this is the hippocampus, we also notice some especially in this group of 72 blocks per week. One thing that we did because we did this in 1998-99 we followed these individuals up to the year 2005 and what we noticed is those who walk more than 72
blocks per week in 1991 that had good brain volume in 1998 had a decreased risk of converting to Alzheimer's disease in 2005. So again we are going back to this healthy lifestyle and basically this is physical activity.

Then this is more a more recent paper was published about a month ago where we tried to just going back to lifestyles and this is another good news, this is the main effect of weekly to daily baked or broiled fish consumption on gray matter. We tried with fried fish and we couldn't find any association. What is interesting is baked and broiled fish and you can see it has a very interesting effect on gray matter after controlling for many variables. The other thing that we found is a strong association between the classic antioxidant and fish consumption in this population. In the paper we discuss this issue, it looks like sort of a magic thing that if you eat fish your brain could be better, everything relates to this healthy lifestyle and that also socioeconomic level is here because if you are going - you go to Giant Eagle and you are going to buy salmon or fish most likely you will spend about 40 bucks or more. So socioeconomic level also has an impact here.

What is interesting is that the levels of antioxidants are higher in our population here than in Iceland where in Iceland people eat fish every day. So one thing that we may be picking up here is that in addition to eating fish these people are also taking multivitamins and antioxidants and the omega-3 so one of the things that we are learning from this is this whole concept of aging is extremely difficult to understand because of these competing risks. For example you have a person with hypertension which could be a very strong predictor of dementia but that person is also exercising, so that is a competing risk factor. So we are moving now, doing more study of statistical analysis to
try to understand that but overall I would say the most important thing is that a healthy lifestyle has an effect on protection. It won't stop the disease but it will help a person to stay at least 2 or 3 years without developing Alzheimer's disease.

So once that we have a person with dementia how do we approach to that person? The most important piece of information will come from the family, so we interview the family and we can interview the patient, we have to access cognition, evaluate the functional activities, a physical exam is important just to detect Parkinsonism. It's a classic laboratory test like we have to order a TSH, a vitamin B12, a CT or MRI just to rule out structural lesions. This would be something that we always have to do to diagnose dementia. Then if you want you can do a lumbar puncture if you feel that there is an infectious process, EEG if you feel that there are seizures, SPECT and PET scans, more cognitive testing and HIV testing because HIV can also affect cognition especially in younger individuals.

So this is just to give you an idea, we always like to look at the MRI as sort of the classic study that when we deal with a person with Alzheimer's disease, and you can see here you don't see anything except some atrophy here in the temporal lobes but this is - I would say this could be normal, it could be what we see in a normal person. Then the FDG-PET you cal order an FDG-PET and that is something that we have been using since 1987 and the classic picture and the classic report that you would get from the (inaudible) is that this is a posterior dementia because of the temporal parietal hypometabolism and they would say it is a posterior dementia consistent with Alzheimer's disease, that would be the report that you would get from the radiologist.
Now we have here this was the Pittsburgh compound B was invented here by our colleague Bill Klunk. We can detect amyloid, the amyloid plaque can be detected using positron emission technology techniques. And you can see here in the frontal lobes this is precuneus, the anterior cingulate gyrus. This is a carbone based compound, so this is not what you can order normally now, they are fluor compounds that were approved by the FDA so if one of your patients asks you for an Alzheimer's disease test you can order this, the test, the insurance companies won't pay for that, they cost about 3 to $4,000 and in some states I heard that some people are charging about $8000 for the scan. The recent why insurance companies and Medicare are not paying for the test is they said because there is no cure, so what's the point to detect amyloid seeing as there is - I cannot give you medication that will revert the symptoms. So but there are three compounds approved by the FDA, they are not - none insurance company in the country would pay for that, and this is happening all over the world.

But the other thing that is important because when you order this the radiologist is going to tell you this is either positive or negative scan. The gold standard of the amyloid ligands is the PIB. The PIB is 20% more sensitive than the fluid compounds. So this creates another problem. If they tell you that this is a negative scan but you know that you may be in that 20% that is not picked up by that scan so we still need to learn more about how to use these technologies and this has - if you put it in context the PIB was invented in 2004 so this is a recent event. We are moving very fast but we need - we need to learn more how to use these technologies.
So in terms of biomarkers you can see here the 75 to 90 - if we do the - if you see the - you use just the clinical diagnosis, you follow all the steps to make a diagnosis the sensitivity is 98%. This is when we say that the person has a disease and when the person dies and we have the brain we are right. Specificity is when we say the person doesn't have the disease and when the person dies doesn't have the disease. You can for example a CSF and especially looking for the beta 42 levels and the idea is that the amyloid, the beta 42 has been deposited in the brain, in the plaque that I showed you, so in the SCF you are going to have low levels of beta 42. And the tau protein is going to be high because the tau protein is going to be deposited inside the neuron. Neurons are being destroyed and they are releasing tau proteins so what you expect to see in the CSF is low levels of beta 42 with high levels of tau.

There are some other markers, the FDG-PET is about - you can see here is 95% sensitivity, 74% specificity. The FDG-PET you can order there are many places in town that they can do FDG-PET, there is a great deal of experience with radiologists since this technology has been around since 1987. In terms of amyloid ligands this is the AV-45 which was the first one approved by the FDA. They did only one study. In order to get the FDA approval they went to a nursing home and those patients with Alzheimer's disease that were very close to dying they convinced them to have a PET scan and when they died they got the scan of the brain. And they did it with 26 patients and that was enough to get the FDA approval.

We know we are developing tau ligands, remember I showed you the tau proteins are inside the brain. We have now 4 tau ligands and that is going to be a hot issue in the next 4 to 5 years because
tau is also present in progressive supranuclear palsy, in multisystem atrophy, there are many diseases that are tauopathies and this technology is going to help a lot to diagnose those cases. So this is starting, we don't know the sensitivity or specificity. Plasma beta 42 you can detect - there are no - there are very few laboratories that can do that. This is a big problem with plasma beta 42, it's associated with (inaudible) and with glomerular function. So if you don't - if your kidney is not working okay your plasma beta 42 can be high. And markers of inflammation there are many studies that show markers of inflammation but I don't think that we understand very well how to use the markers or inflammation in Alzheimer's disease. Everything is at the experimental level. But CSF I would say CSF studies using beta 42 and tau proteins, this is commercially available. There are many laboratories doing that and if you have a patient who wants to have a spinal tap you can order a CSF study. Some insurance companies won't pay for the study and it would cost in the range of $700 to $1200.

So how we move now into the treatment of Alzheimer's disease and what we - how we put together pathology and clinical symptoms and treatment. So in terms of pathology there is a genetic predisposition. There are some people who will never develop Alzheimer's disease and some people who will develop. Age is a critical factor, there are some environmental factors, all these factors are leading to the presence of neurofibrillary tangles, amyloid plaques Lewy bodies, there is inflammation, oxidative stress, mitochondrial dysfunction and finally neuronal death. So if we - we want to prevent Alzheimer's disease and use a primary prevention treatment is when we use it when a person does not have the pathology. So a primary prevention would be something that we give to
the patients and they will never develop the pathology. And I hope that one day we can have something like this.

A secondary prevention is when the symptoms start to show up and people develop something called mild cognitive impairment. The pathology is there and you give something to the patients and the disease will develop later. They will develop the disease, the clinical symptoms but this will happen later than as if the patient would never taken the medication. And at this point what we have symptomatic treatment, and we are testing many disease modifying treatments. So once the dementia is there the only treatments that we have are symptomatic treatment, that's the so-called the Aricept, the Exelon, the Razadyne, the Namenda, all these are symptomatic treatments that we are using here. So all the studies of prevention trials using the cholinesterase inhibitors trying to as secondary prevention fail.

So these are all the medications that we have and you can see here Tacrine was approved and was - this is the classic cholinesterase inhibitors in 1993, Memantine was approved in 2003. So within a decade we have 5 medications but the last medication approved by the FDA for Alzheimer's disease was more than a decade ago.

So this is what we have now. What can we offer to our patients? We can offer just as a combination of Memantine with a cholinesterase inhibitor, this it the study published by Pierre Tariot in JAMA in 2004 and you can see the - I don't know if you can see it here, you can see in blue here the people using a combination versus those that were taking placebo and Donepezil alone. So and this was
done in people that were in the moderate to severe stages of the disease. So you can see the effect of the combination therapy and the follow-up is - it was approximately 24 weeks.

So but the question is and you will see this all the compounds for Alzheimer's disease when you read the package insert and you see this nice graphic showing the difference between placebo and control all these studies were done within 28 or 24 weeks. So it's a very short period of time. You show that those medications are having an effect, they improve cognition so hey are efficacious and they are not killing people, that's why you need to get the FDA approval. There are many studies that said okay well these medications they effect less for one year because there are many studies that show that the effect persists after one year. But it's not they persist, there is nothing biological related to one year, it's because the studies were funded for one year. So the one year factor has nothing to do with biology, it has to where because the studies were funded for one year. But what I would like to know and the things that we have been studying is this long term response, is what happened after one year and in a disease that may last up to 20 years. I'm sure that you have seen patients with Alzheimer's disease for - with the disease for more than 20 years, so that's what we are trying to determine, whether if these medications have a long term effect.

So there are many studies that all these studies by the industry they try to do that in some ways, they tried to go for many months and this is the study with Galantamine. and this is the - this was the 6 months, this was the placebo controlled study that they used for approval with the FDA. And but here everybody was put on the medication. So what they did, they projected this over time. They said okay, this would be - these people would be doing - the people on the medication would do
better than this group in the long term, but this is a hypothetical projection. And the other problem is that all these studies they lose people, so for example this study after 1 year follow-up they lost 60% of the patients. So you start losing study statistical power and it's very difficult to really demonstrate this long term effect.

And this was a Scandinavian study and they did a very interesting study. At one year they were able to keep about 70% of the people in the study. And they were able to show there was some degree, I would say marginal, marginal difference between the two groups once the control was put on medication. And they - you remember the time when Pfizer was advertising this Donepezil, they were saying that you need to put people the sooner the better because if you wait you will never do - these people will never do as well as - and in some ways this is what they showed. I mean it's the only study that tested that, that if you - people that are in the placebo controlled, you put them on medication here they never reach the level of those who started from the beginning with the medication. But this is the only study that was done to show that, that showed that. And the only study done to show that.

So for what we are doing is we try to go beyond that and we are trying to - we are trying to examine the effect of medication. This is once we are trying to determine time to reach the four cardinal endpoints of the disease. And the four cardinal endpoints of the disease are when a person, the time that it takes a person to reach the severest stages of the disease, the time to reach the severe function of the stages, time to reach nursing home admission or in a state in which they will have to go to a nursing home and time to death.
One thing that we found is just people did this in the year 2002. And one of the important things that we had in this study and why it is so difficult to do these studies is the group that never used medication. At this point I would say comparing people with or without medication is practically impossible because everybody has been exposed to medication at one point, or will be exposed to medication. So what we use here, we use our database and we were able to compare people on medication versus those using without medication and we noticed that those taking cholinesterase inhibitors, any, had a decreased risk of going to a nursing home. That's doesn't mean that you won't go to a nursing home, the risk is decreased. And we didn't find any association with time to death.

This is just it's very important because there is a paper published this year from the VA that showed that people taking cholinesterase inhibitors had decreased risk of dying and that's just - you have to be very careful when you read those things because in the paper that we publish we always control for the factors that are associated with mortality, so you need to take into account hypertension, diabetes, heart disease, all those are things that can affect mortality. If you don't take into account those factors most likely you will find this association between successful survivorship and use of medication. But we didn't see that when we put in the model all these other risk factors. And this has been also, the industry did the same thing. This was in - remember we did the first study in 2002 in our database and then Johnson and Johnson did it in 2009 and Pfizer did it in 2004.

So then in 2009 we tested whether the use of Memantine plus cholinesterase inhibitors did - whether the combination therapy had better effect in terms of nursing home admission, and we found out.
We found that people using the combination therapy did much better than those taking cholinesterase inhibitors alone versus those who were never treated. These studies although we look at this in many ways and we couldn't - the results were always there. One thing that I won't say it worries me but is something that we have to take into account because we used a database that you can see there, we followed people for almost 20 years. And there is something called temporal trend. The temporal trend is that when you put all these people in the analysis and you use people for example for the 1990, early 1990 and patients from the year 2000 there is a temporal trend. For example, statins. Statins were - had a tremendous effect on cardiovascular function and we started using statins in the mid-90s. So all these factors that we call temporal trends are difficult to control in these studies. We do our work best, we found this which seems to be a trend, but I'm not sure if somebody can come up with a magic formula that can fix this problem.

So, so far what we have we can say that with the medications that we have is something called compression of morbidity. So this would be the typical course of the disease and with the medications that we have we expand a little bit, we modify the course of the dementia. So we improve function in some ways, but people die at the same rate. So better function but not increase of morbidity. That's what we call compression of morbidity.

A few words - I'm going to just - so, so far we can say that there are no new medications for Alzheimer's disease since 2003. We say that there is a clinical meaningful alteration of the natural history of Alzheimer's disease by current dementia medications. Patients taking cholinesterase inhibitors alone or in combination with Memantine were less likely to be admitted to a nursing home
during a follow-up versus untreated patients. The combination therapy offers a 3.4 reduction in nursing home placement versus cholinesterase inhibitors alone. There was no association between medication use and time to death and we hope that in the future we can have better treatments and we can have good disease modified treatments that can really be useful. Thank you.