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Kendal Williams (Host): Welcome, everyone, to the Penn Primary Care Podcast. I'm your host, Dr. Kendal Williams. Well, welcome to the second part of our discussion of cognitive impairment with Dr. Jason Karlawish. Dr. Karlawish is a Professor of Medicine at Penn. He's the co-director of the Penn Memory center. And I'd like to welcome Jason back. Thanks for coming, Jason.

Dr Jason Karlawish: Great to be back, Kendal.

Host: So last time, we talked about the clinical evaluation of cognitive impairment. And Jason took us through this brilliant description of how he goes through the evaluation of memory, language, space orientation, executive function, mood, all of those aspects of cognitive evaluation. And we talked about the common dementias: frontotemporal dementia, Lewy body disease, Parkinson's-associated dementia, NPH. But we didn't spend a lot of time on the most common cause of dementia in this country, and that's Alzheimer's disease. And the reason we did that is because we really wanted to come back and give it its own time, a full program, if you will.

So, there's a lot going on in this space and there's a lot going on. You see articles in the New England Journal and new drugs that have come out and so forth. And I think for many of us, we need to go back and kind of understand where the science is at. And then, we can move forward into discussing the clinical aspects and some of the newer drugs. But I think for many of us, there's been such advances in the understanding of the pathophysiology on a molecular basis and also a lot of new imaging advances as well.

So, we're going to start there. Jason, let's start with why does Alzheimer's disease occur? What's happening in the brain? What is the abnormality here?

Dr Jason Karlawish: So, Alzheimer's disease is one of several different neurodegenerative diseases. And the common theme is that neurons are becoming dysfunctional and dying, different than cancer, where a cell is growing out of control and, therefore, destroying other cells, for example. In the case of Alzheimer's, the reason why the neurons are becoming dysfunctional and dying is because at least two proteins are misfolding, beta amyloid and tau protein. And when a neuropathologist looks at a brain and sees a certain density of amyloid plaques entangles of tau, he or she will say, "This is the pathology of Alzheimer's disease," along with evidence of neuron loss, neurodegeneration; frankly, ghost neurons, dead neurons. So, beta amyloid plaques tangles of Tau

protein and evidence of neurodegeneration. Those are the sort of three things, which put together, have a pathologist say, "This looks like Alzheimer's disease."

Host: Why does it happen?

Dr Jason Karlawish: Well, the incident early events remain a mystery, but beta amyloid plaques start to form, Tau tangles start to form. And once Tau tangles are forming, together with beta amyloid, that's when clinical signs and symptoms begin to appear. Now, of course, the question of the century is, is beta amyloid plaque accumulation the incident event? Some argue vociferously, they say yes. I argue the evidence is provocative, but we're not yet there to say that we can define the disease on the basis of beta amyloid alone. We may arrive at that point, but I think the data still are not clear and convincing, which is what I think we would need.

Having said that, though, we've implicated a number of genes, for example. There's a rare set of dominant genes, rare meaning not very prevalent in the population, in whom people who carry those genes, if they live long enough, are going to develop the pathology. For the average individual, that is to say the majority of patients, 95% of the cases, that's not the case. There are genes that have been implicated. But honestly, Kendal, we really can't pinpoint a cause, but rather I think many of us think that there are probably causes to why these proteins start to misfold and, therefore, lead to neurodegeneration.

Host: Is it a mutational event similar to the accumulated mutations that lead to cancer?

Dr Jason Karlawish: In the dominant forms, it is, yes. In the late-onset forms where APOE genotypes have been particularly implicated, particularly APOE4 gene. The issue isn't a mutation. There's something that happens with the way the amyloid precursor protein is processed. Amyloid precursor protein exists normally in the cell wall of a neuron, and something happens that causes it to be cleaved in the wrong place. And that cleavage then leads to fibrils, which become oligomers, which ultimately become the plaques. We're getting into the weeds, but these are weeds I think clinicians are going to start to get into. We see the plaques, and we say that's Alzheimer's, along with tangles. The plaques, though, may be sort of the residua of what was actually the toxic event, which was the oligomers, the toxic oligomers and/or the fibrils. The drugs that are coming out give us some evidence around that, but it's mixed evidence. One drug targets oligomers, the other more goes after the plaques. So, this is a work

in progress as to what exactly is the pathologic cascade, what is the incident event, what along the way are the events.

Others, by the way, have implicated dysfunctions in astrocytes and related glial cells in the brain as being potentially having a role in the pathology. I think it's early days and it's good early days, meaning we know what we need to know and what we don't know, comparable to cardiovascular disease, where there were a host of things we talk about now readily that back in the '70s and '80s weren't talked about as pathophysiologic processes that lead to plaques and other events in the heart and brain and whatnot that cause cardiovascular disease.

Host: But everybody's going to have amyloid beta and tau protein as sort of a manifestation of the disease, right?

Dr Jason Karlawish: Well, if you have those, you have the disease. If you don't, you don't. So, it's a definitional issue. Tau protein exists normally in the brain as a functional protein in neurons for transport and function. Tau tangles caused by hyperphosphorylation of tau are pathologic, they're abnormal. Beta amyloid plaques are abnormal, but the amyloid precursor protein exists in the brain as a transmembrane protein.

People may be saying, "Wait a minute. Amyloid? There's amyloid to the heart, amyloid to the liver, amyloid to the kidney." All amyloid is, is a term that describes the particular shape of a protein. It's like saying triangle. Amyloid in the heart is a different protein that has folded into the shape, the look of what we call amyloid, which happens to stain uniquely with Congo red.

So, the amyloid of the heart, the lung, the liver, when people have amyloidosis in those organs, is a totally different protein and set of events. It just forms into these dense deposits, which stain in a certain way and look a certain way. And a pathologist will say, "Ah, that's amyloid," all they're saying is that's a rhomboid. But it might be a rhomboid cut from cheese. It might be a rhomboid cut from cardboard, but a rhomboid is a rhomboid. Amyloid is a shape, a particular shape.

Host: I actually want to make another distinction because it relates to something that does involve the brain, and that's amyloid angiopathy, which you'll see as a descriptor of risk for hemorrhagic stroke, and I believe lacunar as well. I assume that's not the same type of amyloid, right?

Dr Jason Karlawish: Yeah. There, what's happening is amyloid is accumulating in the cell walls of the capillaries. And is it the same amyloid that is in the plaques? Perhaps no, but I don't know that. But what's going on there is amyloid is accumulating in the small tiny vessels in the brain, making them fragile. Pathophysiology is a little ambiguous here, but causing basically small areas of hemorrhage and leak into the brain. So when you look at someone with amyloid angiopathy on a certain weighting of MRI, that brings out the density of hemoglobin, the iron in hemoglobin. You'll see all these little BB-like shots throughout their brain. In the coming years, we're going to hear a lot more about microhemorrhages and amyloid angiopathy for reasons we'll get to later when we talk about the treatments.

Host: There was one protein you mentioned that I just want to go back to, and that is APOE4. We will hear about that. Can you tell us little bit more about that?

Dr Jason Karlawish: Yeah, APOE4 is one form of the APOE genotype. The APOE genotype is you always have two copies. And our two copies of the APOE genotype are some combination of APOE2, 3 and 4. So, you can be a 2/2, a 2/3, a 3/4 or a 4/4. The APOE4 gene sometime in the late "80s, early '90s was well described subsequently, robustly described as a gene that was associated with the risk of developing Alzheimer's disease. An individual who carries one copy has a higher lifetime risk than an individual who has no copies. An individual who has two copies has an even higher lifetime risk. It is not a determinative gene, meaning there are individuals who live into their 80s and 90s who are E4 homozygotes, as we call them, two copies, who do not develop Alzheimer's. Typically, the E4 carriers start to develop the disease in their 60s into their early 70s, as I sort of look at the age of onset.

The lifetime risk estimates, depending on the data set you look at, vary. They are also governed by what your age is, obviously. And there's a gender effect there as well. As I say, 4/4, highest risk; 3/4, lower; and then, 3/3, obviously lower risk. We certainly don't have people who have Alzheimer's who are 3/3s, as we call them, meaning they have no APOE4 gene. If you look in the clinical trials and other studies, about 60% of the people in the Alzheimer's clinical trials are APOE4 carriers, and you see that in general when you look at the cohort studies.

Host: It's sort of a marker of genetic risk, if you will, but not necessarily part of the pathophysiology as we think.

Dr Jason Karlawish: Studies have begun to uncover what might be why APOE4 is leading to it in terms of its role around probably amyloid processing. That's an area of science that's little bit above my pay grade, but there's strong and wide consensus that it raises one's risk, absolutely.

Host: So, now that we know more about the pathophysiology, we can diagnose patients within the preclinical phase by detecting these proteins.

Dr Jason Karlawish: Yeah. So, the concept of preclinical Alzheimer's is a work in progress, and it's a quirky term, defining something like sort of what it's not. Essentially, let's step back and look at the kind of science policy public health idea. We know we have a chronic disease that unfolds over a long period of time and has a period of time prior to the onset of disabling cognitive impairments that the disease is present but not yet symptomatic.. So, why don't we figure out how to diagnose it then because... well then, the because becomes a public health issue. People want to know, they want to make plans, people want to take interventions to reduce the progression, et cetera. And that's oftentimes where people start, "Why would you want to know?" and I just laid out some reasons.

Setting aside the value of knowing, I think the field is still working through. Is it amyloid alone, and if so, how much amyloid? Or is it amyloid and tau that would define preclinical disease? And again, you and I could have... Well, we could interview, actually, some of the experts in this area, and we could start to see that there's clearly evidence from longitudinal studies, there is some evidence from clinical trials, that would support that amyloid is the incipient actor here, and amyloid alone could define preclinical disease. Again, I think the data still aren't there for that clear and convincing statement of amyloid positive as Alzheimer's. I think many would say amyloid and tau, again, we're getting into the weeds, but particularly a certain level of tau, Braak stage III define someone who really has got Alzheimer's disease in their brain, and it's only a question of time before they develop symptoms. And can we diagnose that now? We can. I can use imaging tests and there are emerging blood tests as well that would allow me to tell someone that information.

The reason why we don't do it is, first of all, the science was still a work in progress. The scans are still hard to access, particularly tau scans. They're available. They're even paid for by Medicare, but they're not widely available. But more importantly, we don't have that kind of statin drug, that kind of glucose-lowering drug to give people such that the diagnosis would be actionable in the medical sphere, certainly in the social sphere. You could imagine why you would want to know this. I've had people say to me, "Look, if

I know I have this, I'm going to retire now and move closer to my children." And I have to respect that kind of decision-making deeply. But as a matter of medical policy and practice, that kind of practice is not top of line compared to, "If I do this test, there is a medical treatment I can give you." We could debate whether that's right or wrong, but we are talking about the practice of medicine, not the practice of life planning, which does intersect with medicine, but first there has to be disease and treatment. We're getting into deep areas of health policy here.

Host: Yeah, I mean, I think it's similar to any screening test. If you're going to go out and make efforts to detect something, you have to have an intervention that's going to make a difference if you're to detect that early. And that's why we don't necessarily do screening for pancreatic cancer and some other things, because we don't really have anything to do with that information.

Dr Jason Karlawish: But it is why when you turn, I think now it's down to the 40s, you get your colonoscopy and you get your lipid tests because there's things to do. Someday we may get there with this disease. It is quite possible. I can see a world my colleagues talk about. You get this test and you're put into this group for subsequent followup for another test, various treatments based on the likelihood of developing disease. That is a very plausible future. That is a very plausible future which you and I could see within our practice lifetime.

Host: You had mentioned statins, and I mean, I think that's something that we're doing now. You, we're getting down to very much more precision about who's really at risk and who needs to be on them. But let me go back. I just want to ask one other question, and that is, you mentioned these proteins in blood as being potentially detectable. I have an idea that you at the Memory Center do do lumbar punctures of CSF in some studies, or at least in research. What are you doing there?

Dr Jason Karlawish: Yeah. So, we can now measure the presence of beta amyloid in the brain, and tau protein using what we call metabolic PET scans. So, we have radio tracers that detect beta amyloid and tau protein. We can measure them in spinal fluid. And I can measure them in blood. I hesitate on the blood test because some of the tau blood tests are still works in progress, but the progress being made in blood tests for the biomarkers of Alzheimer's, as well as other neurodegenerative diseases, it's really spectacular in terms of the accelerated pace of it.

So, we have the ability right now to measure all those two biomarkers using those different technologies. Very interesting question, which is, which ones

will start to sort of become the ones used in clinical practice? The imaging markers are almost now the gold standard against which the blood tests are compared, because the imaging markers were validated against pathology, which is considered the gold standard. The problem with the imaging is you have to have a cyclotron and you have to make the radio tracer and you have to inject it. There's an expense there obviously, which is magnitudes greater than the expense for a blood test in comparison, and certainly even greater than the CSF test. The problem with CSF is you have to get CSF. It's a lumbar puncture. It's not a difficult procedure, but it's a procedure and, again, compared to a blood test.

So again, I think we're seeing a world where there's a blood test. And based on the result, you're clearly positive, so we move on or you're clearly negative, so we don't. And there's a middle result. And the middle result necessitates another test that then might move on. And by move on, it might be to imaging and/or spinal fluid. We'll see where the field settles out because all this is taking you up to treatment, okay? The possibilities of treatment, and we'll talk about the treatments in a minute.

What's interesting though about the biomarkers, just kind of to wax historically poetic, we've bridged the skull. I mean, if there was one organ up until recently that just said, " I am going to make it so hard to figure out what's going on inside of me," it's the brain. The ophthalmologist, they're good. They can see the retina. Okay, that's the brain. But every other, you know, psychiatry, neurology, it was our interviews and exams and everything else, CAT scans helped, certainly MRIs helped, I'm not trying to dismiss them. But boy, the brain was really resistant to telling you what's going on inside of me.

That castle wall, pick your metaphor, has been breached now with these tests. It is fascinating what we can start to see what's going on in a brain. And never underestimate the power of MRI, the 3 Tesla, which is just the magnet, most of us are-- well, actually you and I started out with 0.5 Tesla MRIs. 3 Tesla now is a pretty powerful magnet. We use that routinely. You get really good resolution to look for neurodegeneration and regional specific neurodegeneration. And MRI now is our routine test at a workup.

7T MRI is used as well in a research setting. But the level of specificity you can get to measure hippocampal atrophy, medial temporal lobe atrophy is really quite wonderful. And we can imagine a day where potentially MRI is used to track progression, to track how our brain is doing. We could imagine finally back to the blood tests.

We have the ability to measure whether neurons are dying. So if you take a boxer and draw blood before a fight, have him go fight, and draw blood after, you can measure increases in neurofilament and other markers of neuron breakdown because their head's getting bopped. Now, the science around these measures of neurodegeneration is still emerging. But you could imagine a future where we're measuring in the blood markers that are giving us a signal of just overall sort of health of the brain when health is defined in this very narrow way. And boy, do I mean narrow, as our brain cells dying, not getting at issues of function and cognition, which we talked about last week, which is quite important.

So, I'm on a bit of a ramble. But my point is that, again, I think within a reasonable practice time, I think that within five, 10, certainly, I would say 15 years, I stopped using round numbers here of fives, we're going to be talking about these brain measures in the same way that we talk about some of the measures of heart function, metabolic function, LDL, hemoglobin A1c, triglycerides, et cetera. And we're in for a wild time when we do that, I will tell you.

Host: Yeah, I mean, the measures of neurologic injury, if you will, or degeneration, you reminded me of troponins, you know, and how we're just getting more and more sensitive in their ability to detect myocardial injury.

Dr Jason Karlawish: I think the troponin analogy is a very good one. And I think as an internist, I can certainly relate to that, because I was around when troponin came into practice. And suddenly, an MI went from history, EKG. And then, we got the CPK-MBs, you know, along the way to suddenly a troponin test, which really, you know... And the other thing, remember, that it did that suddenly everyone was having heart attacks, because we were saying, "Well, that was a cardiac leak."

Host: That's right. The person who hits their head on the closet door when they reach from getting their shoes is having a bump of whatever the marker will be that we're going to end up measuring.

Dr Jason Karlawish: Exactly.

Host: I think the imaging that most of us are going to be seeing on a routine basis is MRI. So, I want to jump into that and go into a little bit more detail on what you see on an MRI or what are the various patterns on an MRI that can indicate Alzheimer's disease or some of the other neurodegenerative diseases.

Dr Jason Karlawish: Yeah. So, MRI shows you, with good resolution, the presence of vascular disease. As we talked about last week, the problem is vascular disease is a sort of very ultimately like artistic interpretation. How much white matter disease do you see? But it's useful. Number two, it shows microhemorrhages at encounter of CAA, cerebral amyloid angiopathy, or the microhemorrhages that are seen from amyloid angiopathy that occurs oftentimes concomitant with Alzheimer's, but doesn't meet the CAA requirements.

And then, finally, MRI allows us to look for atrophy. Actually also ventricular size, which relates to atrophy. So, atrophy and ventricular size. What we're looking for are the regions of the brain that are disproportionately showing increased space of the sulci between the gyri. So, the classic story is amnestic presentation and you look at the medial temporal lobes and you see clearly atrophy within the medial temporal lobes. We talked last week about LATE, limbic-associated TDP encephalopathy. There you see a dramatic thinning of the hippocampus and the parahippocampal CA structures are just profoundly thin.

In contrast, when someone presents with a variant of the disease that's more aphasic, we call it logopenic primary progressive aphasia, you see an asymmetry between their temporal lobes. Literally, when you look at the coronal, it's as if like, someone took one brain and sandwiched it on the other, where, you know, one ventricle's this size, and the other ventricle's a little bigger. And it's the left temporal lobe where, for most of us, expressive language is situated. And then, finally, parietal atrophy is a very strong marker for for the presence of Alzheimer's pathology. So, ventricular size, particularly asymmetric ventricular size, atrophy in the medial temporal lobes, atrophy in the parietal lobes. And this is very informative for us when we're making a diagnosis.

In Lewy body disease, fascinating. You don't really see atrophy. Lewy body disease is more of a pathophysiologic process of something's going wrong with neurons, more so than neurodegenerative. And that's actually very oftentimes the lack of atrophy helps us say, "Well, this looks more like a Lewy body picture together, obviously, with the history that we're seeing."

Host: So, we haven't talked about this, but there are sort of these different phenotypes of Alzheimer's disease, which I guess reflects more how they initially present than I assume over time you end up with of these elements. But there's, classically, the amnestic phenotype, the dysexecutive phenotype, the aphasic phenotype, and a visual phenotype. So as you were describing these

MRI findings, I was kind of thinking that maybe these different MRI findings fit within these subtypes, whether the hippocampal atrophy reflects the amnestic, the dysexecutive, maybe the parietal atrophy and so forth.

Dr Jason Karlawish: Well said. Absolutely. Yeah. Is it one to one always? No. Oftentimes, we laugh and say, "Well, another case where the MRI fails to match the clinical course." Again, the brain ultimately is about networks, not about regions. And how the brain using its network still functions is a sort of fascinating story, a work in progress.

But yes, you're absolutely right. There's four phenotypes of Alzheimer's. It's not the case that Alzheimer's is an amnestic disorder. It is often, but that is to say, repetitious questions, repetitious stories, forgetting new information, amnestic phenotype. But another phenotype presentation is troubles with getting words out, particularly nouns. That's the logopenic primary progressive aphasic form. Another form is the individual who comes in and says, "I cannot get a pair of glasses that works anymore," and they've dented the car, et cetera, and there, the predominantly visual cortex, occipital and related connections. And their problems are with are visual, spatial abilities, namely our ability to judge distances, et cetera. We often see those folks referred by ophthalmologists. They'll come in complaining, "I can't get a prescription that works." And the ophthalmologist will say, "It's not the anterior chamber or even the posterior chamber, it's the really posterior chamber, namely where all that sensory input is sent back to the brain.

And then, the dysexecutive variant, which is typically a parietal phenomena. The patients will complain of memory. Remember we talked about how memory is oftentimes the complaint everyone makes. But actually, it's more what they're telling you is, "I can't really pay attention and organize things. So, therefore, I don't learn them, and so, therefore, I never remember them, and so, therefore, I forget them."

And so, there's a couple more key points around these different presentations. The stereotype of the amnestic presentation is an individual 70 plus, 75 plus. I kind of have a hunch, as we go forward, many of those people actually have LATE, which we talked about. Older crowd. The visual variant tends to be younger 60s to 70s in its presentation. The dysexecutive variant tends to be these early-onset cases. And when I say early-onset, I mean age of onset, chronologic age. And in my practice and my colleagues, we all note, and the neuropathologists and others will say, we tend to see the dysexecutive presentation in these individuals who present in their 50s, 60s or so. The logopenic variant, 60s, 70s, et cetera. So, the age of onset for these diseases is

the 60s into the 70s into the 80s. And then LATE, I think really starts to kick in once we're into the 80s.

Host: So, I wanted to go through, sort of match this up with the clinical stages, if you will. And then, I also want to jump off from the pathophysiology into therapies. And maybe we'll actually start with therapies and then backtrack and layer those on top of the clinical stages. So, let's see. I hope this will go okay. But because, you know, a lot of the newer drugs at least are built out of the pathophysiology you just described, right?

Dr Jason Karlawish: The newest drugs, yes, that's right.

Host: Yeah. So, let's talk about those, right? So, we have two and they came out sort of consecutively on each other and it gets confusing as to which is which. The first was aducanumab, which most of us probably heard about because of the controversy associated with approval. And then, the later one, which I understand to be less controversial, is lecanemab. So, can you talk about those two?

Dr Jason Karlawish: Yeah. So, lecanemab and aducanumab, and we'll just put a third in the mix, which is going to get FDA review in December, donanemab, are all monoclonal antibodies that target amyloid. They're manufactured antibodies, they're not pooled antibodies, they're manufactured in a factory. And they take advantage of the immune mechanisms, antibodies that target amyloid, particularly that target beta amyloid, the amyloid that forms the plaques. That's their common mechanism. They target different aspects of the amyloid cascade, lecanemab more goes after the oligomers, donanemab more goes after the plaques. And these drugs were first studied in the early aughts was the first use of these drugs. And there have been several others studied.

Let's focus on aducanumab for a moment. It was developed by Biogen, two phase 3 trials. They began to suffer from changes in their design and analyses, which would result in a data set that I fundamentally think just remains uninterpretable for the purposes of making a regulatory decision for approval. FDA didn't see it that way. FDA essentially, we've learned now, kind of just wanted to get that drug approved. And the story of aducanumab really is a story of the failure of regulatory science.

I actually think the drug probably works. I do. But I do not think the data are good enough for me to prescribe it to a patient. I think another study needs to be done. And in that I agree with FDA, which gave it what was called conditional or accelerated approval, meaning we'll let you market it, but you have to do a

confirmatory study. I don't think they should market it, I think they should do a confirmatory study. For all intents and purposes, aducanumab has gone on to history. It may resurrect itself at a cheaper form. The company got a little aggressive with their pricing at about $60,000 in the initial rollout per year per patient, which is outrageous. So, I think we can move on from aducanumab. It really was a failure of regulatory science. I view it as a unique and distinct problem. Although there are larger problems there about the way our FDA is functioning, et cetera, but we won't go there.

All right. Let's talk about lecanemab. Lecanemab is also a monoclonal antibody. It had one phase 3 trial done. Why only one? Under its guidance, FDA is allowed, if a disease is serious and life threatening, to change some of the rules, if you will, that are guidance that surround drug approval in terms of the speed, pace and number of trials, et cetera. One phase 3 trial was done. The readout showed a clear drug versus placebo difference that was statistically significant across all of the primary clinical endpoints and most, though not all, of the biological endpoint. It's the kind of data that all my colleagues look at and say, "There's something going on here greater than chance," namely that this drug is having an effect on the disease.

What does that affect? After 18 months of treatment, individuals who got drug compared to the placebo did not show the rate of decline in measures of cognition and function with the same pace as the individuals in placebo. Let me drill down with some numbers. After 18 months of treatment, people on placebo, about 30% of them progressed to the next stage of their disease based on staging criteria. In contrast, people on drug, about 20% progressed to the next stage, which is interesting because it said even on placebo, 70% didn't progress. It's a slow disease, a lot of variability, a lot of heterogeneity. But your chances of progression to the next stage were reduced by about 10% on drug. So, that to me is the simplest way to express the effect size.

Now things get wild, funky, crazy, because people look at the various measures of cognition and the CDR Sum of Boxes, which is the staging measure. And they start looking at percent differences and sizes based on the way you measure the scale, and like a 0.6 difference on the CDR Sum of Boxes. Is that really worth it and whatnot? I just kind of smile and say, "Well, you're talking about a measure that's not even used in clinical practice." I kind of go back to that global look at the data.

So, that's lecanemab. It got FDA approval. Later this month, we'll be our first infusion at Penn. We are doing a pilot program. We're going to try it on a few

people, learn from the pilot in terms of just our workflows. And then, we're going to be rolling this out before 2023 ends.

Host: How is that priced?

Dr Jason Karlawish: Don't quote me on the exact number, but I believe Eisai owns the drug. And they own it in cooperation with Biogen, but they fully assert their primary ownership rights over Biogen. Eisai, I believe, is priced in the high 20s, high 20,000s. ICER, which is the Institute for Clinical and Economic Review, felt that the price, in order to be cost effective, needed to be in the low 20s. So, it's not too far off compared to how aducanumab was priced, which was this outrageous, absolutely just scandalous price that they initially put out there. And then, they dropped the price. After people complained, they actually dropped the price in half, which proved to you that not all drug pricing is just to recover the cost of drug development. What a shock. It's a once-a-month infusion and we can talk more about some of the details of the drug.

Host: You know, what you quoted are, I think, clinical outcomes that would be recognizable to family members potentially. It looks like 1 out of 10 people are going to show real benefit, something like that.

Dr Jason Karlawish: Yeah. And remember, show benefit. This isn't like taking a medicine for pain, depression, anxiety, or pick any other symptomatic condition where the treatment frankly reduces symptoms. This is more like a treatment that slowed the pace of a tumor, inflammation, et cetera, an anti-rheumatoid arthritis treatment. Am I better with it? Well, actually, yeah, there is less swelling and whatnot with those monoclonals. This is a drug that will slow the rate of decline. And so, it's not after six months my relative quote did better, although people are looking at some of the data and showing that some people actually improve. That could be regression to the mean, et cetera. But this is more a drug modeled after the progression of the cancer was slowed, if you will, so that future events didn't happen as soon as they were going to happen.

Host: It's like palliative chemo, if you will. You know, similar kind of model that...

Dr Jason Karlawish: I would say so, yeah, because this is not a cure. This is not a cure. There are some who don't progress on the drug, meaning they start out at their stage and they don't move from their stage even based on the subscales within their stage. Again, early days, but there's a lot of variability in response to this drug, a lot of variability. They are proof, by the way, of the

value of well done, randomized placebo controlled trials done for a good period of time. They reiterate the importance of that science for rational prescribing.

Host: So, how does it compare to some of our earlier drugs? Donepezil being the first one that was out, and then rivastigmine, galantamine memantine, and so and forth.

Dr Jason Karlawish: Apples and oranges are donepezil, rivastigmine, galantamine, all those are three drugs that are cholinesterase inhibitors. They inhibit an enzyme called acetylcholinesterase. In inhibiting that enzyme, you increase the level of acetylcholine. Acetylcholine is a ubiquitous neurotransmitter in the brain, particularly from the forebrain up into cortical structures.

Once upon a time, actually for a while, we talked about that Alzheimer's disease was a disorder of cholinergic neurotransmission, just like Parkinson's disease was a disorder of dopaminergic neurotransmission, and it was back in the days when neurotransmitters were the sort of secret to all diseases. My tone sounds like I'm being critical or mocking of it. That was just the way we frame the disease, which in the light of history was just that, it was one way to frame the disease, just like I predict we'll look back and say we used to overly frame this disease as amyloid and tau, and there were other actors there.

Setting that aside, increased acetylcholine in an individual patient whose neurons that produce acetylcholine are becoming dysfunctional and dying, and you're going to improve cognitive function. Now, the debate that haunted these drugs was, are you improving it enough given their role in enhancement? And I think what we found over time was there are some patients in whom you couldn't pick up a difference on the drug, and others in whom you could clearly pick up a difference in cognitive function, particularly actually people with Lewy body disease, which is interesting. So much for being a disorder of cholinergic transmission is defining Alzheimer's because Lewy body is, of course, a different disease.

Anyway, that's what the drugs do. That's an entirely different mechanism effect than these anti-amyloid therapies. Entirely different. Benefits are widely considered to be modest. Risks are largely gastrointestinal and some other anti-cholinergic effects, which go away if you stop the drug. Most of them are generic now. And so, their costs have become rather reasonable. The biggest decision I find myself making when I use them is whether to switch over to the patch forms because there is less gastrointestinal side effects on the patch form

compared to the oral form. So, I start on the oral form. If they don't tolerate it, I move to the patch form.

And then, there is memantine, only been shown to work in moderate to severe Alzheimer's disease. Their studies in mild Alzheimer's never quite worked. They got approval for the treatment of moderate to severe Alzheimer's disease. I always found the effects to be even more ambiguous than the cholinergic drugs. Of course, given the way things are, they're used across the entire disease spectrum, and then they've packaged the drug together with donepezil into some combination pill and that makes it even more sexy. I find myself giving issues of polypharmacy oftentimes, not bothering with memantine. And again, since it only works in moderate to severe stage dementia of the Alzheimer's type, I'm not using it in mild stage patients, even though I have plenty of patients coming in on memantine who have not even dementia, but mild cognitive impairment. But that's another story about give doctors prescriptions and we tend to like to use them. There we are.

Host: Well, we'd like to give patients something that they at least might think would work, and it's the same sort of antibiotics for the common cold, people just beg us until we end up relenting to do something for this uncomfortable feeling I'm having. So, lecanemab, I guess, leaving aside aducanumab, but lecanemab seems to be the first real effort into, you know, sort of targeting the pathophysiology directly at least as far as we understand it. And so, hopefully, that'll lead to a breakthrough that leads to other drugs that may be--

Dr Jason Karlawish: Yeah. The other drug, donanemab, very similar design study, very similar results in terms of the magnitude of the effect. And that drug will undergo FDA review in about a month or so. And I think if the data holds up based on what's been presented, it too will get full approval. A key thing about both of these drugs, which we should talk about, is they're linked to the APOE genotype. So, a well described risk for these drugs is microscopic hemorrhages, which can lead to microscopic edema, which can become macroscopic edema in the brain. And if these aren't detected early, it can cause disability and there have been a few deaths.

The risk of developing these bleeds and swelling is well associated with having the APOE4 genotype. It's uniform finding across the studies. If you have one copy, your risk is elevated. If you have two copies, your risk is even more elevated just of having the outcome. In other words, the MRI says, "Oh my gosh. Look, there's microscopic hemorrhages," which are well detected with an MRI, that is to say they're seen by, although there's some subtleties on reading MRIs, and the edema as well. And if it's caught early, it's an asymptomatic

event and you stop the drug, recheck, redose and carry on. If it's not caught early and/or just because of the severity, it can be disabling and require ceasing the drug.

So, that's a link now between the genetics of risk of the disease and the genetics of risk of the drug. And we are routinely doing APOE testing now to better inform an individual's risk-benefit assessment. I would not want to prescribe the drug to someone until I got an APOE genotype. Having said that though, it does introduce a complexity to these drugs because if I tell you, "Kendal, you're an E3/4 carrier. Here's your risk of side effect," I now am telling Kendal about what his blood relative's risk of developing lifetime Alzheimer's disease might be, because you share a genome with them. And so, it does introduce a kind of ironic complexity to this disease, widely called disease of the family, given the roles of caregivers. Now, we're bringing the family in in a very different way. And I do make sure patients and family members think about that before they just simply get the test. Are you going to tell your family members these results? It is not trivial information, and some people really struggle with whether they're going to tell their family, "I know something that might affect you."

Host: Yeah. I'm just going to review this for a second and make sure I understand. So, APOE4 you know, identifies genetic risk, if you will, that we can determine. We don't do that routinely for the reasons you described. But now, you're having to do it when you're prescribing these medications, because these folks are the ones that are most at risk for the side effect you described of brain swelling and hemorrhage and so forth. And so now, you end up knowing that information and having to deal with it.

Dr Jason Karlawish: Yep. That is the clinical reality we're walking into. And we've developed education materials, online education materials, et cetera. I mean, one of the great advantages of the advances in the internet and telemedicine is a lot of this information, people can learn at their leisure and their desire to be doing a lot of work with colleagues at the cancer genetics group to be able to deliver this information to people in a way that's convenient.

Host: So, I want to go back, knowing it's similar to screening tests, really no meaning about screening until you have something to treat the problem you're going to identify. So, I wanted to start with the therapies that are out there and so forth. But now, I want to layer back on a patient who's sitting in our office who may have identified as minimal cognitive impairment. They're early in the disease. Maybe you do an MRI, you do see some hippocampal atrophy, some parietal atrophy. One of these features that suggests they have Alzheimer's

disease. What are you telling these folks about their progression? What are you just sort of in your head expecting in terms of how long before they're at the latter stages and what do you expect, I guess?

Dr Jason Karlawish: So when we think about the stages, let me just talk about the stages of Alzheimer's. So Alzheimer's disease, the pathologic entity now I'm talking, not Alzheimer's disease, meaning you have dementia and is it caused by Alzheimer's, because that's how we used to think about it. So yeah, as we talked about last week, it is possible to say someone they have mild cognitive impairment. By the way, I call it mild cognitive impairment. I know you've been calling it minimal cognitive Impairment, but MCI is this idea of mild cognitive impairment. I certainly have patients who have mild cognitive impairment, meaning cognitive impairments that are causing inefficiencies, not the spectrum of disabilities that define dementia. Cognitive impairment causing inefficiencies with a history and cognitive testing that strongly suggest neurodegeneration, and as you said, MRI and biomarkers that support that Alzheimer's is the cause. So, it's possible to be diagnosed with Alzheimer's without having dementia. That's MCI.

The next stage of the clinical stages is mild stage dementia. After that, moderate stage. After that, severe stage. After that, profound terminal stage. The bottom line vocabulary we use to define the stages relies on cognition and function. In particular function, MCI, inefficiencies in IADLs, technology, transportation, medications, finances. Inefficiencies, takes you longer, makes some mistakes, you catch them. Maybe something that's really hard you actually need some help on.

Mild stage dementia, you need a little help in some of those, or you've really backed off. It's very obvious that she can no longer do the finances. Someone else is doing it, or you've really reduced it and it's just the checkbook, other things not. By the way, the biggest giveaway to me is cooking. People who just the recipes get simpler and simpler and simpler. Not because they're bored with cooking, cooking is truly an executive function task, working memory task. Anyway, mild disabilities in IADLs. BADLs are fine. Bathing, dressing, grooming, feeding, morning routine, no problems. That's mild stage.

Moderate, IADLs more impaired and some beginning of inefficiencies and problems with the BADLs: dressing, grooming not as good, some troubles putting the shirt on, sometimes it's backwards, needing reminders to bathe, et cetera. Severe stage describes someone where the BADLs now are really clearly impaired, needs assistance with bathing and dressing, grooming, might need the

food cut up, et cetera, toileting, might need some reminders. Profound and terminal, described really a need for help in those BADLs. That's the staging.

Kendal, I have not in any way though, described the person as a person. And I think this is really important because, yes, as the function declines, cognition has been declining, but it isn't the case that someone with moderate stage disease can't have a conversation with you, can't enjoy activities, doesn't have preferences. It isn't the case even with severe stage disease. Patient's caregivers will tell me their relative has moments of lucidity and connection that are very much the Jason they always knew, for example. So, we don't stage the disease on the thing that people most dread, which is the loss of the mind. In other words, we don't say, "Oh, wait. Moderate stage, that's where you don't have the same kind of conversational exchanges that you'd like to have. And, you know, your ability to experience joy is inhibited, because of apathy. We don't stage it that way, but that's what families care about. So, I do think we have to be careful that when we say severe stage, they often think, about behavior and the person. We're talking about disability. I'm not denying that someone with severe stage disease doesn't have profound impairments in communication. I'm not. But I just want to caution that our staging system is about function and cognition. It is not about mind. It's been a long ramble, but I think that's important because families care about the stage. They do.

All right. What's the total course of the disease? Very variable because it depends on when you define that it started. But let's start it at MCI. In an otherwise healthy individual, and by that I mean no other concurrent illnesses, 10, 15 years has been the kind of spectrum of survival. What's the pace of the stages? Very dependent on the individual in terms of comorbidities, et cetera. I can't divide it into third, third, third, and whatnot, but that's about the pace that we're looking at, about a 10, 15-year course. Have I had patients who have defied that? Absolutely. I don't think some of them had Alzheimer's in retrospect. I think there were other diseases at work. And I've had patients who have progressed much faster. Some things that predict prognosis or the presence of Parkinsonism, the more a patient has sort of the Lewy body features or Parkinsonian features, I find they progress faster, for example. So, that's a long-winded summary of the stages.

The drugs that we talked about, lecanemab and donanemab and aducanumab were tested in people with MCI, mild cognitive impairment or mild stage dementia. They were tested in those populations, because the field's earlier studies suggested that testing them in mild to moderate disease was not effective. The drugs didn't work in those stages. I think we're going to probably go back and revisit that, but the data do suggest that the more amyloid burden

you have, the less likely you are to respond to the drug. And amyloid burden goes up and tau burden goes up over the course of a mild to moderate disease. So, it may be the case that lecanemab and donanemab simply aren't effective in mild to moderate, especially in moderate disease, and the data that they presented suggests that.

Again, this is a work in progress, but I think the sum is these drugs tend to work early in the MCI stage and early in the mild dementia stage; less likely to be effective in the mild stage, certainly in the moderate stage of disease, although they weren't tested in the moderate stage. Those individuals would have been excluded from these studies.

Host: We have this phenomenon that we sometimes see in medicine that if you get things early, you change the overall trajectory. The thing growing up on a farm and doing a lot of pruning as a kid, I always thought of this as sort of you pruned a branch, you get it going in a certain direction. Yes, it will go in that direction and it will harden eventually and solidify, but it is in a different direction. I'm just thinking about some of this drug. You know, if you get it early, this is degenerative, but you put people on a different slope, if you will.

Dr Jason Karlawish: That is the question, the fight. People look at those curves and they say if they're diverging over time, if we went beyond 18 months, would that continue? Okay. New natural history versus we've bumped up and have parallel slopes. When you look at the cholinesterase inhibitor data, they're parallel slopes. They're parallel slopes. These data suggest non-parallel slopes. But here is where, you know, depending on the room I'm in with, who's on the panels, the fights are vigorous. Unfortunately, the randomized trials were to stop at 18 months. We don't have that extension data. They open label it and they have the people who are on placebo for a while, so you can look at slope changes, modeling starts to get pretty funky. But yes, that is what we think is happening. That you are altering that pace of decline on a group level, on a group level. Individuals, obviously, much more variable.

Host: Reminds me of the early statins, the West of Scotland study that they looked at and this was a study where they gave pravastatin, which is a relatively weak statin, to half a population and the other, did not. And it was simply, these are just randomly selected individuals of moderate risk. And they had a difference with-- I don't remember the times exactly, but within a year, but a lot of the people that received the statin, actually stopped it after the year and then they test them five years out and they had still had benefit from that year that they took the statin, suggesting that they were sort of put on a different curve.

Dr Jason Karlawish: And so Lilly, who is the manufacturer owner of donanemab, they actually type dosed the drug up to clearing amyloid below what we call it a centelloid value. No one on the podcast should worry, "What's a centelloid, Jason?" But someday I think we'll be talking about centelloids as a way to measure amyloid.

They would dose it till you got below a centelloid value. And then, they stopped the drug and their data suggests that these individuals, even after drugs stopped, continued to show the trajectory of decline that was created by being on drug. It's a very clever strategy on the part of Lilly because it gave an endpoint to treat and to stop drug. These are early days, and we may see a future where you treat until you lower amyloid to a certain level, stop and monitor. There's a number of advantages of that. First of all, it's one less drug to take. Secondly, there's obviously some economic societal benefits. And with risks of ARIA, you reduce the chance of exposure plus these drugs do create autoantibodies. In other words, our body starts to create an antibody against the drug. And so, it's a strategy that actually might limit the chance of auto-antibodies.

We could envision a future where you're asymptomatic, your amyloid test is positive, and you go on a fairly risk-free curve-altering drug, and you're followed. And if you remain fairly stable, great, your pravastatin is working. If on the other hand, things are getting worse, we escalate to a more powerful statin, if you will. The statin metaphor, I think, is problematic on a number of levels, but we'll run with it, because we're internists. And we can envision that's the kind of future that we'll have.

I'll just provoke the listeners with I am very excited about this future of treating the disease, but what we haven't talked about, and we'll come back for another podcast probably in a year or two, is when do you stop treatment? And how do you talk about stopping treatment? And what do you do after you stop treatment? And I think this is an area which causes me a lot of this "I don't think I know. This is an area which causes me a lot of reflection." Because unlike cancer and heart disease, where you kind of battle on until you finally say enough already, and enough may be months, years, whatever days before death. This is a disease that's very different in terms of your ability to self-determine your own care, and how things unfold in the years to follow. And these treatments sort of put in plain sight now these questions that were hidden for a long time, which was why would you want to live longer with this disease? And I have patients who are adamant that they want to, and I have some who are ambivalent and others who don't want to. And so, I think we're in for some wild conversations not just as a field of medicine, but as a society.

Host: Patients will always, for whatever situation you face, will want to know what they can do to improve. And, we do know that folks that have a higher cognitive function to begin with do better or longer.

Dr Jason Karlawish: Doctors, yes, this is what you should tell your patients. You need to go, if you are worried about their cognitive function, if you've diagnosed cognitive impairment, mild cognitive impairment, whatever, you need to say to them, you need to find another human who is available, trustworthy and reliable to watch over you, come into visits with you, to see me and to help out if you need help making decisions. And they may say, "That's a great idea." This sounds a lot like a caregiver, right? And the answer is, yeah, what I'm doing is deconstructing the idea of a caregiver. , I think a very important treatment for a brain, whether it's a brain at risk or a brain with early symptoms, is to have another human watching over that brain. And so then, the next thing is, "Well, how do we train that human to be a good caregiver?" And I'm pleased that Medicare announced the GUIDE model. I forget what it stands for. It's an acronym, but it is a demonstration project for a health care system to implement caregiver training services and supports. And that I think is an extremely important intervention to help keep a brain healthy.

The patients I've had who have a good caregiving network of reliable, trustworthy, and available humans tend to do well. The ones where that network is dysfunctional and not present tend to do poor, they tend to decline. So, it wasn't what you wanted to hear, which was Mediterranean diet, good sleep, cardiovascular exercise, but I didn't want to leave that out because I think, as doctors, I think, especially internists, we're deeply respectful of the role of family, although we're also fiercely respectful of the patient as an individual. We only have one chair in the exam room, right? But it's time to get two chairs and a stool for you, the doctor, by the way.

Host: And another one for the medical student.

Dr Jason Karlawish: They stand.

Host: Yeah. How much does exercise, Mediterranean diets, brain stimulation, that kind of thing, how much does it matter.

Dr Jason Karlawish: The Lancet Commission reviewed the epidemiologic data and most of it is epidemiologic. They reviewed the data on lifetime risk factors for developing dementia, dementia, not Alzheimer's, but dementia. And they identified that about 40% of the lifetime risk is these modifiable risk factors, hearing, cardiovascular care, exercise, et cetera. And I emphasize

lifetime because they found that the data show that, for example, well, education is a risk factor, lack of it, that's an early childhood exposure. Hearing loss tends to be later in life, et cetera. So, that's why it said life course. But the overall risk to a population could be reduced by as much as 40%. That's a pretty impressive public health benefit.

Host: How about alcohol?

Dr Jason Karlawish: I think, we're back and forth about alcohol as a field in terms of whether it's risky. I think the data consistently show that the sort of one to two drink a day, whatever that means has not been associated with increased risk.

Host: Do you tell your patients who come in to see you to not drink or do you have a-- I mean, obviously if they're heavy drinkers...

Dr Jason Karlawish: I right now still only care for people with cognitive impairment generally. I don't say don't drink, but I say, "Look, for a brain that's dealing with this disease. Alcohol has an effect on cognitive function. You need to be very mindful of how much alcohol you can tolerate now." And I certainly have patients who need to reduce or otherwise cut back or the families basically make it happen because they clearly can see how it affects cognitive function. But no, I don't categorically say you must cease drinking.

Host: So Jason, this has been excellent. I really appreciate you taking your time. I mean, this has been two hours of time. The audience doesn't know this, but this is recorded after long days of work. And I mean, I know for me, this has been illuminating of an area I frankly didn't understand very well, particularly when it comes to the pathophysiology of Alzheimer's disease. And when I tried to read about it, you know, I'm not sure that was all that helpful often because it was just a lot of complicated stuff. So, it's just really valuable. And we will have you back, as the field advances, you are now our designated expert to come back and update things. ,

Dr Jason Karlawish: If listeners want to learn more about what we do, pennmemorycenter.org is our website. And we have a very well done website with information about the disease aspects of caregiving and care advances in research, et cetera. We also have a weekly newsletter, which has up-to-date information you get every week on Wednesday and Sunday.

Host: Wonderful. That's great. So with that, I want to thank you again for coming and thank the audience for joining the Penn Primary Care Podcast. See you again next time.

Disclaimer: Please note that this podcast is for educational purposes only. For specific questions, please contact your physician. And if an emergency, please call 911 or go to the nearest emergency department.