Alzheimer's disease:
Simple blood test, diagnostic clarity

PODCAST 49 - Part 1

00:17
Dr. Jane Caldwell
Hi, I'm your host Jane Caldwell. Welcome to the *On Medical Grounds* podcast, your source for engaging, relevant, evidence-based medical information. Alzheimer's disease, or AD, is the most common cause of dementia and accounts for an estimated 60 to 80% of dementia cases. It is now known that changes in brain physiology and function may begin 20 years or more before symptoms appear.

Even though the need for an early diagnosis has been established, AD remains a diagnostically challenging disease for providers. Just a little over two decades ago, the diagnosis of AD was made through autopsy. Today, the pathology is much better understood and diagnosis is often made through a combination of clinical signs, biomarkers in cerebrospinal fluid, and amyloid PET scans. However, many of these tests have their own challenges and may be costly for patients. Multiple companies have filed for FDA approval for plasma biomarkers for AD and two have received Breakthrough Device Designation.

On May 16th of this year, the FDA cleared the first plasma biomarker test, which was the Lumipulse® G pTau 217/β-Amyloid 1-42 Plasma ratio. This is a blood-based test for the detection of Alzheimer's in patients with mild cognitive impairment. In our discussion today, we will address some of the challenges facing AD diagnosis. We'll explore new testing options, such as plasma biomarkers, and establishing diagnosis of AD especially in the early stages when clinical presentations often overlap with other forms of dementia.

Our guest today is Dr. Douglas Galasko. Dr. Galasko is the Associate Director of the UC San Diego Shiley Marcos Alzheimer's Disease Research Center. He has conducted research on Alzheimer's and related disorders for over 35 years, publishing over 500 research articles. As a researcher and a specialist with the Center for Brain and Memory Disorders at UC San Diego, he has helped to develop biomarkers to diagnose and track progress in these disorders, initially using cerebrospinal fluid tests and more recently blood tests. Dr. Galasko is a member of the American Academy of Neurology and the American Neurological Association. Hello, Dr. Galasko and welcome to *On Medical Grounds*.

Dr. Douglas Galasko
Hello.

03:04
Dr. Jane Caldwell
So in a nutshell, what is our current understanding of the neurobiological basis for Alzheimer's disease?

Dr. Douglas Galasko
Alzheimer's disease is a progressive disorder in which proteins misfold and accumulate in the brain.

The initial protein that does so is called amyloid or amyloid beta protein and it forms aggregates or clumps that the brain cannot get rid of. Over time these enlarge and these are outside of nerve cells and they incite a reaction around them. So they go from what are called diffuse plaques to neuritic plaques and occupy increasing area within the brain.

Sometime along the course of amyloid, there is simultaneous development of tau pathology in the form of neurofibrillary tangles. This protein called tau, which is inside of nerve cells, aggregates and forms clumps or tangles, progressing typically from areas of the brain in the medial temporal cortex, which is important in memory and learning, to more widespread areas eventually being found in many areas involved in cognition in the brain. At the same time as tau accumulates there is evidence of neurodegeneration. This is a complex procedure in which there is evidence of inflammation and inflammatory response within the brain as well as loss of synapses or the connections between nerve cells and then degeneration of the processes of nerve cells and death of some of the nerve cells themselves. All of this develops over a period of decades and there is a long pre-symptomatic period of Alzheimer's disease where amyloid and to some extent tau can be detected and then a symptomatic period.

05:12
Dr. Jane Caldwell
Thank you for that. How do we stage Alzheimer's disease?

Dr. Douglas Galasko
There are number of approaches to stage Alzheimer's disease.

Clinically, we can think of the division of Alzheimer's as being mild, moderate, or severe, or going through a stage of what has been called mild cognitive impairment, where somebody has mild symptoms, such as memory loss but is able to largely compensate, followed by more overt dementia, where they are increasingly reliant on help with other people, followed by moderate and then severe dementia, and severe dementia, becomes unable to look after their basic needs such as dressing, grooming, bathing and so forth and needs help.

In addition to clinical staging, we can think of trying to stage the pathology within the brain and a proposal called Amyloid Tau and Neurodegeneration or ATN for short has been developed based on decades of research. In this formulation, one needs to try to measure or estimate the extent of the presence and extent of amyloid pathology, tau pathology, and neurodegeneration and this can be done using biomarkers. Initially, imaging biomarkers such as PET scans, MRIs and CSF biomarkers were used. There is the possibility of bringing blood-based biomarkers into the staging system for A, T, and N. And thinking about Alzheimer's as a chronic disorder with a slow buildup, it is possible to have features of A, and to some extent T, without the presence of any symptoms.

07:05
Dr. Jane Caldwell
Tell us about your clinical work with the diagnosis of dementia, specifically AD.

Dr. Douglas Galasko
I practice at UC San Diego in a memory disorders clinic where I will see people who are referred with memory changes. The most benign concerns would be people who are showing changes related to aging of the brain alone, in which case they may have problems such as difficulty thinking of words or names or losing their train of thought, but otherwise are generally intact in terms of carrying out daily activities. I will also see people with mild cognitive impairment or dementia and in that case, I will do an evaluation aimed at trying to identify what is causing or contributing to dementia. So Alzheimer's disease is the most common cause of dementia but it is only one of many and in older people who have memory disorders when we follow them over time and eventually look at the brain under the microscope, we usually find that there is evidence of more than one pathological process. So Alzheimer's disease may be accompanied by vascular changes, for example, or by the buildup of other proteins, a protein called alpha-synuclein that contributes to Lewy bodies and is noted in Parkinson's disease, and another protein called TDP-43.

So dealing with this complex situation, I try to make as clear a diagnosis as possible with a focus on Alzheimer's disease. I also look for whether there are treatable or reversible conditions such as mood disorders, sleep disorders, vascular brain health, general disorders such as hypothyroidism or vitamin B12 deficiency or whether somebody is taking medications that may be contributing adversely to cognition. And then I try to integrate all of this into an overall diagnosis and I'm increasingly informed by the use of biomarkers to try and decide whether there is Alzheimer's pathology in the brain as one of the important contributors to memory changes.

09:34
Dr. Jane Caldwell
I understand that early diagnosis is the best case scenario for slowing the progression of the disease. Could you please tell us more?

Dr. Douglas Galasko
Exactly, we would like to intervene as early as possible because there is likely to be less pathology within the brain and less irreversible change.

To make an early diagnosis, we need to identify symptoms at a very early stage. And there are several challenges to this. First off, early in the course of memory changes, the person experiencing them may be in denial or may be able to compensate. And the changes may also be brushed off as something that could be aging alone so that a family member might not necessarily be as concerned about these changes as they could.

In order to make an early diagnosis, ideally one needs to have the patient referred by a primary care physician at an early stage. Primary care physicians are extremely busy and have to focus on a host of different medical conditions, not simply memory problems. As a result, they may not have the time, sometimes not the expertise, to take an adequate history about memory problems.

Early in the course of memory decline, there may be what is called anosognosia or denial of any substantial memory problem. And so ideally, one needs to spend some time taking a history, some time formally testing memory and other aspects of cognition, and also interviewing somebody, a spouse or relative or friend, who is very knowledgeable about the patient and can give additional information about their daily functioning.

11:44

Dr. Jane Caldwell

New disease modifying treatments have been shown to impact AD pathology but are most beneficial, as we've discussed, in early stages of the disease. Current research indicates that plasma pTau, including pTau 217, is a predictor of amyloid status and is associated to an extent with the burden of AD neurofibrillary tangles. How is pTau 217 assayed and in your experience, can it differentiate between AD and non-AD dementia?

Dr. Douglas Galasko

So the ability to measure biomarkers in the blood has really been transformative for the clinical approach to memory disorders and Alzheimer's disease. The tau protein that builds up in the brain also is detectable in the CSF or spinal fluid where we have been able to assess biomarkers for many, many years.

In the spinal fluid, it exists as a series of fragments. So we don't detect the whole tau protein, we detect a number of pieces of tau, but the levels are increased. In the brain, tau is hyperphosphorylated, meaning that phosphate is added to it as it forms aggregates. And in the CSF, we can detect a number of these phosphorylated sites of tau called pTau.

One of them is called pTau 217 and over the last five years we've been able to detect several forms of tau including pTau 217 in the blood in addition to the spinal fluid. In order to detect pTau 217 in the blood we have needed to be able to establish very sensitive and specific assays. So there are two kinds of assays used to measure pTau 217 in the blood. The most common types of assays are called immunoassays, ELISAs or something similar, in which an antibody is used to capture a piece of tau from the blood and another antibody that may recognize the pTau 217 site is used as a reporter antibody. The combination is highly specific and when the reaction is amplified, it is possible to get a readout showing very, very low concentrations of pTau 217 in the blood. Another approach to measure pTau 217 involves mass spectrometry. Here typically an antibody is used to initially capture the pTau 217. It is then isolated and fed into a machine called a mass spectrometer that is very sensitive at detecting a specific fragment of pTau 217. So a number of highly accurate and sensitive assays have been developed and are now available through several different laboratories. Many studies have shown that pTau 217 is sensitive to the presence of amyloid in the brain. It seems a little paradoxical. One would expect pTau 217 to be most sensitive to tau and it correlates to some extent with the burden of tau, but it correlates the most strongly with the presence of amyloid. It is thought that at some point amyloid causes some kind of reaction that leads to tau pathology and the buildup and the breakdown of tau with the release of pTau 217 and this is relatively specific for Alzheimer's disease. So in other kinds of dementing disorders, in dementia with Lewy bodies or frontotemporal dementia for example, one does not have this amyloid-tau interaction and one would not be able to detect an increased level of pTau 217. So therefore being able to detect pTau 217 as elevated or increased in the blood gives us insights into the presence of amyloid in the brain. And it turns out that these changes can develop quite early, sometimes even before the presence of major symptoms of cognitive decline.

16:25

Dr. Jane Caldwell

Wow, that's a great explanation. Well, you're sort of leading me to my next question. Let's talk about amyloid 1-42. Why do we use a ratio between pTau 217and β-Amyloid 1-42?

Dr. Douglas Galasko

So it is possible to measure amyloid biomarkers in spinal fluid and in blood as well. And many years ago, we made the finding that a particular form of amyloid called β-Amyloid 42, which is a longer form of the amyloid protein, is highly prone to aggregate and it clumps and gets deposited within plaques. There are other forms of the amyloid beta protein that are more common than β-Amyloid 42. The most common of these is β-Amyloid 40 or 1-40 and it is much less prone to aggregate. So normally the amyloid proteins are released from nerve cells and get into the spinal fluid and potentially get into the blood. When the β-Amyloid 42 protein builds up in the brain, we believe that there is less of it available to get into to the spinal fluid and potentially to get into the blood. And so levels of β-Amyloid 42 would be decreased as the amyloid builds up within the brain. We can measure β-Amyloid 42 using very specific kinds of tests or assays in the spinal fluid and in the blood. And we find that levels of β-Amyloid 42 are decreased in Alzheimer's disease. It turns out that levels are generally pretty low and there are other factors that can impact the concentration of β-Amyloid 42. So normalizing it for something else can increase the accuracy of the test. Initial research looked at combining β-Amyloid 42 with its related protein β-Amyloid 40 and so a ratio of β-Amyloid 42 to β-Amyloid 40 gives a more precise readout to measuring β-Amyloid 42.

Similarly, it's possible to combine an amyloid biomarker, a direct amyloid biomarker such as β-Amyloid 42 with an indirect marker such as pTau 217. And so the ratio of pTau 217 over β-Amyloid 42 may be able to increase the precision and accuracy of detecting amyloid compared to using either of these markers individually.

19:13

Dr. Jane Caldwell

I see. During the review of the Lumipulse-G pTau 217/ β-Amyloid 1-42 plasma ratio, the FDA evaluated data from a multicenter clinical study of 499 individual plasma samples from adults who were cognitively impaired.

The samples were tested using the Lumipulse G ratio and compared with both the amyloid PET scan or the CSF test. Have you found in your clinical work that plasma biomarker ratios are concordant with other diagnostic tests such as these?

Dr. Douglas Galasko

So, we have been using measures of plasma biomarkers such as pTau 217 or the pTau 217/β-Amyloid 42 ratio in the clinic in some scenarios and we've tried to use this as a guide in some patients as to whether they may have amyloid or are unlikely to have amyloid. If they are likely to have amyloid, we will often follow this with a conflux such as a lumbar puncture to measure CSF or an amyloid PET scan. And generally, I have found that there is strong agreement between people who have a high level of plasma pTau 217 or a high ratio of 217 to β-Amyloid 42 and the presence of amyloid detected by another method. But that's my experience in a relatively small number of people in a clinical setting. As you mentioned, the study that was presented to the FDA looked at data from 499 adults with varying levels of cognitive impairment. In addition to that study, there have been many studies looking at pTau 217 in relation to amyloid PET, tau-PET, and CSF biomarkers in many different patient populations and research cohorts and the findings uniformly indicate that plasma pTau 217 can detect the presence of amyloid and that cut-offs can be developed that allow this to be done very, very sensitively with an accuracy that can be higher than 90%.

21:50
Dr. Jane Caldwell
Are patients hesitant to have the CSF tests?

Dr. Douglas Galasko
So, CSF tests have been done in a number of studies where plasma was also collected and stored. And again, the relationship seems to be quite strong. And in some studies where plasma and CSF and PET scans were done, it turns out that the plasma biomarkers related to pTau 217 perform as accurately, in some studies even slightly more accurately, compared to amyloid PET than the CSF biomarkers.

So this gives us a lot of confidence in the ability to be able to use plasma pTau 217 in clinical situations.

22:45
Dr. Jane Caldwell
So why do you believe these plasma biomarkers are preferable to the CSF measurements in PET imaging?

Dr. Douglas Galasko
And so the reason that plasma biomarkers can have a big impact, especially compared to CSF biomarkers, is convenience. It's much easier to do a blood draw than to do a lumbar puncture. It's less time consuming and there's less pain involved. And many patients are resistant or hesitant to undergo a lumbar puncture for a variety of reasons.

There are beliefs out there that lumbar punctures are extremely painful, can cause side effects and long lasting problems. While these beliefs are not accurate, they still color patients' preferences. And in an era where blood-based biomarkers are showing such accurate results, it seems very, very reasonable to start to offer plasma biomarkers in the workup to try and detect amyloid.

23:56
Dr. Jane Caldwell
Is cost also an issue for CSF biomarkers and PET scans?

Dr. Douglas Galasko
So, cost can be an issue with regards to biomarkers. It turns out that for CSF biomarkers, the cost of measuring the actual biomarkers has worked out to be fairly similar to the cost of plasma biomarkers. This may change over time because it could become a question of scale. It is likely that more and more clinicians are going to be ordering blood-based biomarkers and as there is more and more demand and laboratories get a lot of tests to be done, they may be able to scale and develop efficiencies and bring down the cost to some extent. In addition for CSF biomarkers, one has to think of the additional cost of the procedure of doing the lumbar puncture. PET imaging is extremely expensive and both CSF and blood-based biomarkers are much cheaper than PET imaging. At the moment in the US in order to submit a patient and have them approved for anti-amyloid immunotherapy, Medicare or CMS has approved either amyloid PET imaging or CSF biomarkers and will reimburse for these. At present, CMS has not yet approved the use of blood-based biomarkers as standalone to allow amyloid immunotherapy to be started. So in terms of figuring out the cost, I think it's necessary to also think about what is the workup that is being done and is somebody who has a blood-based biomarker also going to have a CSF biomarker and

an amyloid PET anyway, which might be the procedure in a specialty clinic, in a less specialized clinic where there may be more uncertainty about the presence of amyloid or not, then a blood-based biomarker could be drawn.

There's one other point to be made about the approval of the Lumipulse β-Amyloid 42 and pTau 217 ratio and that is that the approval was done with a high cutoff indicating the high likelihood of amyloid being present by PET scan and this likelihood would be more than 90%. And then there is a low likelihood cutoff, meaning that if somebody's blood level of the ratio of pTau 217 over β-Amyloid 42 falls below this level, there is an extremely low likelihood, again, more than 90% certainty that this person does not have amyloid in the brain. So what about a gray zone in between these two cutoffs? This gray zone might occur as often as about 18 or 19 percent. That was how common it was found in the study of 499 patients. If one orders a plasma biomarker test and it falls within a gray zone, then it's not possible to give the patient an interpretation that amyloid is present or absent.

In that case, it will be essential to proceed to either CSF testing or an amyloid PET scan to come up with a definitive readout. And so there's a little bit of potential ambiguity in ordering and interpreting blood-based biomarkers that while their initial cost may be relatively low, if there is an indeterminate result, then further testing will be necessary.

28:09
Dr. Jane Caldwell
I see. I know that AD is a long-term disease and final outcomes are hard to quantify, but do you believe that patient outcomes are improving due to early testing?

Dr. Douglas Galasko
I think that they definitely are.

If one ignores treatment for a moment, being able to identify memory problems at an early stage allows the patient to be much more involved in planning their future and planning their care. It also enables the family to be involved and since Alzheimer's is a long-term disease, a number of very important decisions need to be made at these early stages. It also prevents Alzheimer's presenting with some sort of catastrophe, for example, somebody having a traffic accident because of driving impairment or somebody being scammed or committing a financial indiscretion because of their impaired memory or cognition. So early diagnosis allows a number of steps to be put in place to allow for greater safety of the person who has the memory problem, which in the best of all worlds will allow them to function relatively independently for as long as possible. We also are advocating having people live in their own homes for as long as possible. Again, early diagnosis allows assessments of home safety issues, caregiving issues and other very important aspects of planning that again can provide a much smoother course downstream. Those would be some of the social factors where an early diagnosis can improve the situation.

One other aspect is that patients and families often are not quite sure what's going on when they're seeing these changes in their loved one. Sometimes they are afraid that it could be Alzheimer's disease, but sometimes they just don't have an answer. And being able to get an early workup, even if the outcome is the news that there is Alzheimer's disease present, sometimes being able to name the problem can be an important step in providing some level of closure of uncertainty and the ability to begin to plan for the future. So those are some of the social impacts.

Then we have treatment impacts. Being able to make an early diagnosis means being able to look at other aspects of health. I've mentioned vascular health before, trying to optimize blood pressure treatment, diet, cardiovascular health, recommending things such as good sleep, physical activity, social activity, treating mood disorders if they're present. All of these are really part of an overall holistic approach to trying to stabilize and improve the patient's function for as long as possible. Then we get onto drug treatment. There are medications that have been approved for the treatment of cognitive symptoms of Alzheimer's disease for many decades. The most widely used of these are the cholinesterase inhibitors.

And while the effects of cholinesterase inhibitors are relatively modest, they have been shown in clinical trials to often help to stabilize cognition and to keep people functioning at a particular level for somewhat longer. So an earlier diagnosis does allow us to offer cholinesterase inhibitor treatment. And finally, the most recent breakthrough in Alzheimer's therapy has been the ability to use antibodies that are directed against the abnormal amyloid protein in the brain; to try to remove this protein. There are several antibodies that have been approved in the U.S. by the FDA for the treatment of amyloid in Alzheimer's disease. Two of them are now in widespread use, donanemab and lecanemab, and while their use is complex, they are given intravenously by infusion. Donanemab is given once a month and lecanemab once every two weeks. And there are potential side effects that need to be monitored with clinical monitoring and with MRIs. And the initial treatment would be targeted for about 18 months. So we're talking about a fairly complex treatment.

It has been shown in clinical trials that these antibodies can successfully remove amyloid from the brain and that this treatment is associated with significant slowing of progression of Alzheimer's disease. The antibody treatment does not halt slowing of progression nor does it reverse progression, but there are demonstrable effects across clinical trials and it looks as though these effects are durable when people are followed for longer periods of time, 24 to 36 months. So early testing with cognitive assessment, clinical assessment, and biomarker assessment, including tests like plasma pTau 217 or the ratio of 217 over β-Amyloid 42, are an important part of thinking about a pathway where somebody might qualify for treatment with an anti-amyloid antibody and there might be an impact on slowing of disease progression even though, as I said before, this does not reverse the disease or arrest the disease.

34:37
Dr. Jane Caldwell
Here's my final question. What gives you hope when you look at our current understanding of AD?

Dr. Douglas Galasko
The development of biomarkers has been a diagnostic revolution in Alzheimer's disease. We used to use a diagnosis of probable Alzheimer's disease based on our clinical assessments of a particular kind of pattern or profile, and we were wrong a lot of the time, especially when we tried to make an early diagnosis. Some of the early clinical trials for Alzheimer's disease, in fact, enrolled people who did not have Alzheimer's.

So when we do a clinical trial for Alzheimer's disease, at present, we are able to use biomarker testing to screen people for whether they qualify or not and being able to use blood-based biomarkers is markedly more efficient than doing something like an amyloid scan or a lumbar puncture. And we can then screen to make sure that if we do enroll someone for an Alzheimer's disease clinical trial, they actually have Alzheimer's disease. The same obviously applies to treatment in the clinic. If we want to treat somebody

for Alzheimer's disease in the modern era, we need to establish and verify that they have Alzheimer's pathology in the brain. There are ongoing efforts to try to apply anti-amyloid therapy even earlier. There are several clinical trials being done in people who do not have symptoms of memory decline but test positive for a blood-based biomarker and followed up by amyloid PET scan. In one of these trials, blood-based biomarkers alone are being used to identify people who have amyloid. And then the idea would be to treat these folks with an anti-amyloid antibody for long enough to remove the antibody, the amyloid buildup in the brain. Then follow these people over time and see whether there is an impact on memory decline, it is possible that with very early treatment such as this, we may achieve the greatest benefit that's possible from anti-amyloid antibodies.

Having said that...

Treating amyloid does not seem to be the definite answer to everything that is important in Alzheimer's disease. We need to consider other pathological processes and we are now well on the way to being able to develop biomarkers that may allow us to detect and stage some of these other kinds of processes. We are able, for example, to detect the burden of tau pathology using tau PET scans and there are some emerging CSF and blood-based biomarkers that have a reasonable correlation with the burden of tau PET pathology. There have been a number of clinical trials that have targeted tau so far unsuccessfully but there are more efforts coming at this from different directions and so being able to do something about the buildup of tau in the brain is potentially going to have an impact.

I mentioned before that neuroinflammation is very important in Alzheimer's disease. There are cells called microglia and astrocytes that contribute and a number of pathways and mechanisms have been identified and again are being targeted in clinical trials. As we develop further clinical trials, we may be able to look at combination treatment. So just as cancer often uses combination treatment or HIV uses combination treatment, it may be that to treat Alzheimer's effectively, we need to combine treatment of amyloid with treatment of other kinds of pathological pathways. I also mentioned that if we look at the brain of somebody who had Alzheimer's developing in later life and who eventually died in, let's say, their 80s, we often find evidence for more than one pathological process in the brain. One of these processes is the buildup of a protein called alpha-synuclein and we currently have biomarkers to measure alpha-synuclein pathology using spinal fluid. We have been trying to develop biomarkers for synuclein pathology in the blood. So far this has been elusive but there are a lot of ongoing efforts and I would be hopeful that we could be able to detect multiple pathology and that this would give us the ability to develop direct targeted personalized and individualized treatment for people who may have more than one pathological process in their brain in the future. So to repeat: the presence of biomarker tests has really revolutionized how we approach Alzheimer's disease and related disorders that can cause memory and other problems in the brain. And as we develop a larger panel and a larger range of biomarkers, it's going to give us much greater ability to detect what is going on beneath the surface of the brain. We also would be hopeful at being able to measure these biomarkers over time to detect whether they are changing and whether our efforts at particular kinds of treatment are impacting these biomarkers.

So for example, it would be very convenient in someone who has, let's say, an anti-amyloid antibody treatment to measure a blood-based biomarker such as pTau 217 at the beginning of treatment and then at some point during the course of treatment to guide us in how the treatment is doing and what else we might want to do in future. So I think we have a remarkable toolkit that has developed and this toolkit

is only going to get better as time goes by and this is going to enable more interesting and more exciting efforts to develop clinical trials and to eventually spill over into effective treatment and quite possibly prevention for Alzheimer's disease and a number of related disorders.

41:30
Dr. Jane Caldwell
Wow, that's great news. Dr. Galasko, thank you so much for taking time from your busy schedule to speak with us today.

Dr. Douglas Galasko
You're very welcome. It was pleasure.

Dr. Jane Caldwell
And thank you for listening to the *On Medical Grounds* podcast. OMG is your source for engaging, relevant, evidence-based medical information. This podcast was sponsored by Fujirebio Diagnostics, makers of the Lumipulse-G Beta Amyloid Ratio Test.

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