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Tau and Neurodegeneration in Alzheimer's Disease: Bridging Pathology and Clinical Progression Through Biomarkers

ReachMD Announcer:
Welcome to ReachMD. This program, titled "Tau and Neurodegeneration in Alzheimer's Disease: Bridging Pathology and Clinical Progression Through Biomarkers," has been organized and funded by Biogen. It was hosted by ADPD and was previously recorded, so the Q&A functionality is not available. Dr Michelle Mielke and Professor Henrik Zetterberg have been compensated by Biogen for their participation, and this program is intended for US healthcare professionals only. And now, here's Yuval Zabar.

Dr Yuval Zabar:
Again, welcome you.

I, I want to welcome you all.

My name is Yuval Zabar.

I am a medical director at Biogen.

And today we're going to do a presentation on tau and neurodegeneration in Alzheimer's disease.

With us, we have two esteemed speakers, Doctor Michelle Mielke and Professor Henrik Zetterberg, who will provide us with their expertise and knowledge in this area.

Next slide.

So on the agenda today, there are three main topics that we will cover.

I'm going to ask our speakers some pointed questions to address the following subjects.

So first, we're going to explore the pathophysiology of Alzheimer's disease as it's related as it's related to clinical progression.

Second, we'll do a deeper dive into biomarkers of tau and neurodegeneration and how they correlate with clinical progression.

And then lastly, we'll talk about the current and the potential future implementation of these biomarkers, both in research and in clinical practice.

The presentations will be followed by a Q&A section for the live audience attending today.

Please submit your questions in the chat.

Next slide.

This is a link to the Biogen Alzheimer's disease education platform called Know tau.

You can use the QR code at the bottom right-hand side if you wish to explore the website.

I'm going to show this slide again at the end of the presentation for convenience in case you missed it this time around.

Next slide.

So now I'd like to say a little bit more about our speakers.

Doctor Michelle Mielke is a Professor of Epidemiology and Neurology at the Wake Forest University School of Medicine.

She serves as the Associate Dean of Research there, and her research primarily focuses on the epidemiology of Alzheimer's disease and cognitive aging, with a particular emphasis on sex differences, cardiovascular risk factors, and biomarkers.

She has over 400 peer reviewed publications, and her work has really significantly influenced our understanding of Alzheimer's disease.

Professor Henrik Zetterberg is a Professor of Neurochemistry at the University of Gothenburg.

He holds also an honorary professorship at the University College in London, where he directs the UK Dementia Research Institute's Fluid Biomarker Lab.

His research focuses on developing and validating blood and CSF biomarkers for neurodegenerative diseases.

He has over 1000 peer reviewed publications and his work in translating biomarker research into clinical practice is really fundamentally changing how Alzheimer's is diagnosed and monitored.

Next slide.

These are our speaker disclosures.

Next slide, a quick disclaimer.

There are no approved products that are directed at tau and the efficacy and safety profile of tau directed drugs has not been established.

Next slide.

So I'd like to just do a very quick introduction to the pathophysiology of Alzheimer's before we launch into our main presentation next slide.

So we now understand Alzheimer's disease is a complex interaction of multiple pathophysiological processes.

Of course, there's the hallmark pathophysiologies of amyloid beta plaques, tau tangles, and neurodegeneration, but there are other proteinopathies such as synucleinopathy.

There are metabolic derangements as well as neuroinflammatory mechanisms, all of which interact towards disease progression.

Next slide.

As I mentioned, the hallmark pathophysiology of the disease includes amyloid plaque, tangles, and neuronal degeneration.

These comprise the current ATN framework, which allows us the opportunity to diagnose Alzheimer's on the biological basis through the use of biomarkers.

Earlier this year, we conducted a webinar that explored the relationship between amyloid plaque and tau and how they might relate to synaptic damage and neuronal loss.

This presentation will focus more on the relationship between tau pathology and neurodegeneration as they relate to clinical progression.

Next slide.

So we'll move on to our first question.

This is for Professor Zetterberg.

Can you tell us what is physiological tau and how does tau become pathological?

Prof. Henrik Zetterberg:
Many thanks, Yuval, for that very important question.

And we have prepared some slides to discuss it.

If you look to the left, you see a picture of physiological tau.

So physiological tau is primarily found in the axon and there it serves several functions.

So in healthy neurons, tau participates in regulating microtubule stability and axonal transport.

It is also involved in regulating synaptic function and potential also in plasticity.

There are some indications that that the tau is involved in DNA maintenance and nucleolar organization, but that is much less well established, especially in relation to Alzheimer's pathophysiology.

If we go to pathological tau, this is something that happens in the axon in close linkage or association with amyloid effects on the synapse, we can click once more.

In AD phopsho-tau, beta amyloid basically somehow directly or indirectly induces tau phosphorylation and phosphorylated tau detaches from axons and redistributes towards the somatodendritic compartment.

So in Alzheimer's, we have an Abeta-induced loss of normal tau function in the axon.

In addition, pathological tau may in itself lead to impaired axonal transport.

There is also strong evidence on neurotoxic tau aggregation that may propagate and then we have a strong link between tau pathophysiological changes, especially this tau phosphorylation and synaptic dysfunction and synapse loss.

The temporal order is a little bit disputed.

If we have synapse dysfunction that induces tau loss of function or if tau loss of function contributes to tau dysfunction.

One could also think that these are interacting pathways that that work in a synergistic manner.

Next slide please.

So Tau misfolding and aggregation is at core of Alzheimer's disease pathophysiology.

So normally tau is a monomer that sits on the tubulin dimers in the microtubule.

This monomer gets phosphorylated and then it lets go of the tubulin dimers.

It becomes basically free floating, and this free-floating tau can then attach to other free-floating tau molecules and form tau oligomers that eventually oligomerize further and form insoluble aggregates so that you end up with a tau fibril, and now we have moved to the right in this in this nice figure.

This may aggregate further into paired helical filaments and actually tau inclusions that are quite big, and then eventually this can be seen as neurofibrillary tangles in the neuron.

Next slide, please.

These neurofibrillary tangles are depicted in this immunohistochemical analysis here.

So, to the left in this picture you see normal brain tissue and then you see brain tissue with more diffuse tangle pathology.

You see brain tissue in the middle where you can actually detect pretangle tau assemblies and these mature into real tangles that actually are both pre tangles and natural tangles were depicted beautifully by Alois Alzheimer in his early investigations of Alzheimer's brain tissues.

And then we have ghost tangles.

And what is a ghost tangle?

Well that is when the neuron harboring the tangle has died and then these very difficult to solubilize tangles remain in the brain tissue as ghost tangles.

Tau that is part of pathologically folded can propagate and take normal tau and misfold it.

So this is the hypothesis behind tau propagation.

That may be amyloid initiated, but this process could actually also become amyloid independent.

Although most researchers agree that the amyloid is a big trigger of this.

Next slide please.

Post-translationally modified tau may lose its normal function and it may gain an abnormal function in terms of self-propagating tau

toxicity.

Post-translational modifications that have been described for pathological tau includes phosphorylation.

That's the main change.

And then we have a number of other post translational modifications, the pathophysiological relevance of which is much less strongly, much less known.

I could say. Tauopathies include primary tauopathies where you have mutations in the tau gene, the *MAPT* gene, those we see in PSP, CBD, and Pick's disease.

And the primary tauopathies, they have some type of primary tau dysfunction that could involve altered splicing, altered folding, altered expression, and other factors.

And then you get tau pathology that you see in the middle and tau gain of toxic function.

Secondary tauopathies, the main one is Alzheimer's disease where beta amyloid triggers that tauopathy, and there we have a strong mediating link with a ApoE, especially the epsilon four isoform or variant of the gene that that gives you a ApoE4 isoforms.

This contributes when it comes to beta amyloid's ability to induce tau dysfunction, and eventually we have a little bit of a vicious circle in regards to tau gain of toxic function, which eventually leads to neuronal dysfunction and degeneration.

Then we have a lot of other copathologies, synucleinopathies, epilepsy, traumatic brain injury, and other conditions where tau dysfunction may be gained.

And then eventually we have this common pathway.

We have neuronal dysfunction that leads to neurodegeneration.

Next slide, please.

Hyperphosphorylation of tau has a pathogen physiological role in Alzheimer's disease.

So in Alzheimer's disease, we have this phosphorylation of tau, which leads to pathological tau and tau pathology in this toxic loop that is depicted in this figure.

Next slide, please.

Dr Yuval Zabar:
Thank you, Professor Zetterberg.

The next question is for Doctor Mielke.

How does tau correlate with cognition in people living with Alzheimer's disease?

Dr Michelle Mielke:
So thanks Yuval.

That's a great question.

Before I jump to the answer, I first want to talk about how we characterize tau severity in the brain.

So Braak staging is a way to measure the severity of tau pathology and Alzheimer's disease.

And on this side, Braak staging is measured using a tau PET tracer.

As we can see, tau pathology in Stage I starts in the transentorhinal cortex and then spreads to the entorhinal cortex and hippocampus in Stage II. In Stages III and IV, we see increased involvement in the temporal cortex and at the most severe stages, V and VI, tau pathology extends to the primary sensory cortex. Next slide.

So utilizing Braak staging, multiple studies have shown associations between tau pathology and cognition.

The study shown here has examined multiple cognitive domain composites and found that cognitive impairment started to appear in Stage II with memory dysfunction, and Stage II is compatible with neurofibrillary tangle accumulations, which is restricted to the medial temporal regions. At later Braak stages and tau severity, we then start to see changes in other cognitive domains such as executive, language, and visuospatial function.

Now it's also important to note on the bottom with MMSE, MOCA, and CDR, that by the time an individual gets to stages V and VI, they have cognitive impairment and often moderate dementia.

Next slide, please.

So expanding on tau PET, what are some of the other biomarkers that are used in the diagnosis and progression of Alzheimer's disease?

Next slide.

So we know that Alzheimer's disease pathology starts decades prior to clinical symptoms.

The first pathology that typically appears is amyloid plaques and this can be measured by CSF and PET biomarkers.

Closer to the time of the onset of clinical symptoms, tau pathology starts to appear, which can also be measured by CSF or PET biomarkers.

And then around the time of symptoms and thereafter, neurodegeneration is also ongoing.

And again, this can be measured by either fluid or imaging biomarkers.

Next slide, please.

So the AT(X)N framework was a way to categorize biomarkers for the biological diagnosis and staging of Alzheimer's disease.

As you can see, we have biomarkers of amyloid deposition or A, tau pathology in purple or T, neurodegeneration or N in orange.

And for each of these, there are imaging and fluid biomarkers that are available.

In addition, in the 2024 reframing of the ATN framework, they added an X category, which is indicative of emerging biomarkers that are reflective of other disease mechanisms or pathology.

So in this case, X here refers to biomarkers of neuro inflammation, as shown in green, but can also refer to, for example, cerebrovascular disease or other pathologies such as alpha synuclein.

Next slide.

Now as I mentioned, for each of these biomarker categories, there are either imaging or fluid biomarkers that are identified and can be used.

So although either can be used, it is important to note that they do measure different things.

So, for instance, imaging biomarkers are direct measures of disease pathology and in general measure the accumulation of pathology.

In contrast, fluid biomarkers are indirect measures of the pathological processes.

Next slide, please.

So there are many amyloid biomarkers that can be used in the diagnostic workup of Alzheimer's disease.

Amyloid PET is often thought as the gold standard confirmatory test for Alzheimer's disease because it does enable the direct visualization of the regional cerebral amyloid beta deposition.

However, both in clinic and for research purposes, CSF biomarkers are also very commonly used for the diagnosis and reductions in the CSF Aβ42/40 ratio indirectly indicate the presence and ongoing formation of amyloid plaques.

More recently, plasma markers have become available and a low plasma Aβ42/40 ratio has exhibited high accuracy of detecting brain amyloid pathology compared to amyloid PET or CSF.

Next slide.

Dr Yuval Zabar:
Thank you very much, Doctor Mielke.

That was a lot of information in a very short amount of time.

We're going to move on to the next question, which is back to you, Professor Zetterberg.

What can tau biomarkers tell us about the progression of Alzheimer's disease?

Prof. Henrik Zetterberg:
Thank you, Yuval.

Here we will discuss a lot about differences also between imaging and biofluid based biomarkers.

So tracking tau pathologies provides additional diagnostic and prognostic insights, and this also relates to the closer association and correlation with tau pathology in the tissue and cognitive impairment.

In Alzheimer's disease, tau correlates more strongly with clinical progression than amyloid, highlighting the need for biomarkers of tau pathology.

So tau PET was observed to be superior to Aβ PET and MRI for predicting cognitive decline, but more research is needed to demonstrate the ability of tau PET to inform prognosis for individuals with AD.

The tau protein in biofluids, we have many different types of tau biomarkers to measure and the ones most of you have heard about, and some of you know a lot about, are the phosphorylated forms of tau. The classical Alzheimer biomarker in biofluids was CSF p-tau181.

But now, the other phospho-tau forms are also available in CSF.

Now we also have plasma tests for these particular biomarkers.

And among the phospho-tau forms, there is now a consensus that p-tau217 seems to be a little bit more diagnostically accurate for Alzheimer's disease pathophysiology than the other ones.

So there are a number of reasons for that.

Tau phosphorylation happens in response to amyloid in Alzheimer's disease, and phospho-tau increase in biofluids reflects an amyloid effect on neurons.

And this goes for most of the phospho-tau forms, although some have been more related, more claim to be more related to amyloid and others more related to tau.

But I think these are, it's a little bit of details this to me that most phospho-tau forms are a marker of are markers of an amyloid effect on neurons.

But there is one tau biomarker in biofluids that stand out, and that is the biomarker you see to the right here, MTBR-tau243.

And in CSF this is a tryptic fragment that correlates a bit with total tau levels.

But it also seems to relate more strongly to tau PET signal.

And in plasma there is a possibility of measuring a semi-tryptic endogenous MTBR-tau243 fragment that potentially could be produced from tangles.

This has not been established yet, but that's a hypothesis that is very it's a very fascinating hypothesis.

And increased levels would then correlate with and potentially be a quite direct biomarker for tau tangle pathophysiology.

But here you see the differences.

Tau PET gives you a tissue change phospho-tau levels in biofluids, shows a neuronal reaction to amyloid, and we then have a potential tau tangle marker in biofluids in the form of MTBR-tau243.

There are also a couple of other more C-terminal tau fragments that potentially could have this association.

Next slide, please.

There are several phospho-tau epitopes in CSF and most of them have shown this link to amyloid positivity.

The fold change varies a bit across the different biomarkers and over and over p-tau217.

But in CSF, also p-tau231 have looked quite relatively strong fold change that is important in a clinical chemistry context because the larger fold change, the less susceptible the biomarker is to different confounding factors, and biomarkers with a large fold change, they are often claimed to be robust biomarkers.

In both these cohorts, the TRIAD cohort from Pedro Rosa-Neto and the Biofinder cohort from Oskar Hansson and Sebastian Palmqvist, the best biomarker performance was observed for p-tau231, p-tau217, and p-tau205.

And then I should remember that these were CSF results.

Next slide, please.

In plasma, plasma p-tau217 in the middle have consistently shown that the largest fold change and also this interesting stepwise increase in relation to severity of Alzheimer's disease pathophysiology, in this case as reflected by amyloid PET centiloids.

So the more when there is a little bit of amyloid in tissue, p-tau217 increases, and the more there is, the higher the level and this could potentially reflect, but this is a bit speculative, the number of neurons affected by amyloid. Plasma p-tau181 is a quite good biomarker.

p-tau231 seems to be the biomarker that increases earliest in response to amyloid.

But these are as I've mentioned before a little bit of details and not entirely established.

It might also be assay dependent some of these differences between the different phospho-tau forms.

But though all of you have heard a lot about p-tau217 and there is there are reasons for this because this biomarker over and over turns out to be the most robust in plasma.

Next slide, please.

Plasma p-tau217 has demonstrated high discriminative accuracy for diagnosing Alzheimer's disease.

And in the left panel you see AUCs for detecting Aβ positivity.

And then this is a comparison between Aβ-negative cognitively unimpaired people and Aβ-positive Alzheimer's groups.

And you see that you get an almost complete concordance with amyloid PET or CSF measures of Aβ pathology.

There are studies indicating equivalence of plasma p-tau217 with CSF p-217 for identifying concurrent Aβ PET and tau PET positivity.

And there are also quite good results for the other phospho-tau forms.

It's important not to forget them.

Next slide, please.

So tau biomarkers correlate with neurodegeneration and Alzheimer's disease and may describe Alzheimer's disease progression.

I have just said that tau biomarkers in biofluids reflect amyloid, but we then have this link between an amyloid-induced tau phosphorylation that mobilizes tau so it becomes free floating.

This mobilized tau, the internal part of it will be secreted from neurons.

The C-terminal part of the MTBR containing region will stay inside the neuron and this part of tau normally undergoes intraneuronal clearance by lysosomes and proteasomes.

But when lysosomes, proteasomes are exhausted by age, copathologies, or too much tau, then free floating tau containing these parts of tau may oligomerize, fibrillize and form tau tangles.

So high levels of phospho-tau are associated with or indicate that this process is ongoing.

It's a direct marker of amyloid and it will be a predictive marker of tau tangle pathology linking, putting for almost like a Swiss army knife biomarker that reflects both amyloid and tau changes.

If we go into details, plasma p-tau217 and tau PET, they have a strong association both of them with cognitive decline in clinical progression to MCI among cognitively unimpaired individuals.

Plasma p-tau217 may be increased along the AD continuum, getting higher and higher the more advanced the disease is, and although both plasma p-tau217 and 181 are predictive of abnormal Aβ PET, p-tau217 has this type of it has a higher diagnostic accuracy and this type of stepwise increase in its levels, which may be useful if we want to stage Alzheimer's disease.

Next slide, please.

MTBR-tau243 is a potential biomarker of aggregated tau pathology and potentially a biomarker that that performs a little bit more like

tau PET, and longitudinal changes in CSF MTBR-tau243 by baseline indicates also that when you enter the Aβ-positive, tau-positive stage, then the biomarker is up.

And this has also been shown in relation to other markers using mass spectrometry techniques.

Next slide, please.

Dr Yuval Zabar:
Thank you, Professor Zetterberg. If I may, maybe I can keep you on for this next question as well.

What can neurodegeneration biomarkers tell us about Alzheimer's disease?

Prof. Henrik Zetterberg:
Yes, that's also a very important question.

So we could think that some of the phospho-tau information will be enough to measure neurodegeneration.

But then again, we need to think of what the phospho-tau markers indeed do reflect.

Aβ-induced tau phosphorylation that predict neurodegeneration.

But then it's wonderful if you also have direct markers of neurodegeneration and one of the most important biomarkers is MRI, I mean that's the standard.

I would say it's almost the reference test for neurodegeneration in Alzheimer's disease and other neurodegenerative dementias.

So MRI is used to examine, to estimate brain atrophy in regions characteristic of Alzheimer's disease.

And here we have another important difference between biofluid-based biomarkers and imaging.

The regional anatomic distribution of the neurodegeneration will likely not be captured in a reliable manner by biofluid-based biomarkers, but MRI will show it directly. FDG-PET measures cerebral glucose metabolic rate and this is also labeled as a neurodegeneration biomarker.

So when you have neurodegeneration you will downregulate cerebral glucose metabolism.

It could reflect frank neural loss, but it can also reflect the neuronal hypermetabolism and also reduced activity of other cell types in the brain.

Then we have the fluid-based biomarkers of neurodegeneration and they are a little bit more tricky to discuss I think.

So for many years we described total tau as a neurodegeneration marker and it is to some extent.

Total tau is the regular, the general tau that leaks, that can leak from dying neurons and this happens in stroke, and it happens in encephalitis, and it happen also in Creutzfeldt-Jakob disease.

Then you get a total tau increase that is not correlated with phosphorylated tau.

But in Alzheimer's, total tau and phospho-tau are strongly correlated.

And this has made total tau a little bit questioned as a neurodegeneration marker in Alzheimer's disease.

When you have neurodegeneration, you have synaptic loss, and then we have a synaptic marker that works quite well, at least when we measure it in CSF and that's neurogranin.

So when you have Alzheimer’s disease, amyloid, tau pathophysiology, neurogranin levels are increased and potentially this could then reflect synaptic degeneration, but it is not completely understood if that is the case.

The most well-established neurodegeneration marker is neurofilament light.

And this is something that that this is something that this marker is released from neurons when they are injured by any mechanism.

So that happens in neurodegeneration and also upon stroke, traumatic brain injury, and other disease processes in the brain that that kills off neurons.

And neurofilament light can be measured in blood.

The problem with neurofilament light when we discuss Alzheimer's is that when people are older than 70, 75, 80, this marker is very

noisy.

I believe this is because of a lot of degenerative processes, cerebrovascular and other types of degenerative processes happening in parallel in the aging brain.

And then this marker doesn't become a really reliable marker.

At least it's hard to interpret.

You have to link it to other markers also.

So if we want to measure neurodegeneration in Alzheimer's disease, I won't say that MRI is likely the most reliable measure, but it works very well in familial Alzheimer's disease.

When neurodegeneration happens in 45-, 50-, 60-year-old people, then you see a quite clear increase in CSF and blood NfL levels. Next slide please.

Now, so several fluid degeneration biomarkers have shown potential use in Alzheimer's disease.

Neurogranin is increased in AD, it's a marker of synaptic dysfunction.

It increases also very early in response to amyloid pathology onset, and it almost looks like it increases in parallel with phospho-tau as a neuronal reaction to amyloid.

But if we look at other neurodegenerative diseases, neurogranin levels are relatively normal, which makes that a bit of a problem if we want to label it as a neurodegeneration marker.

NFL is a non-AD specific neurodegeneration marker associated with external damage and loss irrespective of underlying cause. It works to detect early-onset Alzheimer's disease neurodegeneration, but in people who are old, the biomarker is noisy and difficult to interpret.

And then we have, I think also if we click one more, then we have total tau, the most contested neurodegeneration marker, I think.

So total tau in Alzheimer's disease increases in close correlation with phopsho-tau and that makes it a little bit difficult to interpret in terms of if it really is a neurodegeneration marker or if it is a marker that more reflects an amyloid effect on neurons.

CSF and plasma NFL are the only fluid neurodegeneration biomarkers listed in the current Alzheimer's Association frameworks that you've all mentioned before.

And Michelle, combining CSF total tau, CSF neurogranin, and CSF NfL may improve AD diagnostic accuracy compared with individual biomarkers.

So it may be that these this treatment of biomarkers together with the imaging can give a quite comprehensive view of the ongoing degenerative processes in the Alzheimer's brain.

Next slide, please.

Plus, NfL was shown to be elevated in brain regions vulnerable to Alzheimer's disease pathophysiology.

And here you see what it looks like in terms of the NfL concentrations in the AD continuum.

But you can clearly from the left graph see the problem or the challenge with the NfL as a biomarker in Alzheimer context.

The right most figure shows that there is a correlation between NfL change and neurodegeneration-affected brain regions in Alzheimer's disease.

So it definitely has some potential for measuring AD type neurodegeneration.

But if there is a lot of if the patient has a lot of cerebrovascular disease and other potential contributing factors, this would be a little bit hard to tease out.

Next slide, please.

Biomarkers beyond ATN may reflect neuronal dysfunction.

We have, as we've mentioned earlier in this session, multiple disease processes going on in Alzheimer's disease. We have astrocytic activation that is reflected by increased levels of YKL-40 and GFAP.

GFAP works surprisingly well in blood.

So plasma GFAP levels are strongly linked with astrocytic activation in Alzheimer's disease, especially if you relate this to amyloid.

Then if a previous increase in concordance with phospho-tau levels.

And then if we click one more, we have microglia.

Soluble TREM2 has been discussed a lot as an Alzheimer biomarker reflective of microglial activation in Alzheimer's disease.

It increases early in the disease process in response to amyloid.

Then most studies indicate that it actually decreases when you enter a more frank neurodegenerative phase of the disease.

And this type of increase and then lowering has made it very hard to interpret, especially if you want to use this as a pharmacodynamic marker of microglia targeting therapies.

Next, if you click once more, we have SNAP-25.

That's another presynaptic marker.

It's a presynaptic biomarker, a protein expressed into presynapse and that could complement neurogranin if we want to measure synaptic dysfunction in Alzheimer's disease.

Next slide, please.

Dr Yuval Zabar:
Thank you very much, Professor Zetterberg.

So I think we're going to shift a little bit the discussion and talk more about the implementation for the use of biomarkers of tau and neurodegeneration in practice.

And so the next question is really for you, Doctor Mielke. What are the current recommendations for using these biomarkers?

Dr Michelle Mielke:
Well, thanks, Yuval.

There are several current recommendations.

Most of them to date have been research focused.

So in the context of clinical trials, tau and neurodegeneration biomarkers can inform clinical trial designs.

And how do they do that?

They can facilitate patient screening, selection, and stratification.

In early-stage clinical trials, they can provide evidence of target engagement and in later stage clinical trials they can provide or they can help monitor treatment efficacy.

In addition, tau biomarkers can support the development of investigational drugs through the representation of specific tau pathology.

Now in addition, neurodegeneration biomarkers are also important in clinical trials specifically to demonstrate that the investigational drugs can affect the downstream events related to tau pathology.

Next slide, please.

So we've talked about the 2024 AT(N)X criteria and again, this criteria highlights the role for both tau and neurodegeneration biomarkers to inform Alzheimer's disease diagnosis on the left, staging and progression in the middle, and then also the identification of copathologies on the right hand side, such as cerebrovascular disease.

Now again, this is for research purposes and it's important to note that many of these biomarkers are not currently available for clinical use.

Next slide, please.

And so again, as I mentioned, a lot of the recommendations have been focused on the use of these biomarkers for research purposes, which brings about the question as to how we start implementing these biomarkers in clinical practice.

And certainly there's several gaps that we need to bridge in order to make these more useful and interpretable for patient care.

A couple of these criteria are listed right here.

Certainly it's going to be important to harmonize protocols, particularly for those areas that are more rural or underserved and to determine similar cut points.

It's also very important to educate healthcare providers particularly in when biomarkers should be used and when they should not be used and then to implement approaches to really maximize their use throughout the patient pathway to benefit the diagnosis and featuring or staging the progression of Alzheimer's disease.

Now it's also important to note that really Alzheimer's disease in the general population is often diagnosed very late.

And so there also needs to be a paradigm shift in AD care, emphasizing the very early detection of cognitive impairment and using the biomarkers to estimate the etiology, which will allow a longer time for treatment and intervening before more severe symptoms occur.

And this will require scalable and efficient tools.

We'll have to standardize cognitive and functional assessments and then also incorporation of biomarkers.

Next slide, please.

So at this point, blood biomarkers are available clinically.

And so it is important to also consider various aspects of the use of blood-based biomarkers.

Next slide.

So certainly compared to CSF or neuroimaging, particularly PET biomarkers, blood-based biomarkers have several advantages.

They are more feasible and accessible particularly in rural and underserved areas.

And so as a result, we'll increase or reduce the time to diagnosis and further expand access to early detection and care.

Blood-based biomarkers are also cost effective and quite a bit cheaper compared to PET imaging and blood-based biomarkers are also less invasive compared to, for example, a lumbar puncture for the collection of CSF or for PET imaging as well.

So this will, you know, certainly help reduce some of the anxiety for patients as well as their family members.

Next slide, please.

So there are two types of blood-based biomarkers that can be used, triaging tests or confirmatory tests.

So triaging tests have high sensitivity and very high negative predictive value and as a result a negative result rules out that an individual has Alzheimer's disease pathology with high probability.

But there is need to have another confirmatory test such as CSF or PET to confirm that the person actually does have Alzheimer's disease pathology.

In contrast to this, a confirmatory test has both high sensitivity and high specificity.

So such that a negative result will rule out Alzheimer's disease pathology and a positive test can help confirm Alzheimer's disease pathology with high probability.

Next slide, please.

Now as we go forward and further bring these blood biomarkers into clinical practice, there are a lot of things that we still need to work through in terms of their implementation.

For example, it's very important to ensure the standardization across real-world settings, including in primary care.

This can include whether we use one or two cut points and the consideration of racial and ethnic differences.

It's also important to point out that there are certain chronic conditions such as chronic kidney disease that can significantly elevate the levels of these biomarkers.

And so education is needed in terms of interpreting the biomarkers in this context, because with the elevation for example by CKD that could result in false positives or with other conditions or medications, it could result in false negatives.

And so then, you know, it's certainly again very important to not just use the biomarker to diagnose somebody, but to use the biomarker as one part of an overall investigation into the underlying causes of the cognitive impairment.

There are also ethical and social issues that we need to consider certainly including the equitable access to testing and care of the blood-based biomarkers, but then also if confirmatory test is needed of subsequent PET or CSF testing.

There also may be coverage and reimbursement issues for the blood biomarkers, particularly if they are used in the asymptomatic stage for prognostic purposes, which is not currently recommended as a result of concerns of coverage.

And then lastly, we also certainly need to understand the impact of these biomarkers on the potential for stigma and discrimination and work with patients and providers to understand their thoughts on this process and what is most important to them.

Next slide.

Dr Yuval Zabar:
Well, thank you very much, Doctor Mielke and Professor Zetterberg, for your excellent presentations.

We covered a lot of ground in a very short amount of time.

So just as a quick summary, I just wanted to cover the major themes of our discussion.

So first, I think what we heard was that there is a convergence of pathophysiological changes in Alzheimer's disease on neurodegeneration and that tau and neurodegeneration biomarkers in Alzheimer's are associated with worsening cognition and clinical decline.

And secondly, we heard that tau and neurodegeneration biomarkers may play a role, an increasing role, in the care pathway for people who are living with Alzheimer's disease.

And they may have a variety of different roles in the future, such as extending from diagnosis, but also staging, prognosis, and potentially also identification of copathologies.

That said, of course, as these biomarkers are implemented into practice, there are important practical and ethical considerations that we'll need to consider to make sure that these biomarkers are utilized appropriately.

ReachMD Announcer:
This program was organized and funded by Biogen. If you missed any part of this discussion, visit Industry Features on ReachMD.com, where you can Be Part of the Knowledge. Biogen-273125, Date of preparation November 2025

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