

**World Dementia  
Council** Leading the Global Action  
Against Dementia



Virtual  
Dialogue

# Lessons from innovators: biomarkers

## Transcript

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# Lessons from innovators: biomarkers

## Meeting transcript



**Lenny Shallcross**, *Executive Director World Dementia Council*

Thank you for joining the meeting. As you saw when you joined, we are recording this because we publish a transcript after the meeting. I will come back to you if you speak, so you'll have a chance to edit your remarks. You can speak freely during the meeting and edit away at leisure afterwards before publication. If you're not speaking, please keep yourself on mute to avoid background noise. Along with publishing transcripts, we also publish reviews of all the meetings we hold in *Alzheimer's & Dementia*, so you will see a write-up there.

I realize many of you have participated in World Dementia Council meetings before, but briefly, it was set up by the UK government following the G7 Summit. It does two main things: convening global leaders to connect and share their perspectives, and publishing reports and recommendations. We hold virtual meetings like this, as well as in-person summits.

We're holding one in Istanbul in April next year just before the Alzheimer's Association International Conference Satellite Symposium. Our annual meeting will be in London on 20 October, and we'll have another in China in November 2026. We also run a series of convenings at major events and conferences.

Across the second half of this year and into next year, we are exploring different themes, one of which is innovation and how it drives progress in dementia research and policy. This meeting focuses on diagnostics; early in the new year, we will hold one on AI. We are also working on innovation in technology and how it can close the equity gap, alongside projects on advocacy and brain health.

In the interest of time, I'll stop there and say we have two chairs today. You don't have Howard — you have Laura, the Executive Director of Alzheimer's Drug Discovery Fund, ADDF. Howard had to drop out last night because of another commitment. While I was sleeping, Howard dropped out and Laura replaced him, which shows the benefit of sleeping to solve all your problems. I highly recommend it.

You've also got Stacey, a Council member who, as I'm sure you know, is President of FBRI. Randy, Mike, Charlotte, and Henrik will be speaking. Laura will introduce them, and since we've started a little late, I'll simply say thank you for joining us, and Laura, over to you.



**Dr Laura Nisenbaum**, *Executive Director of Drug Development, Alzheimer's Drug Discovery Foundation (ADDF)*

Thank you, Lenny. I just want to thank the World Dementia Council for bringing us all together for such an important and timely discussion. As Lenny mentioned, I am stepping in for Howard today. He sends his regrets, but I'm really excited to be here because biomarkers and innovation in biomarkers has been a central theme for me in my own research and scientific career. And as we know, biomarkers are essential to unlocking the future of treatment for Alzheimer's disease.

We see this potential in combination therapy and precision medicine, just as has been done for other devastating diseases such as cancer. When Howard co-founded the Alzheimer's Drug Discovery Foundation almost 30 years ago with Leonard and Ronald Lauder, the mission was simple: to accelerate the discovery and development of drugs to treat, prevent, and ultimately cure Alzheimer's disease. From the very beginning, we understood that biomarkers would be essential — which is why ADDF was built on three pillars: therapeutics, biomarkers and prevention.

The progress over these three decades has been extraordinary. Biomarkers have transformed the field and ultimately enabled the development of the first disease-modifying therapies. Back in 2018, we weren't where we are now. Leonard Lauder and Bill Gates recognized a critical gap and launched what we called the Diagnostic Accelerator — a \$100 million fund designed to fast-track accessible and scalable diagnostic tools. Since then, we've funded more than 70 projects focused on developing blood tests, ocular scans, and now digital tools.

But our journey in biomarkers began long before that. Back in 2000, Howard received a call from a now-famous CSO, Dan Skovronsky. He was then at the University of Pennsylvania and wanted to adapt the same dye that Dr. Alzheimer had used to detect pathology in microscopic slides — the Congo red dye — to create the first PET scan. That effort ultimately became Amyvid. It was spun out into Avid Radiopharmaceuticals, later acquired by Eli Lilly and Company, and the test became the amyloid PET scan. Approved by the FDA in 2012, it launched a new era in the development of anti-amyloid therapies and enabled the creation and approval of the first disease-modifying drugs. Since then, we've seen tremendous progress — first with blood tests from C2N, and then the first FDA-cleared IVD from Fujirebio. These are truly monumental advances. But I think we've only just scratched the surface. Beyond blood biomarkers, we're now beginning to see digital biomarkers powered by AI, which we believe will allow us to integrate blood, imaging, and digital tools to complete the picture of each patient's true health.

Through the Diagnostic Accelerator, we've also invested in a program called SpeechDX — the first of its kind study designed to enable the development of prognostic biomarkers, which we know are critically needed. We've done this through the creation of a large longitudinal dataset combining biomarker, speech, and clinical information.

Looking ahead, we recognize there are still major unmet needs — including biomarkers for co-pathologies such as TDP-43 and alpha-synuclein, as well as for the underlying pathobiology of dementia, including inflammation, metabolism, and vascular health, among others. To deliver on this promise, we'll need to understand each patient's unique biomarker profile so we can match the right patient with the right drug at the right time. It's a complex challenge, but I have no doubt that we're going to get there.

With that, it's my pleasure to introduce our panel of truly world-class experts who will share their perspectives on the past, present, and future of Alzheimer's biomarkers. First, I'd like to introduce Professor Mike Weiner from the University of California, San Francisco, who will reflect on how the field has evolved, the challenges that remain, and where we are heading in the development of new biomarkers. Mike, over to you.



**Professor Mike Weiner**, *Professor, University of California San Francisco (UCSF)*

## THE MAJOR PROBLEMS IN ALZHEIMERS CLINICAL RESEARCH INNOVATIVE APPROACHES

Michael W Weiner MD  
Professor UCSF  
PI ADNI

Twenty-one years ago, we launched the Alzheimer’s Disease Neuroimaging Initiative (ADNI), which has given us a great perspective on the role of biomarkers in Alzheimer’s research and clinical trials. I’m going to briefly summarize what I think the major problems are and a few innovative approaches that interest me.

## WHAT ARE THE MAJOR PROBLEMS IN AD CLINICAL RESEARCH?

- We need
  - Treatments that stop progression of and prevent onset of symptoms
  - Diagnostics which predict future decline and monitor therapeutic response
- What are the major problems?
  - Clinical research and clinical trials are extremely expensive due to high cost of trained staff for recruitment, assessment, longitudinal monitoring
  - Almost all clinical research is performed on more affluent, highly educated people who get their care from specialty clinics or academic centers
  - People with low income, education, low SES, and poor access to health care have more comorbidities and other problems which affect brain health
    - Therefore, the results of clinical trials and diagnostic methods are not generalizable to the entire population
    - This issue is even more important with emergence of GLP-1 agonists which may improve brain health, especially in populations with obesity, diabetes, hypertension, substance abuse

Clearly, we need treatments that stop disease progression and prevent symptom onset, as well as diagnostics that can predict future decline and monitor therapeutic response. What are the big challenges here?

The first problem is money. Clinical research and clinical trials are extremely expensive, in large part because of the high cost of trained staff needed for recruitment, assessment, and longitudinal monitoring. We have to pay a lot of people to do clinical research and clinical trials.

The second problem is that almost all clinical research is performed on more affluent, highly educated people who receive care from specialty clinics or academic centers. Those with lower incomes, lower education, and poorer access to healthcare often have more comorbidities and other factors that affect brain health, yet they rarely participate in clinical research.

If you look at all the papers that underpin our current knowledge — including foundational pathology papers in which we say, for example, that 80% of all dementia is related to amyloid and tau pathology — nearly all of that research comes from highly educated populations. We have very limited pathology and biomarker data from the half of the population that falls within lower socioeconomic groups.

This issue becomes even more important with the emergence of GLP-1 agonists, which have been shown to improve brain health — particularly in populations with obesity, diabetes, hypertension, and substance use disorders. These comorbidities are far more prevalent among lower socioeconomic groups.

The next slide shows data from the United States Census, examining people by decade of age — for example, ages 55 to 64 and so on. This is the recent census.

Table 6: Age 55+ education level (%) by age group

	55-64	65-74	75-84	85-96
<9th grade	5.01	4.88	6.28	10.35
9th-12th grade-no diploma	6.09	5.36	6.26	8.13
HS grad, GED	28.35	27.92	30.29	36.75
Some college-no degree	19.15	20.66	19.08	15.59
AD	9.30	9.14	6.66	4.66
Bachelor's	19.56	18.24	16.33	13.79
Grad/Prof	12.53	13.81	15.10	10.72

It illustrates the percentage of the population with less than a ninth-grade education. Ninth grade to 12th grade with no diploma, and high school education or graduate equivalent — in other words, these three upper rows represent people with a high school education or less. If we look at my age group, I'm just turning 85, you can see that more than 50% of the U.S. population aged 85 or older has a high school education or less.

Now, in the Alzheimer's Disease Neuroimaging Initiative (ADNI), which is similar to other major studies, only about 10% of participants have a high school education or less. Clearly, we have a big mismatch, and that's a major problem. So how are we going to solve this? How do we approach it?

## INNOVATIVE APPROACHES TO THESE PROBLEMS: RECRUITING LOW SES POPULATIONS

- ADNI is launching the TEAMS ADNI project
  - We propose to enroll 100-200 people with low SES from networks of Federally Qualified Health Centers (FQHCs), primary care clinics who serve the Medicare population. These patients lack private health insurance and many are not even covered by Medicare
  - We are working with the Clinical Director's Network, an organization which conducts clinical trials using networks of FQHCs
  - All participants will have a shortened ADNI battery with clinical assessment, blood tests, and as many MRI and PET scans as feasible
- The competitive renewal of ADNI (ADNI 5) will focus on enrolling a population which matches the US population by race, ethnicity, and SES (using education as a surrogate for SES)

At ADNI, we've decided to make this issue a priority and have launched what we call the *Teams ADNI* project. It's a subproject within the overall ADNI, and we're trying to enroll 100 to 200 people with low socioeconomic status — essentially defined as having a high school education or less, or not having health insurance.

We're working through networks of what are called Federally Qualified Health Centers (FQHCs). There are about 7,000 FQHCs across the United States — primary care clinics that serve people on Medicaid. Individuals on Medicaid typically lack private health insurance, and most aren't even covered by Medicare. There are roughly 80 million people in the U.S. enrolled in Medicaid. We're working with an organization called the Clinical Directors Network, which has a long history of conducting clinical trials through these FQHC networks. All of our participants will complete a shortened ADNI battery that includes blood tests and, where possible, MRI and PET scans.

Our next competitive renewal, *ADNI 5*, beginning in 2028, will be led by Susan Landau — I will not be the PI. This next phase will focus on developing a much more generalizable population that better matches the U.S. census, using this approach to include people with lower socioeconomic status.

## INNOVATIVE SOLUTIONS TO REDUCING COST AND INCREASING GENERALIZABILITY

- The launch of Chatbot GPT demonstrated the power of AI conversational voicebots or voice agents
- Our group has developed the voice Clinical Dementia Rating (vCDR) which interviews the study partner (family member or close friend) and then the patient. Automatically generates box scores, sum of boxes, categorical scores. The vCDR has no within or between rater variability, reducing variance and increasing statistical power. We begin validation in 2026
- AI powered automated voice agents will be used in AD clinical research and clinical trials for: education, marketing, consenting, screening, assessments, longitudinal monitoring, adverse events, scheduling of blood tests and scans. Ultimately will lead to huge cost reductions.

A second innovative solution that might help reduce cost and improve generalizability was inspired by the launch of ChatGPT, which demonstrated the power of AI conversational voice bots or voice agents. We've been working with John Morris for many years. Previously, we developed something called the *electronic Clinical Dementia Rating (eCDR)*. Over the last year, together with my colleagues Dr Rachel Nosheny and Dr Pedro Pinheiro-Chagas at UCSF, we advanced this to create the *Voice Clinical Dementia Rating (VCDR)*, which is completely automated. It works via mobile phone, landline, or the internet.

The system first interviews the study partner or family member to gather background information about the participant. Then, in a subsequent call with the participant, it uses that information to appropriately tailor the interview questions. The system then generates scores — box scores, sum of boxes, and categorical scores. The beauty of the VCDR is that it is very low cost compared to using a human rater. It also offers key advantages: it doesn't require scheduling, it's available 24/7, and it eliminates within- and between-rater variability, which is a major issue with many clinical assessments. This variability is a big problem, especially with the traditional CDR, which is scored by clinician judgment rather than an algorithm. The VCDR helps address that issue by reducing variance and increasing the statistical power of clinical trials. We're now completing development of the full VCDR and will begin validation studies including at Washington University with John Morris's group in 2026.

I'm convinced that AI-powered automated voice agents will play a major role in Alzheimer's disease clinical research and clinical trials — used for education, marketing, consenting, screening, assessment, and longitudinal monitoring, adverse events, scheduling blood tests and scans. Ultimately, in just a few years, all of us will be interacting with these automated voice agents for all kinds of purposes. I expect this will lead to huge cost reductions in conducting clinical trials and will also improve data quality overall. The data will be better because there'll be less of this within and between rater variability.




**Dr Laura Nisenbaum**, *Executive Director of Drug Development, Alzheimer's Drug Discovery Foundation (ADDF)*

Thank you very much. Thank you, Mike. It's really great to see the innovation within ADNI, which has been such a longstanding mechanism for the development of biomarkers. I'm looking forward to seeing how these additional innovative aspects add to our understanding of patients and the changes that occur for them.


With that, I want to turn it over to Professor Randy Bateman from Washington University in St. Louis, who's going to discuss the timelines of biomarker development and how these markers evolve over the course of the disease.




**Professor Randy Bateman**, *Professor, Washington University St Louis*



**KNIGHT FAMILY**  
**DIAN TU**  
Dominantly Inherited  
Alzheimer Network  
Trials Unit




**Washington University in St. Louis**  
SCHOOL OF MEDICINE




**DIAN**  
Dominantly Inherited  
Alzheimer Network

## The biological interpretation of changes and order of Alzheimer's disease biomarkers


**Randall Bateman M.D.**  
Charles F. and Joanne Knight Distinguished Professor of Neurology  
DIAN and DIAN-TU PI and Director  
Washington University School of Medicine



**SILO CENTER**



**hopecenter**  
for neurological disorders



**Knight ADRC**  
Alzheimer's Disease Research Center  
WASHINGTON UNIVERSITY ST. LOUIS

I wanted to cover what I thought were a few salient points at this time in the field's development of biomarkers and their utility. We've entered an era where we're using biomarkers, particularly blood-based biomarkers, clinically to help diagnose patients in our clinic and to determine whether we would treat them with anti-amyloid therapies. We've achieved high sensitivity and high specificity in multiple biomarkers, largely for amyloid plaques but, more recently, for tau tangles. However, there are major gaps in the field that we need to address in order to make full use of these biomarkers to accelerate treatment development and implementation.

## Alzheimer's disease biomarkers – the challenge

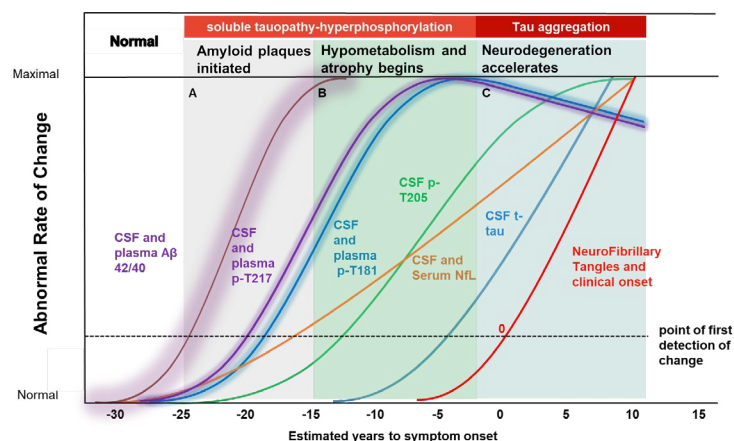
- Highly sensitive and specific Alzheimer's disease blood biomarkers have recently become reality for amyloid plaques and tau tangles.
- **But in order to utilize for research and clinical trials, we should understand what exact molecular processes these biomarkers are actually measuring.**
- **Further, we need interpretable biomarkers of other processes including neuroinflammation and neurodegeneration, and also other diseases**

WDC

The major one, I think, that we face is that it's challenging that we don't fully understand the exact molecular processes that each of these biomarkers is actually measuring. And because of that, it leads us to ask questions, and have uncertainty, in how to apply biomarkers. I think this applies to the imaging biomarkers, as well as the soluble biomarkers in cerebrospinal fluid and in blood. The exact molecular representation of what is being measured is understood at a basic level, but perhaps not at the level that we need to have it understood to really guide our development of treatments.

I also think it's well recognized that we have a gap in the field in terms of other biomarkers beyond amyloid plaques and tau tangles, for things such as neuroinflammation and neurodegeneration and other non-Alzheimer's disease-related pathologies and processes. And I'd like to just cover a few of these for the group to consider.

**Not all tau species are the same – each changes at different stages, correlates differently with amyloid, atrophy, hypometabolism, tangles and clinical stages**



WDC

Adapted from Barthelemy et al, Nat

In the Dominantly Inherited Alzheimer's Network (DIAN), we and others have been able to deduce the order and rate of changes of some of the most commonly used biomarkers in terms of stage of disease. And this has now been almost entirely replicated in late-onset sporadic Alzheimer's disease, the most common form of Alzheimer's.

Shown on this graph at zero is the estimated years to symptom onset. And in the DIAN population, this is really when the tau pathology begins to increase – right at symptom onset. Within one year of symptom onset, we see the tau PET pathology increase. I'll show later some

data that indicates we now have soluble biomarkers that can measure a similar timing and change in process, which makes us think that those biomarkers represent tau pathology, though they may not represent identically the same thing.

Similarly, when we look at things like CSF and plasma amyloid beta 42 to 40 ratios, shown here at the far left as some of the first changes that occur in the process that we can detect, those changes, although they mirror what we see by amyloid PET some three to five years later, may be measuring mechanistically and molecularly different processes.

The phospho-tau 217 comes up about the time that amyloid PET is increasing in both CSF and plasma, similar to phospho-tau 181. But then other species like phospho-tau 205 change later, and the total tau later still.

And then the historical biomarkers that have been attributed to neurodegeneration, such as neurofilament light chain, have a different profile and increase over time, typically in these stages. The time at which these changes occur is important information for us.

However, the different kinds of markers and what they mean for us at a biological level are still not fully understood.

### What do tau biomarkers tell us about mechanisms of tauopathy? 4 take-aways

- 1) Soluble tau vs. aggregated tau (soluble tau biomarkers are not equivalent to tau PET) – some tau species track tau PET (aggregated tau) changes and some don't
- 2) Tau species represent different processes: phosphorylated and tau fragment species (e.g. MTBR, 181, 217, 205, etc.) indicate different stages and change in different, sometimes opposite, directions.
- 3) Tau site phosphorylation ratio measures phosphorylation vs. tau phosphorylation concentration measures total amount. i.e. phosphorylation rate isn't concentration:  

$$(\text{phospho-tau} \div \text{non-phospho tau}) \neq [\text{phospho-tau}]$$
- 4) Tau assay differences in sensitivity and specificity, design of clinical studies (i.e. cross sectional vs. longitudinal; stage of disease), and statistical modeling all affect conclusions on biomarker relationship with mechanisms of disease.

WDC

I think there are important points to make about tau biomarkers along these lines. One is that soluble and aggregated tau, even though they can track and reflect each other, are not identical and don't really represent the same things. The aggregated forms of tau, as measured by PET scan, are really binding sites of a radiotracer that inserts itself and is detected by radioactive decay. The soluble marker appears to be related to those tangles in different forms but is released into the extracellular space, is soluble, and can be sampled and detected.

These tau species represent different processes. At one time, the field considered most phospho-tau to be largely equivalent, but we've learned that is not the case – not all tau species measure the same thing. In fact, they appear to measure very different things. And so, I'll show some data on the microtubule binding region of tau, which is a distinctly different part of tau than the phospho-tau species. But even within the phospho-tau species, there can be changes that occur that not only don't track each other but can even move in opposite directions. What is clear is that the biology of these phospho-tau species is exquisitely tightly controlled at a molecular and biological level within the brain. And there's important information there that we can gather and use in the development of treatments.

Another point is that measuring a concentration in a fluid – the amount of analyte per unit volume – is different from measuring a ratio or a rate. We've been using this concept in biomarkers for some time. For example, a 42 to 40 ratio, and now a p-tau 217 to total tau ratio – these are not equivalent, and they measure different parts of the physiological process.

The fourth point, which I think is well recognized by people who run these assays but not as much by those who don't, is that the assays themselves are really different. Not all p-tau assays that measure the same target have the same performance. The same is true for amyloid beta and other markers. We have to consider, in our biological interpretation of what's happening, the properties of the assay and how those properties influence our biological interpretation.

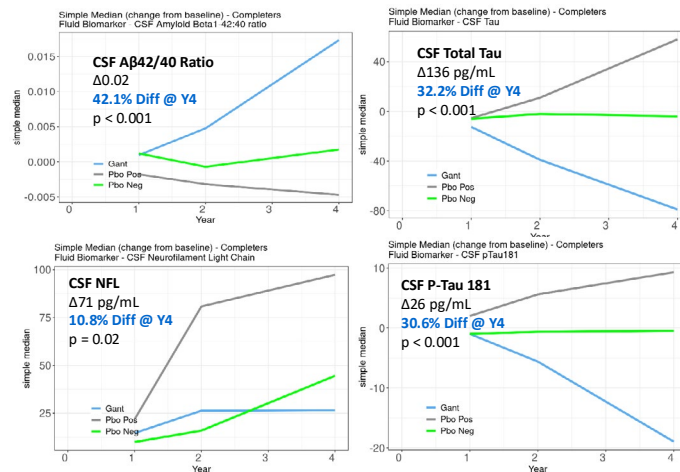
### t-tau & p-tau181 decreases with amyloid plaque removal, regardless of tau PET change

Across multiple biomarkers, statistically significant change-from-baseline effects favoring gantenerumab were observed.

- Dose up-titration (~Year 2) associated with accelerated curve separation, across biomarkers
- Gantenerumab improved tau and neurodegeneration biomarkers CSF tau, p-tau, and NFL indicating reduction in downstream disease activity.
- Illustrated are median change-from-baseline plots for completers. P-values are from MMRM (log scale) for all groups. Percent difference calculated as scale from abnormal (100%) to normal (0%) and represents the range of potential improvement to normal values.

Source : Roche outputs, DIAN-TU calculations effect  
Roche unvalidated graph

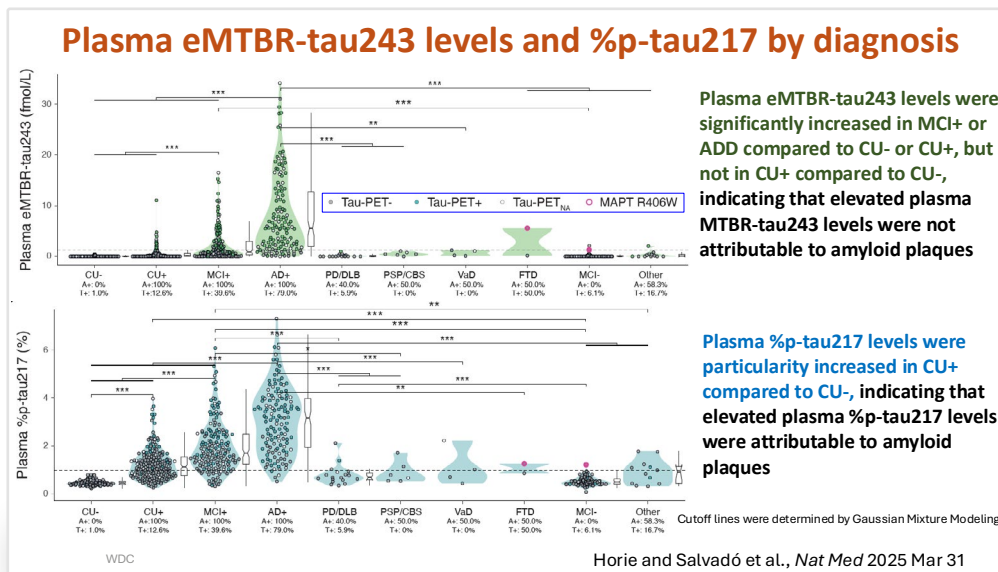
WDC



I wanted to share a few case examples here. Here you can see this is the DIAN-TU trial of gantenerumab. Showing during this time period, the drug normalized amyloid beta 42/40 ratio by about 40% and reduced cerebrospinal fluid total tau and phospho-tau 181 by about 30%, with all of these measures trending toward normal (in the blue lines). The neurofilament light chain, however, showed only a small, roughly 10% difference at year four.

Initially, the interpretation was that amyloid was being removed at some level, which was also supported by the PET data showing that soluble total tau and phospho-tau 181 had improved by about 30%. However, we now know that these markers largely mirror the amount of amyloid plaques at that stage of disease, and the removal of those plaques produces this effect. The change in phospho-tau is actually something occurring between the plaque itself and the tau tangle pathology that we see in the brain, thus, soluble p-tau is not equivalent to aggregated tau tangle pathology.

It's a link between that, a biological process, and so it's telling us something about that. But when we looked at tau-PET at those times, there was no difference in tau-PET. The tau pathology was really the same while the soluble tau biomarkers were getting better, indicating that the biology was being affected, but the existing pathology was not being affected so much, and the neurodegeneration was blunted by some amount, but not a lot.



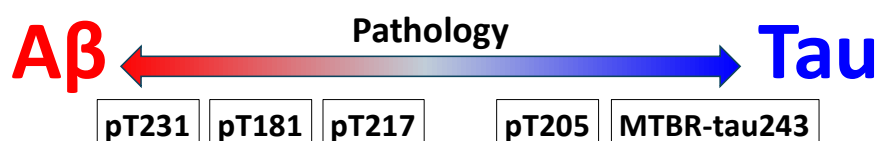
Shown here in comparison is a study that was recently published on blood plasma MTBR tau 243. This is the second half of the tau protein that actually ends up aggregating in the brain in Alzheimer's disease. And what you can see is when you compare cognitively normal folks, the CU minus, to those with amyloid plaques, to those with MCI or AD dementia, you see, as expected, the percent p-tau 217 goes up substantially with amyloid plaques, while the MTBR changes almost not at all.

And at the MCI stage, again, with more plaque present, the 217 really is quite increasing, and we have some mild increase here at the MCI stage. But it's not really until we hit dementia that this [tau MTBR-243] region of tau really increases in this population, and it's fully established in the AD dementia.

And in other neuropathological diseases, we don't see changes in either of these biomarkers, with some rare exceptions like some mutations and things of that nature that seem to be able to recapitulate some of the Alzheimer's process. But I think the message here is that not all tau is created equal. Tau can indicate different things, and the specific molecular events of what happens in these unique cases [of non-AD tauopathies] can tell us something about how tau is causing disease in the pathology.

## Summary

- **CSF and plasma MTBR-tau243 are specific fluid biomarkers of tau pathology (Tau PET) in Alzheimer's disease with very low contribution of A $\beta$  pathology (Amyloid PET)**
- **The combination of CSF MTBR-tau243 and pT205/T205 are nearly as strongly associated with MMSE as tau PET, which suggests high clinical utility of a biomarker panel containing MTBR-tau243**



WDC

And so, in summary, we continue to explore this area of research to understand the relationship between our soluble biomarkers and the actual pathology in the brain—the amyloid plaques that exist as deposited aggregates in the brain, and the tau tangles that exist as aggregated tau within neurons.

I'll end there, giving recognition and thanks to all the many people and groups who have contributed to this research.



## ACKNOWLEDGMENTS

### The research participants

**Current Members of the Bateman Lab:**  
Tayo Ajenifuja  
Brendan Androff  
Nicolas Barthelemy, PhD, Asst Professor  
James Bollinger, PhD  
John Coulton, PhD  
Reid Coyle  
Chloe He, PhD  
Cynthia Hodge, MBA  
Kanta Horie, PhD, Visiting Assoc Professor  
Rama Krishna Koppiseti  
Paige Lawler  
Yan Li, PhD, Asst Professor  
Melody Li, MS, OTR/L  
Samir Lopez Chahin  
Justin Melendez, PhD  
Soumya Mukherjee, PhD  
Nicholas Oatts  
Vitaliy Ovod, MS  
Manohar Pradhan  
Chihiro Sato, PhD, Asst Professor  
Chris Steger  
**Clinical Coordinators**  
Melanie Burton  
Lauren Cumberbatch  
Rickey George  
Adrienne Koelewijn  
Andrea Peterson-Brown  
Lisa Soke  
Wendy Sigurdson, BScN, MHSc, RN  
Diane Salamon, RN



**Collaborators: Biofinder:** Oskar Hansson, Gemma Salvaldo, Shorena Janelidze  
**ADRC:** John Morris, Suzanne Schindler, Chengjie Xiong, Tammie Benzinger, Anne Fagan, Brian Gordon, David Holtzman  
**SILQ Center:** Nupur Ghoshal, Donald Elbert, Paul Kotzbauer, Tim Miller, Ross Paterson, Bruce Patterson

**Prior Members of the Bateman Lab:** Alaina Baker-Nigh, Anna Bareiss, Abby Brand, Melissa Budeller, Karen Browning, Derica Cartwright, Jingdao Chen, Rose Connors, Paul Dalbo, Justyna Dobrowolska, Tamara Donahue, Brian Finn, Audrey Gabelle, Tinishia Greene, Melinda Hamilton, Terry Hicks, Yafei Huang, Kim Ingersoll, Tom Kastan, Farhan Khatchi, Haiyan Liu, Brendan Lucey, Paul Moiseyev, Sergio Molina, Kelly Moor, Kwasi Mawuenyega, Ling Munsell, Caroline Ogunware, Katrina Paumier, Rachel Potter, Yuriy Pyatkovsky, Randy Qian, Kara Ramsey, Kaleigh Roberts, Anna Santacruz, Theresa Schneider, Shirley Shih, Melissa Sullivan, Menxuan Tang, Kalyan Tripathy, Kate Walter, Michelle Wegscheid, Alex Wen, Norelle Wildburger, Kristin Wildsmith, Wanwan Xu, Lily Zhang





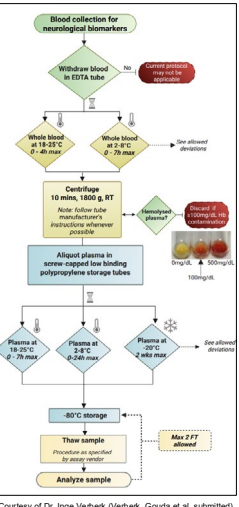



**Dr Laura Nisenbaum, Executive Director of Drug Development, Alzheimer's Drug Discovery Foundation (ADDF)**

Thanks, Randy. Thank you for taking us through the exquisite science that goes into understanding what biology is changing and how that impacts the pathobiology, which will then allow us to understand how to treat these different biological processes in the future. With that, I'm now going to turn to Henrik from the University of Gothenburg, and he will explore what's coming and where the biggest gaps remain. Henrik, I turn it over to you.



**Professor Henrik Zetterberg, Professor of Neurochemistry, University of Gothenburg**



Courtesy of Dr. Inge Velbek (Velbek, Gouda et al. submitted)

### Limitations in AD blood biomarker protocols for global implementation

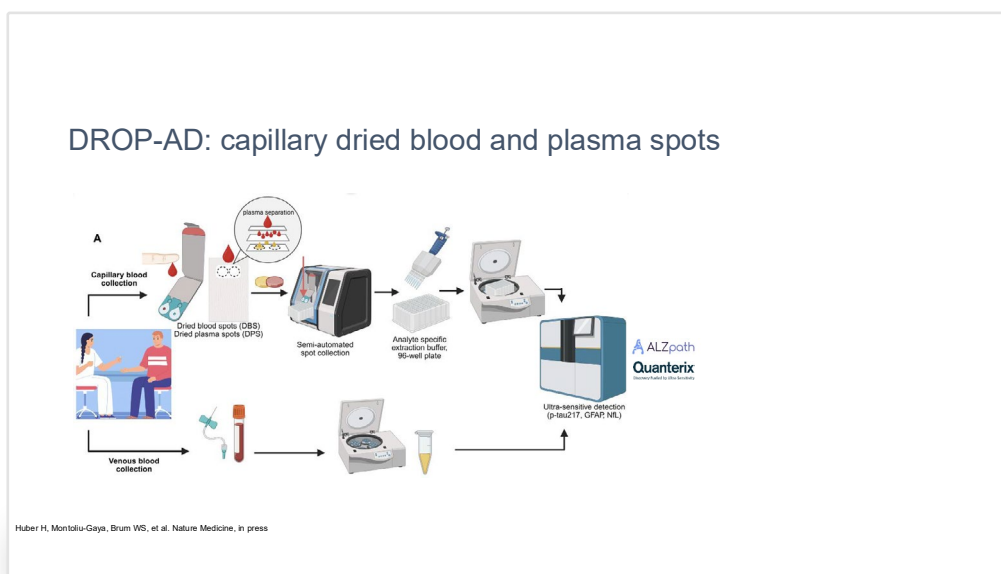
- Venepuncture requires a *face-to-face* visit
- Ideal p-tau217 measurements requires <4 hours to -80 storage or measurement.
- Variations in the protocol or haemolysis lead false positives in p-tau217 measurements.

**DROP-AD:** To create a collection method that removes venepuncture, that can be guided by care-giver or self-guided and produces reliable measures of AD biomarkers.

Yes, Lenny asked me to update everyone a little bit on what is happening with simplified collection protocols for AD blood biomarkers. Because, of course, as Mike alluded to and as many of us know, it's still a little bit difficult sometimes to collect blood samples. You need to have a venipuncture; you need to visit a clinic. Ideally, for p-tau 217 measurements, they require less than four hours of processing time. And that is challenging in some settings.

There are also variations in the protocol or haemolysis that can lead to false positives in p-tau 217 or baseline measurements. Another issue that has recently appeared, though not related to sampling, is the effect of heterophilic antibodies in creating false positive results as well. So, we still have some things to address, although these biomarkers are excellent.

We have been working on a project that we call DROP-AD, and the goal of this project is to create a collection method that removes the need for venipuncture, can be guided by a caregiver or self-guided, and produces reliable measures of AD biomarkers.



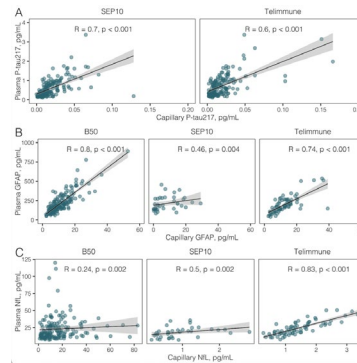
Here's the setup of the DROP-AD project, which has now been conducted in several clinics in Europe, and we are also starting to collect samples in India and in African countries.

The idea is to work on capillary dried blood and plasma spots. To the left here, you can see the setup with study participants undergoing both venous blood collection and capillary blood collection. We then place the blood drop on a sampling device that either collects a whole blood drop, which we allow to dry, or allows the drop to pass through a filter that leaves cells on one side and plasma in a collection device on the other. The dried plasma spot is what we eventually use for biomarker extraction. This is the plasma separation step: capillary force moves the whole blood across a filter that retains the cells on one side, and in the end, you end up with the dried plasma spot.

We have also worked on a semi-automated spot connection to allow for high-throughput analysis. And then we have an automated extraction protocol, which gives us a fluid that can be analyzed by an ultrasensitive measurement tool. The measurement tools or methods we have been working with in this project are single molecule arrays by Quanterix and nuLISA by Alamar. We always compare these results to venous blood collection done according to standard sampling protocols.

## DROP-AD: capillary dried blood and plasma spots

- SEP10 & Telimmune can be used for p-tau217 – dry plasma spots (DPS)
- B50 & Telimmune can be used for GFAP
- Telimmune only for NfL



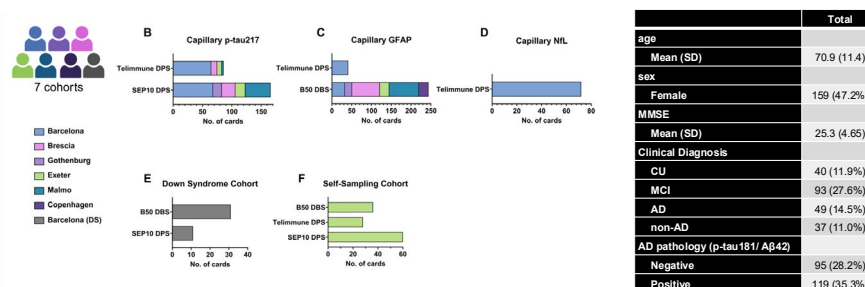
Huber H, Montoliu-Gaya, Brum WS, et al. Nature Medicine, in press

Here are some summary results of what we have found regarding the type of cards to choose. The commercially available cards are the Capitainer®SEP10, Telimmune cards, which were originally developed for metabolomic studies and postnatal screening for metabolic conditions. And then we also have more Whatman paper-like whole blood protocols. For phospho-tau 217, we get reasonably good correlations for both the Capitainer dried plasma card and the Telimmune dried plasma card, whereas whole blood doesn't work — it's not shown here on this slide.

The B50s, whole blood, and Telimmune can both be used to measure GFAP with good correlations, although for one reason or another, in our hands, this worked less well for Capitainer.

Telimmune showed the best results for neurofilament light, and here we always compare the dried plasma spot results in relation to a regular venous blood sample.

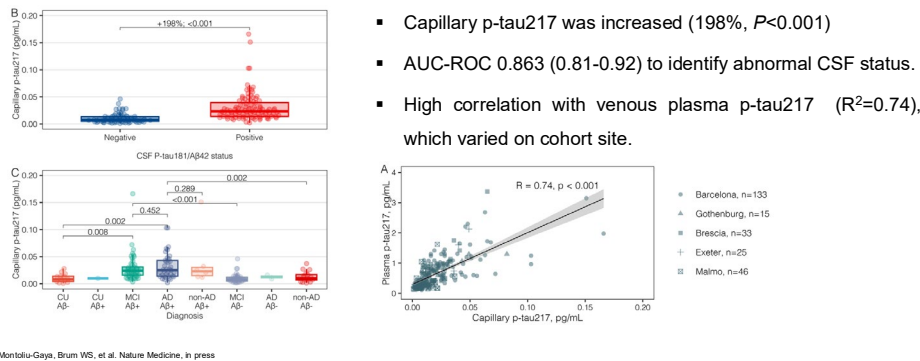
## DROP-AD: capillary dried blood and plasma spots



Huber H, Montoliu-Gaya, Brum WS, et al. Nature Medicine, in press

We have also performed a prospective sample collection study involving seven different research sites across Europe And we have performed capillary p-tau 217, GFAP, and NFL measurements. In Spain, through Juan Fortea, we also gained access to the Down syndrome cohort that he is examining. We additionally conducted a self-sampling cohort, since all of the other collections were instructed. In this study, we taught people how to do finger-prick testing and collection at home.

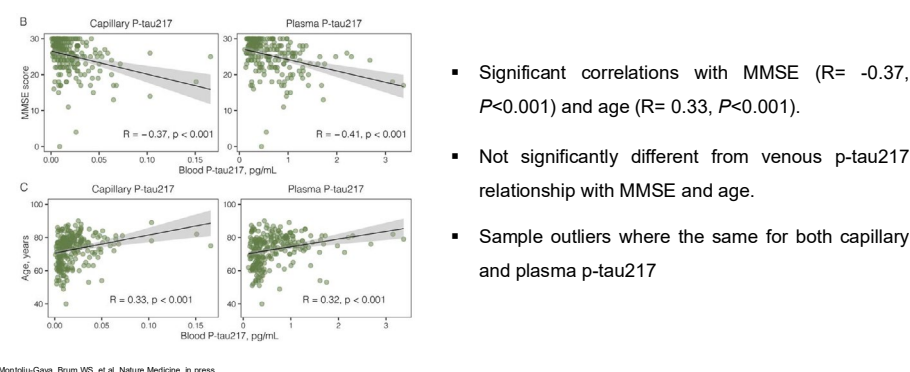
### DROP-AD: capillary dried blood and plasma spots



Here you see the results for capillary dried blood and plasma spots for capillary phospho-tau 217. The graph shows individuals who are CSF phospho-tau 181 divided by Aβ42 positive and negative, and we see about a 200% increase in capillary phospho-tau 217 collected on these dried plasma spots. And the AUC is 0.86 to detect an abnormal CSF status. So, you can see that we lose a little bit of diagnostic performance with this method, but it's still relatively good.

Here you can see what it looks like when we divide the study participants into cognitively unimpaired negative and positive MCI, Aβ-positive, AD Aβ-positive, and then other disease groups. Here is the correlation between capillary p-tau 217 on the x-axis and the regular venous plasma concentration on the y-axis.

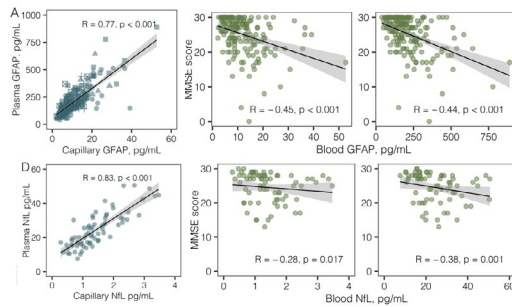
### DROP-AD: capillary dried blood and plasma spots



In this figure, we have pooled all the data, and I will show you what it looks like at the individual sites.

If we look at correlations with cognitive deterioration over time, we see significant correlations with MMSE and age. We see no significant differences compared to venous phospho-tau 217 in regard to these correlations, and some outliers were the same for both capillary and plasma phospho-tau 217.

### DROP-AD: capillary dried blood and plasma spots



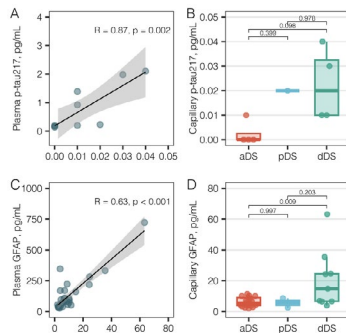
Huber H, Montoliu-Gaya, Brum WS, et al. Nature Medicine, in press

- Significant correlations with plasma (NFL, R= 0.77,  $P<0.001$ ; GFAP, NFL, R= 0.83,  $P<0.001$ )
- GFAP not significantly different from venous GFAP relationship with MMSE and age.
- NFL has slightly weaker relationship with MMSE and age compared to venous NFL

For GFAP, we see quite good correlations between capillary on the x-axis and plasma on the y-axis, and we replicate most of the findings for this marker. Neurofilament light looks similar, and we see these types of correlations with MMSE, correlation over time, and age.

NFL showed a slightly weaker relationship with MMSE and age compared to venous NFL, so capillary NFL performed a little bit less well.

### DROP-AD: Capillary blood biomarkers in Down syndrome

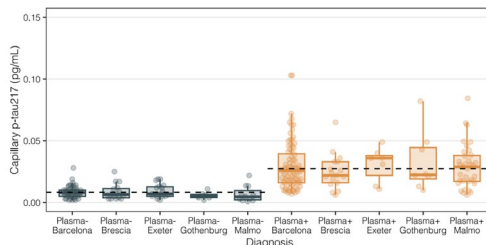


- High correlations of capillary p-tau217 (R= 0.87,  $P=0.002$ ) and capillary GFAP (R= 0.63,  $P<0.001$ ) with venous plasma
- Higher level of capillary p-tau217 and capillary GFAP with Down syndrome with Dementia (dDS)
- Positive participant and care-giver experience

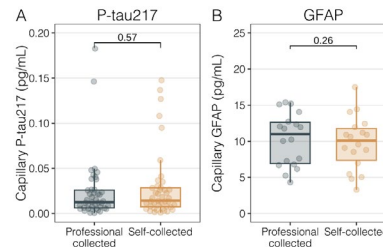
Juan Fortea and team

Here you see the results from the Down syndrome individuals: here are asymptomatic Down syndrome individuals, and here are people with Down syndrome who were suspected to have some progression. It's actually one person here; I should clarify that. These are Down syndrome individuals with diagnosed dementia, according to Juan Fortea and his clinical team. Here you see the GFAP results as well, showing increased levels in Down syndrome.

### DROP-AD: Reproducibility & Stability



- Highly reproducible across cohorts – DBS<sup>capillary</sup> cut-off maybe possible.



- Highly reproducible results in self-collected sampling (NfL not tested).

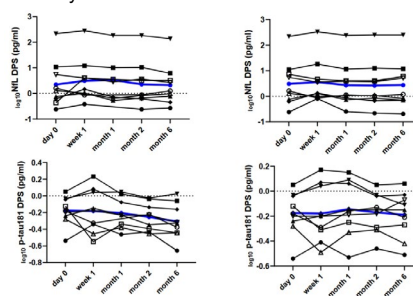
Huber H, Montoliu-Gaya, Brum WS, et al. Nature Medicine, in press

This is what it looks like in regard to reproducibility across cohorts. Here you see people who are negative for the CSF, positive for the CSF, and the results from the different sites.

So, it looks like quite a replicable study result. This is also what it looks like when we compare results with capillary p-tau 217 — capillary plasma collected by a professional sample collector performing the finger prick — and then when the same individuals do the finger prick and collection themselves on the sampling device after training. It looks like it actually works quite well.

### DROP-AD: Reproducibility & Stability

Stability of AD biomarkers on DBS over 6-months



Huber H, Montoliu-Gaya, Brum WS, et al. Nature Medicine, in press

Here you see what happens with these dried bloods — actually, dried plasma spot results — over time when we store these cards. NfL is very stable in these samples when stored over several months, and it also looks like we have stability for 181 in these spots. There is a slight decrease in phospho-tau 217, but it becomes apparent only after a couple of months of storage.



Dr. Hanna Huber    Dr. Leila Montellu-Gaya    Wagner Brum

## Conclusions

- The **DROP-AD project** shows detectable levels of p-tau217, GFAP and NfL from capillary blood (finger-stick collection).
- The levels are highly associated with traditional venepuncture plasma measured.
- The levels are stable for several weeks and highly reproducible.
- Capillary DBS analysis removes guided sample collection and preanalytical variables (e.g., centrifugation, cold-chain transfer and controlled storage)
- Improving the sample collection and analyte extraction protocols further to avoid hemolysis, intermixing of interstitial fluid, and platelet activation is warranted



Dr. Nick Ashton

To conclude this, the DROP-AD project shows detectable levels of phospho-tau 217, GFAP, and NFL from capillary blood collected through finger prick collection. The levels are highly associated with traditionally measured venipuncture plasma, although the absolute levels are different, the levels are stable for several weeks and quite reproducible. Capillary DBS analysis removes the need for guided sample collection and pre-analytical variables such as centrifugation, aliquoting, transfer, and controlled storage.

There are additional things we are working on in the lab right now — improving sample collection and analyte extraction protocols to avoid haemolysis, intermixing of interstitial fluid, and platelet activation. We are also aware that finger pricking is not always perceived as a pleasant procedure, so we are exploring other methods for collecting whole blood through a TASO device. There are also a couple of other devices, and we are working on a website where we will update information on new types of sample collection methods.

This project was conducted to a large extent by Anna Huber, Leila Montelugai, and Wagner Broom, under the supervision of Nick Ashton while he was in Gothenburg, as we are all working on this activity together. Also, with Nick now in Phoenix, Arizona, he remains affiliated with Gothenburg. Thank you very much for the attention, and I'm happy to discuss.



**Dr Laura Nisenbaum**, *Executive Director of Drug Development, Alzheimer's Drug Discovery Foundation (ADDF)*

Thank you, Henrik, so much. It's so great to see that there is research going on to understand how we can make biomarkers more accessible, both in research and hopefully as we develop diagnostic tools incorporating this technology.

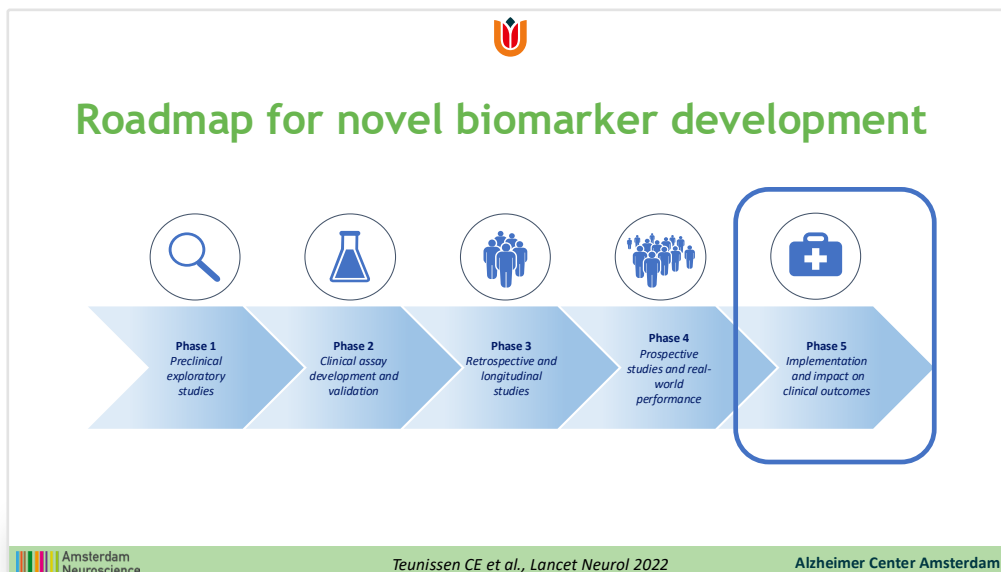
With that, I'm going to turn to our last speaker, Professor Charlotte Teunissen from Amsterdam University Medical Centres, who's going to talk about her crucial work bringing biomarkers into clinical practice and what will be needed to make that translation happen.



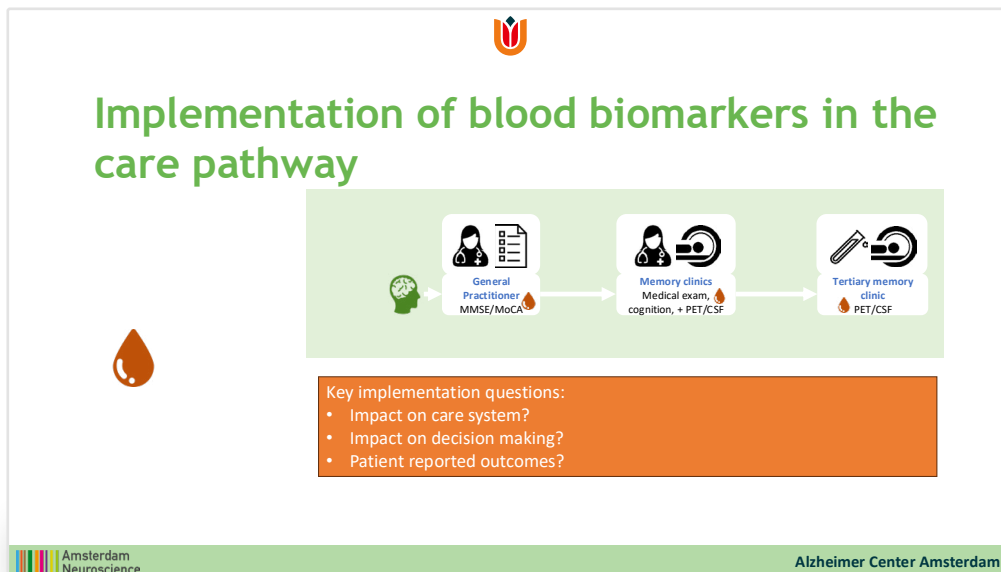
**Professor Charlotte Teunissen**, *Professor of Clinical Chemistry, Amsterdam University Medical Center*




I will discuss clinical implementation and patient considerations. Of course, we do a lot of biomarker research, including discovery work in my lab, but today I will focus on clinical implementation.



Clinical implementation is really important — it’s the fifth phase of biomarker development and implementation, ultimately by definition. It’s remarkable that for the blood-based biomarkers, which were first published only five years ago, we are now already discussing implementation and the impact on clinical outcomes.

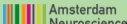



## Implementation of blood biomarkers in the care pathway



Key implementation questions:

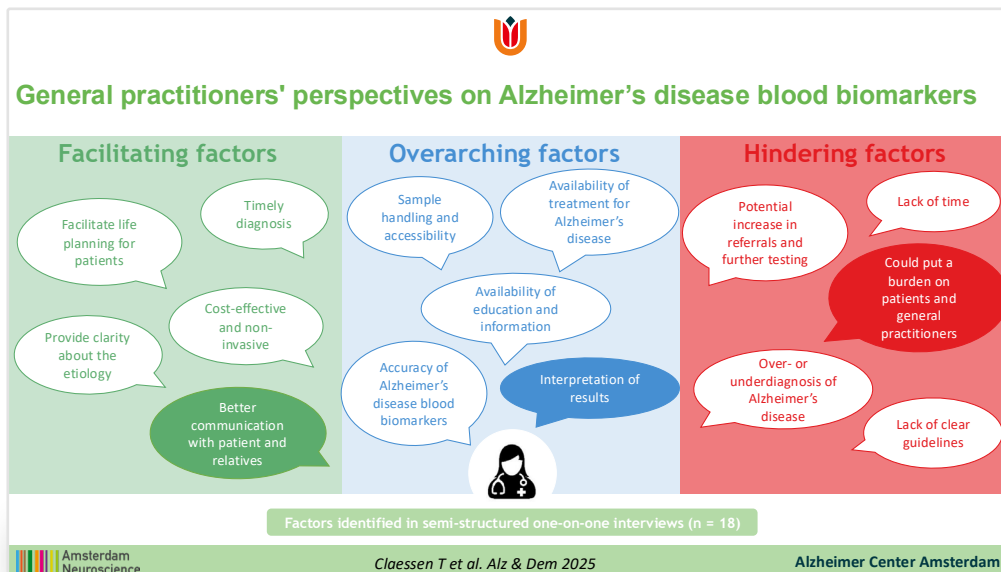
- Impact on care system?
- Impact on decision making?
- Patient reported outcomes?

 Amsterdam Neuroscience
  Alzheimer Center Amsterdam

What are we doing currently, or what do we need? For proper clinical implementation, we can of course just begin doing it, but it's also very important to achieve incorporation of blood-based biomarkers into regulatory systems such as clinical guidelines, and to ensure reimbursement of costs. There are several projects in which we are trying to address this issue, and I think that will be very important in the coming period. One of these projects is the Davos Alzheimer's Collaborative, which has a strong focus on clinical implementation. The questions are: what's the impact on the care system? What's the impact on decision-making? Does it lead to different decisions, or does it lead to quicker decisions and less burden on the care system? And what are the patient-reported outcomes? We like the test, but do they, the patients, also like having a blood test? What's really upcoming is the combination with digital biomarkers as a substitute for cognitive testing.

The current consensus guidelines state that we should apply blood-based biomarkers only in situations where a patient has objective cognitive decline — that's what multiple guidelines advocate. For that purpose, the measurement of cognitive decline using digital biomarkers can be very helpful. Digital cognitive tests are the first step, but perhaps other digital biomarkers could also play a role.

Here you see on the slide the blood drops at every stage of the patient journey. Of course, we don't need to do a blood draw at every stage, but we do think there is a clear place for blood biomarkers. Either they can be applied already with the GP or in memory clinics, and also in the tertiary memory clinics. Of course, those different silos — or often organized silos — need to communicate with each other.



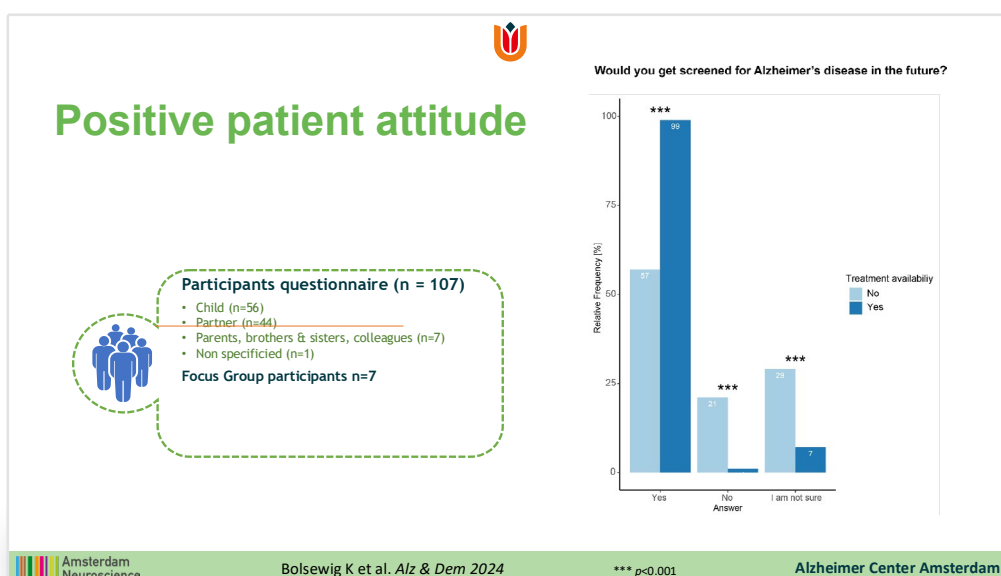
In the Netherlands, we started a study to define how the blood-based biomarkers agree with the doctor's diagnosis, but we encountered some resistance with participation in our studies. We went back one step and asked them what their problem was.

These are the outcomes of the study, and we worked with them using a theoretical framework – a theoretical domains framework – which is often used in qualitative research on human behavior. We asked the doctors what they saw as facilitating factors, hindering factors, and also overarching factors that we couldn't categorize as either facilitating or hindering. Here you can see some of the results.

Some facilitating factors that help the use of biomarkers are that they are cost-effective – we know that. But also that it allows better communication with patients and relatives.

Some overarching factors include questions around sample handling and accessibility, education, and interpretation of results. In my perception, these are easy factors to solve, and we should focus on patient education and interpretation tools.

There are also some hindering factors, such as lack of time. Now it's up to us to show that it hopefully also saves time, and our impact studies should demonstrate that. It could, at the same time, put a burden on the patient's general practitioners. We can't take away all the worries, of course, but we'll see how it works out once we start implementing.



Those were the doctors, and perhaps they have all kinds of worries and are not so happy to start novel innovations — but what do the patients think or want? The patients are really open to a blood test, and that's what is shown in these results.

We asked people whether they would like to get screened for Alzheimer's disease in the future. Screening here really means population screening. We asked this question to people who have a close relative — either a parent, a partner, or a friend — with Alzheimer's disease, so they know what it is. We asked them whether they would want to get screened, and we presented two scenarios: one where treatment is not available, shown in light blue, and one where treatment is available, shown in dark blue.

It's very clear that even when no treatment is available, 57% would choose to get screened and tested for Alzheimer's disease. But in the case where treatment is available, almost 100% of individuals would choose to get screened for Alzheimer's disease. That's really reassuring.

The patients want it — it's a positive message — and now we have to get the primary care physicians, and perhaps also some secondary care physicians, on board. We can start with pioneers, but I think, ultimately, we will get there. Thank you for your attention.



**Dr Stacie Weninger**, *President, Foundation for Biomedical Research and Innovation (FBRI)*

Thank you, Charlotte, and thank you, Laura, for introducing everyone and helping to set the stage. There is a lot we could talk about here, and we have a little over half an hour for what I hope will be a robust discussion. We really do hope this will be more of a discussion rather than just a Q&A. So yes, please, everyone, take part in this.

Just to set the stage a little and reflect on what I've heard — and maybe what I think we need to talk more about as well — it's a really exciting time in the world of biomarker development. I think we truly are at the cusp of being able to offer some meaningful therapeutics to patients with a broad range of dementias.

For a long time, I know I and many others in the field have said biomarkers are key. We need biomarkers to help us develop those therapeutics. We need biomarkers to tell us who we should enroll in trials and whether a therapeutic is working. And ultimately, we need those biomarkers, as Charlotte was just talking about, to really enable physicians and clinicians globally to determine who should receive which therapeutics and to assess whether those therapeutics are working. I'm quite excited as I see many different commercial organizations trying to develop these tests that will be scalable and deployable across the world.

I think Randy touched on some issues that do worry me, particularly around consistency. As we have many different companies offering their own versions of these tests, how do we maintain consistency from one physician's office to another if they're using tests from different providers? How do we ensure that what we're measuring really is the same thing?

We also need to understand how these biomarkers might vary across different populations. As Mike nicely opened with, many of our clinical trials have been conducted in a very specific type of individual. How do we look across socioeconomic and ethnic groups when thinking about global use? The work that Henrik and his colleagues are doing to develop methodologies that allow the entire world access to blood biomarker testing will really enable progress, but we still need to understand population differences.

I know many of you are aware of studies underway not only in different socioeconomic groups but also across different ethnic and geographic backgrounds. One study I've been particularly excited about is looking at differences in India between rural and urban cohorts. Henrik, I know you've been helping to measure biomarkers in these different groups, which I think will inform where we're heading in the future.

One thing we didn't talk much about in the opening presentations, but that was touched on, is the need for biomarkers for different pathologies. I'm quite encouraged by where we are in the Alzheimer's disease space regarding A $\beta$  and tau — we've learned so much, and we now have some excellent biomarkers there, along with NFL and GFAP, which are broader markers.

But, as Randy mentioned, we also need biomarkers for other pathologies. We're still far behind when it comes to Parkinson's disease, frontotemporal dementia, and other dementias. Co-pathologies are the norm, not the exception, so we need to understand, in both clinical trials and practice, what co-pathologies a patient may have. They will respond differently to different therapeutics and may require combinations. We also need biomarkers for other processes — neuroinflammation, endolysosomal function, and more — both to stratify patients and to understand which patients should be enrolled or treated with which therapeutics.

There's a lot to talk about here, and I'm going to open it up for discussion. This conversation can go in many directions, but I think we're at an exciting point in the field, and it's a great time to be having this discussion. Donna, I think you were the first to raise your hand, so we'll start with you.



**Professor Donna Wilcock**, *Professor of Neurology, Indiana University School of Medicine*

Really great presentations. I had a couple of points and a couple of questions. I was really interested in your finding, Charlotte, around people's desire to get screened. I think we need to equip primary care providers with the tools and resources to appropriately counsel those patients if they get a positive test result but are cognitively normal. Right now, we don't have therapies approved for that population — that might change when AHEAD or TRAILBLAZER-3 read out — but at the moment, they would know they're amyloid positive, and there's nothing they can do.

What we're experiencing in our clinic is that primary care providers are ordering these tests for patients who come in saying, "Oh, I think my memory might not be what it used to be," without any cognitive assessment, ordering the test, and then referring them to our treatment program. That poses a challenge, and I think we need to give primary care providers more tools to help these patients and ensure they're sending the right patients into the treatment programs.

Echoing what Stacie and Randy said, co-pathologies are the rule, not the exception. We know that depending on the level of different comorbidities, responses to amyloid therapy are going to be very different. But I will say I'm excited to see the progress being made, particularly with alpha-synuclein, which we can now assess with RT-QuIC assays. I'm also really excited about some of the cryptic peptide work happening with TDP-43, and I think there are a couple of very promising vascular biomarkers that will be sensitive to MRI. We are moving the needle — it's behind Alzheimer's, but the right efforts are moving in the right direction, and I'm excited to see where it goes.

But I'd love to hear from people about what we do now. In the U.S., there's direct-to-consumer testing — people don't even need to go through their doctor; they can just go online and order these tests. And there's no counselling, no real resources. What can we do as a field to equip people and educate them about what it means to be amyloid positive but cognitively normal?



**Dr Stacie Weninger**, *President, Foundation for Biomedical Research and Innovation (FBRI)*

That's a great point, Donna, and it also echoes something Randy mentioned — that we need to understand what's actually happening at a molecular level underlying these biomarker changes, because that's going to be important for how we think about these discussions in the future. But even today, you're right — people can go and just get this test done themselves. Charlotte or Randy, would you like to comment?



**Professor Randy Bateman**, *Professor, Washington University St Louis*

Can I just try to address one thing? In the clinic today, in our specialty clinic, we see exactly what you described, Donna. Today, we have approved tests that are reimbursed for PET, CSF, and sometimes blood, depending on the payer — for amyloid tests like amyloid beta 42 to 40, p-tau 217, and similar ones. But there's not really accessibility or support to do anything beyond that.

One of the first co-pathologies that we're not even measuring in the clinic is tau pathology, and we know that has an effect on calculating the probability of benefit for an individual patient.



**Professor Donna Wilcock**, *Professor of Neurology, Indiana University School of Medicine*

It also helps with staging — if someone is amyloid positive, they could still be 10 years away from developing any impairment. But if they're both amyloid and tau positive, obviously, they're much closer to that stage.



**Professor Randy Bateman**, *Professor, Washington University St Louis*

That's where the research we're currently working on is focused — trying to determine whether the symptoms are due to Alzheimer's disease, and what stage patients are at, and actually informing patients and families about the magnitude of benefit they can reasonably expect. Because we're balancing that against risk, safety, burden, and cost, among other factors.

We're not even fully addressing the main Alzheimer's pathology yet, let alone moving beyond it. Understanding other pathologies will take much longer before we can know how they affect clinical decision-making, but we need to start implementing these measures in research now. We're desperate for these other biomarkers.

And just to address Marcos's question from the chat — how do we unravel these molecular processes and biological pathways for blood-based biomarkers and these other co-pathologies? Personally, I think as a field, we need much more investigative work on that front. We need to figure out how we can measure these other pathologies, what they mean, and what they tell us. If we can do that, we can implement them in clinical trials — both those already completed and those ongoing or planned — and start to answer the question of whether these co-pathologies should influence how we assess an individual's benefit and safety profile when considering different treatments. And certainly, they will influence how we think about the design and the implementation of different targets for dementia. And there's a lot of those [non-amyloid, non-tau] targets that I think those programs are being held back simply because they don't have these biomarkers.

And so, I want to underscore the emphasis for the field that we really need to be doubling down on these other pathologies and get the biomarkers developed so we can research it, because it takes years to get down that road.



**Dr Stacie Weninger**, *President, Foundation for Biomedical Research and Innovation (FBRI)*

I totally agree. And Henrik, do you want to comment just on some of the work going on on other pathologies?



**Professor Henrik Zetterberg**, *Professor of Neurochemistry, University of Gothenburg*

Yes, I mean, we have actually — I regard this seed amplification assay for alpha-synuclein as quite a good breakthrough. It's really replicable across laboratories, but of course, it requires a CSF sample. For TDP-43, I think the downstream markers of TDP-43 loss of function are very interesting. This loss of normal TDP-43 function results in cryptic exon-encoded peptide expression that gives a sort of positive biomarker from something that shouldn't be there, which could be a good thing when dealing with less abundant pathophysiology.

I think we also need to work much more on cerebrovascular disease, and I know Donna and her team are very active there. There are some biomarkers that look promising, like placental growth factor, but they're operating in a different space. We need to examine their diagnostic utility much more.

And then, of course, neuroinflammation is a hard nut to crack because of the contamination of the blood signal by peripheral immune cells. But maybe there will be some breakthroughs there as well.

Just a reflection I had during this discussion is that perhaps the term “diagnostic biomarker” has made things a little bit difficult. To me, the diagnosis is made by the doctor, with the help of the biomarkers. It's so important to put them in context. I think Randy said it, and others

as well — is the biomarker abnormality really linked to the symptoms the patient is seeking medical advice for? That’s challenging but also very interesting. I tell all medical students that it’s an exciting time now, because they can start to think a little bit like clinical chemists when it comes to brain diseases. All clinical chemistry tests have their pros and cons, weaknesses and strengths, but they must be interpreted within a complete clinical context to avoid error. I agree with you, Stacie — it’s a very exciting time.

We also learn a lot through clinical implementation. Even though we talk about some problems, in Sweden now you can order p-tau 217 and NFL if you are a practicing doctor, and it’s left a little bit to the doctor’s judgment not to order it inappropriately. But of course, mistakes can happen, and Sweden is a small country. People can call the laboratory and discuss strange results and so on. I realize this is more difficult when you have more commercial tests and direct-to-consumer advertisements.



**Dr Stacie Weninger**, *President, Foundation for Biomedical Research and Innovation (FBRI)*

That’s an excellent point as well — biomarkers are a tool to help physicians make diagnoses, and that’s something we really need to keep in mind. The other thing I’d be remiss not to mention is that, as you say, we’re going to learn as we use more of this in the clinic. The way we learn is through data sharing and information sharing.

And that is something that I think, globally, we really need to think about — how can we learn more in today’s world? Mike, you were talking about using AI to help in the assessment of individuals. How can we actually use these new tools and new capabilities to learn from what we see in the clinic? The only way to do that is to be more open to sharing information — clinical data and beyond. This requires patients to have a willingness to share, so we can use emerging technology to learn more globally, outside of clinical trials themselves. What do we see happening in the real world? Binita — I’ve seen you’ve had your hand up for a while, so maybe we’ll turn to you.



**Dr Binita Rajbanshi**, *Neuropharmacologist, University of California San Francisco (UCSF)*

Yeah, sure. Thanks for the amazing panel. Regarding the biomarker itself — as Henrik mentioned during his last talk at AAIC — there is variability depending on when the sample is collected, such as before or after certain activities like exercising or fasting. That variability exists.

And in the field itself, we still don’t fully understand why specific variants of tau — for example, p-tau 217 or p-tau 181 — appear early on, but not the other variants of tau. I think that’s due to the structure of tau itself. From a chemistry perspective, tau is a naturally and intrinsically disordered protein. To date, we don’t know the full structure of the complete tau protein. We do know the structure of some truncated variants, but not the full-length form. I think, in the tau pathology field, that’s one of the fundamental problems we’re facing. Until we resolve that, we would not be able to find out the molecular physiology of understanding like why specific variants of tau appear early on compared to others. But with the recent innovation of quantum computing, maybe we can resolve that.



**Professor Randy Bateman**, *Professor, Washington University St Louis*

I like the concept — the idea of quantum computing. I never really thought of that before, but you may be right. Quantum computing may be getting good enough that it could actually model, at an atomic level, all the variants we can identify by mass spectrometry and help us understand their shape and structure. It’s really quite a challenge, even with tools like AlphaFold AI.

There was a question about AI and machine learning. I don’t think about this topic often, but the challenge is that, yes, AI can understand folding structures in more basic environments. However, the complexity within the neuropil and the brain is such that we actually don’t know

the precise shape, form, or movement of these proteins. That's part of the mystery of what precisely happens to tau that leads to its misfolding and aggregation. I think that's a critically important step. There's a lot that the cryo-EM field has taught us. But yes — who knows — maybe we can contact Google's Willow chip developers and see if they can run tau for us and see what comes out of it.



**Professor Mike Weiner**, *Professor, University of California San Francisco (UCSF)*

I have two questions for my fellow panellists. The first is: are the C2N and the Fujirebio tests ready for prime time to substitute for amyloid PET for clinical decision-making for treatment? I'd like to ask each of my three fellow panellists — is that a yes or a no? And the second is: what is the status today of an alpha-synuclein test in plasma?



**Professor Charlotte Teunissen**, *Professor of Clinical Chemistry, Amsterdam University Medical Center*

It depends on the use. In terms of treatment, those current treatments have such a high burden that, even though the tests are performing well — with reported performance over 90% sensitivity, as is the case with C2N — I would still like a bit more certainty. It's a little more doubtful for the Fujirebio test. Even then, if you have a positive test and you're considering starting treatment, and all other conditions are met, I would still feel more comfortable performing an amyloid PET or CSF analysis. So, are they ready for prime time? I think yes — but it depends on the purpose.



**Professor Henrik Zetterberg**, *Professor of Neurochemistry, University of Gothenburg*

I agree with Charlotte at the moment — before making big decisions on treatments, it's still good to confirm a positive test result. But I think that will change, and I hope we will have blood-based confirmatory testing as well.



**Professor Randy Bateman**, *Professor, Washington University St Louis*

For disclosure, I'm a co-founder of C2N Diagnostics, but I've seen a mountain of data on PET scans, CSF, and blood tests. We've published, in our own lab at Washington University, direct head-to-head comparisons of CSF, PET, and the mass spec p-tau 217 assays, as well as MTBR, and all of that is published.

The bottom line is that the best blood tests today — and Charlotte, I think you're right, those with sensitivity and specificity above 90% for both — not only rival but actually match or even beat PET scans. And so, I'm going to challenge and disagree with the assessment that they're not ready for clinical use, for two reasons.

First, the data clearly show — and anyone can do these studies, order the test, run it, and compare — that the blood test performs just as well as PET or CSF when you're looking for the ground truth of whether a person has amyloid plaques. So why would we not use a test that is much more accessible and less expensive to assist in diagnosis, when it's literally just as good and, in some cases, better?

Second, in the U.S., when we're seeing patients, we can't get enough PET scans, and we can't do enough CSF tests for the entire population. Are we going to tell patients, "We're sorry, we can't treat you in time for your dementia — you'll have to progress to a stage where it won't be beneficial because we don't have enough PET scans or can't do enough CSF tests"? To me, as a physician, that's really not acceptable. We're one of the biggest centers in our country treating people, and we're still straining with PET scans and CSF tests.

For those two reasons, I think the tests should be rigorously demonstrated, with thousands of measurements and well-controlled studies — but I also think it's already been clearly demonstrated that they can and should be used now.

And Mike, I think the harder question — and the one we're trying to deal with at the university — is how do we integrate this into primary care? Because as a specialty clinic, we can't handle,

in the U.S., the sheer scale of potential testing. Somewhere between one and five million people could theoretically be tested and identified as candidates for treatment, and specialty clinics simply can't manage that volume. At some level, someone needs to work out how to build screening processes into the primary care system to assist us with this, because there are just too many people [to evaluate] and too many patients. And we know that if we delay treatment too long in those individuals, they won't benefit.



**Professor Mike Weiner**, *Professor, University of California San Francisco (UCSF)*

Randy, do you have any concern that most of the validation studies of these blood tests have been done in highly educated people with health insurance? There's a large population of people who have more renal failure, more diabetes, more obesity, and hypertension. And we know that, especially for the immunoassays, renal failure can affect the tests. I think there are going to be some reports at CTAD suggesting that, for some of the immunoassay tests, the current cut points lead to false positives and false negatives.



**Professor Randy Bateman**, *Professor, Washington University St Louis*

Henrik and Charlotte can probably comment more on that, Mike, in terms of the specific effects on the immunoassays. My understanding is that it's there, but it's not enormous. We're really talking about a subset of people where this could impact the results enough to potentially change a decision.

I think the bigger issue is what you alluded to at the beginning, which is that we need to make sure these tests work in the general population. We have the SUNBIRDstudy running in our region, where we're working both in clinics and in the community, and we're making it representative of the general population — including lots of comorbidities. Depression and low education, which you pointed out, are important factors because those cofactors can influence outcomes.

In our initial Seabird and Sunbird studies, at least with our assays, we haven't yet seen a difference in performance, but we're continuing those studies and analyses, and it may or may not turn out to be assay-dependent. But as we move toward thinking about how we treat patients and how we include primary care, that question has to be answered — we have to know how these tests perform in the clinic.

That's why we're doing those studies now, and I'm delighted to hear that ADNI 5 is going to focus on that as well. I think that's an important step, and I know a lot of other groups already have similar studies underway.

Henrik, I'm so impressed with your ability to go into countries where they don't even have reliable access to blood collection or venipuncture, and you're still managing to carry out that work. I'm really glad to see that moving forward, Mike. But I wonder, Henrik and Charlotte, what your thoughts are on that — in particular, the primary care question. I think that's a big challenge. In the U.S., our primary care doctors simply don't have the time — they're already overwhelmed — and adding something new like this is difficult. That's a separate issue, but I'd really like to hear your perspectives.



**Dr Stacie Weninger**, *President, Foundation for Biomedical Research and Innovation (FBRI)*

And just to point out a comment from the chat as well — from a Canadian perspective — that question also came up about how we integrate primary care use with secondary and tertiary care. I think that's a challenge we're seeing everywhere.



**Professor Charlotte Teunissen**, *Professor of Clinical Chemistry, Amsterdam University Medical Center*

I think so too. It's very good if we can collaborate and share experiences with each other. The first thing we encountered is that there is quite a lack of knowledge about the difference between Alzheimer's disease and dementia. There's a very strong educational effort needed there.

In the Netherlands, I believe implementation in primary care is perhaps a bridge too far at the moment, because of this lack of education and, indeed, the lack of time. But I do think there's a benefit in helping primary care physicians make decisions about referrals. Once they decide to refer, they can apply the blood test to make those referrals more effective and efficient. That's my hope — how it will slowly integrate toward primary care.

I'm not too worried that it will be overused — that's another possible concern, over-diagnosis. But due to conservative attitudes and the lack of time, I don't think primary care physicians will adopt it too quickly. My worry is more that the test exists, it can help patients, and yet they won't be able to benefit from it.

Of course, this will change once the drugs are also reimbursed in the Netherlands — then there will be more testing, and I hope that will open the eyes of primary care physicians. What we're doing now is a coordinated effort with more public communication — advertisements and interviews in newspapers — to raise awareness that we now have fantastic treatments, and to build more understanding both among physicians and in the general population.



**Professor Henrik Zetterberg**, *Professor of Neurochemistry, University of Gothenburg*

In Sweden, we've tried to update the diagnostic algorithm for primary care physicians. Before a patient can be referred to a memory clinic, the primary care doctor must carry out what's called a basic memory evaluation or cognitive evaluation. That includes a CT scan, a basic clinical assessment of memory and other cognitive domains, family and clinical history, and some basic blood tests.

What we're now trying to do is include, already at that stage, phospho-tau 217 — and, if the patient is not too old, potentially neurofilament light potentially. That's something we're actively working to implement. But we've met a bit of resistance, actually, with primary care physicians feeling it's too early. Whereas I, and other specialists in Sweden, think now is exactly the time to do it — carefully, of course — not overstating the meaning of the blood biomarker result, but emphasizing that it must be interpreted in context. It's not an "Alzheimer's test"; it's a test that determines the likelihood of the patient having Alzheimer's-related brain changes.



**Dr Stacie Weninger**, *President, Foundation for Biomedical Research and Innovation (FBRI)*

What we are seeing in the US is as we see more and more testing being done by primary care physicians, it's becoming increasingly difficult to refer patients because of the very long wait times. It's often hard to get into a memory clinic at all. That's another challenge we'll have to face as testing expands and more people want access to treatments. How do we make that more accessible, especially when treatment should, at least for now, still be handled by specialty clinics? That's a challenge we need to confront.



**Professor Charlotte Teunissen**, *Professor of Clinical Chemistry, Amsterdam University Medical Center*

That's not due to the test or the test result — it's due to the high prevalence of Alzheimer's disease. And as societies, we should be getting ready for that.



**Dr Stacie Weninger**, *President, Foundation for Biomedical Research and Innovation (FBRI)*

I completely agree with you on that. And, Mike, you had your second question, which we haven't gotten to yet — alpha-synuclein. Where do we stand on that? Henrik, I don't know if you'd like to comment on the seeding assay or the skin biopsy. These were great steps forward in providing a yes/no result, but we still need quantitative biomarkers of synuclein, and we need to understand that better. I know you have been working on some things.



**Professor Henrik Zetterberg**, *Professor of Neurochemistry, University of Gothenburg*

Yes, I think the yes/no answer from the CSF test, which replicates across different laboratories, is a very good step forward, but it's not quantitative, as you mentioned. It doesn't work well in blood. Extracellular vesicle-based tests have turned out to be quite difficult to replicate.

There was a strong publication a year ago on the diagnostic performance of measuring alpha-synuclein in vesicles and relating that to alpha-synucleinopathy in the brain, but that's been hard to replicate.

There are also a couple of blood tests — total alpha-synuclein is not informative, though it's easy to measure. A few assays use antibodies that should selectively bind misfolded alpha-synuclein, but there's interference from normal alpha-synuclein when it's present in high excess, which it is in blood. We simply need to continue working on this.

Biomarker development in Alzheimer's has been greatly facilitated by amyloid PET and CSF biomarkers, which allow accurate diagnosis and enable the use of proteomic and targeted assays for different phospho-tau forms in plasma and thereby see if it works or not. And hopefully if we can dichotomize people into alpha-synuclein positive and negative, perhaps we can then use exploratory approaches in blood to detect new markers that relate to this pathology.



**Dr Stacie Weninger**, *President, Foundation for Biomedical Research and Innovation (FBRI)*

That's a great point. And TDP-43, of course — cryptic exons and so on — we also need good biomarkers there.



**Dr Laura Nisenbaum**, *Executive Director of Drug Development, Alzheimer's Drug Discovery Foundation (ADDF)*

Thanks, Stacie. I wanted to return to some of the key points that have been raised — around co-pathologies, heterogeneity, and the need to develop biomarkers for novel mechanisms like neuroinflammation, vascular pathology, metabolism, and mitochondrial dysfunction.

Just to make sure this community knows, I also want to share that at ADDF, we'll be opening a new round of funding through the Diagnostic Accelerator in 2026 — an additional \$50 million — focused specifically on these key needs: heterogeneity related to co-pathologies, and prognostic biomarkers to identify who with amyloid in the brain will go on to develop cognitive symptoms. The points raised here make clear how essential it is to understand the heterogeneity that exists in our patients.



**Dr Stacie Weninger**, *President, Foundation for Biomedical Research and Innovation (FBRI)*

That's a great point as well. This is critical not only from a diagnostic point of view — determining what therapies someone should receive — but also for clinical trials and research. There are huge differences in how someone responds to therapeutics depending on the pathologies in their brains, what else is going on, and the biology driving their disease. For some patients, it may be more endolysosomal dysfunction; for others, how their microglia respond to the disease pathology; and for others, particularly in Parkinson's, it could be more mitochondrial-driven. These are incredibly important new areas for biomarker development. We've made a lot of progress, and I'm excited about where we're heading. Mike, I'll give you just a minute for a final comment on that.



**Professor Mike Weiner**, *Professor, University of California San Francisco (UCSF)*

Less than a minute. I think we haven't talked about the impact of the GLP-1 agonists, but they're going to be huge. There's so much data suggesting they're beneficial for brain health. Whether they'll impact the ATN cascade is unclear, but I think they're going to improve overall brain health, and we'll need biomarkers to track their effects and guide patient selection. I think there are more than a hundred companies developing GLP-1 agonists right now. This is going to be a whole new world for all of us — and not just for Alzheimer's, but for preventing dementia, which is what we ultimately want to do.



**Dr Stacie Weninger**, *President, Foundation for Biomedical Research and Innovation (FBRI)*

And maybe even more specifically, I'm excited — and, full disclosure, have some conflicts — about some of the NLRP3 inhibitors coming along that might target particular inflammation processes. It's an exciting time. And with that, I just want to thank all the panellists and participants for what's been a really robust discussion. And Lenny back to you to close.



**Lenny Shallcross**, *Executive Director, World Dementia Council*

Thank you all for participating. We'll be back with the transcript and will include everyone's presentations on our website. Wherever you are in the world, I hope you have a great rest of your day. Thank you very much.



# World Dementia Council

Leading the Global Action  
Against Dementia

The World Dementia Council (WDC) is an international charity. It consists of senior experts and leaders drawn from research, academia, industry, governments and NGOs in both high-income and low- and middle-income countries, including two leaders with a personal dementia diagnosis. The WDC has an executive team based in London, UK.

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