Summit 2023

Dementia in a new era:
prevent, diagnose, treat

World Dementia Council
Leading the Global Action
Against Dementia

Biomarkers,
where do we stand?

Transcript of a session from the
World Dementia Council summit
20 March 2023

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The World Dementia Council has 24 members working across six continents. Council members are global leaders who work in research, academia, industry and civil society. They attend meetings, vote on key issues and participate in the organisation's work. The council also includes members who are living with dementia.

The Council also has multiple associate members consisting of international organizations as well as national governments. They help to ensure that the council's agenda aligns with other global dementia initiatives, providing the council with important strategic advice, guidance and intelligence. As they do not have full membership status, associate members don't vote on issues such as the election of a new chair or new members, or on matters of governance.

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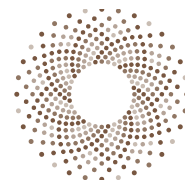
Chair

Philip Scheltens

Professor of Cognitive Neurology and Director Alzheimer Center, University of Amsterdam Medical Centers

Prof. dr. Philip Scheltens studied at the VU University Amsterdam, Netherlands, gaining his MD in 1984, and PhD in 1993. He became Professor of Cognitive Neurology and founder of the Alzheimer Center at Amsterdam University Medical Centers in 2000, which he directed until 2022. Currently he devotes most of time heading the Dementia Fund at EQT Life Sciences, that he started in 2020. He has been the (inter)national PI for over 35 studies, including phase 1-3 multicenter clinical trials. He supervised >75 PhD theses since 2000. He founded the Dutch national plan against dementia and served as chair of the board. He is co-editor-in-chief of Alzheimer's Research & Therapy and co-leads various EU projects. He authored over 1100 peer reviewed papers and > 75 book chapters and co-edited several major textbooks. He is member of the Royal Dutch Academy of Arts and Sciences (KNAW) since 2011. In 2016 he was awarded the European Grand Prix for Alzheimer's Research. In 2020 he was Knighted in the Order of the Netherlands Lion by the King of the Netherlands. In 2021 he was elected honorary member of the European Academy of Neurology and was appointed chair of the World Dementia Council.

Speakers

Professor Karen Duff

Professor and Director, UK DRI Hub Dementia Research Institute (DRI) University College London

Professor Duff is the Centre Director of the UK Dementia Research Institute at University College London and Professor Emerita and Special Lecturer at the department of Pathology at Columbia University Medical Center, New York. She received her PhD from Sydney Brenner's department at the University of Cambridge in 1991. She undertook postdoc positions in London with Alison Goate from 1991-1992, and John Hardy at the University of South Florida from 1992-1994. She was an Assistant Professor at the University of South Florida from 1993-1996, Associate Professor at Mayo Clinic Jacksonville from 1996-1998, and Professor at the New York University Nathan Kline Institute from 1998-2006 followed by Columbia University from 2006-2019 where she was deputy director of the Taub Institute. Professor Duff explores disease mechanisms and test therapeutic approaches to Alzheimer's disease, FTD and other dementias. Her current interests are exploring the mechanisms involved in the spread of pathogenic proteins within the brain, understanding the basis of selective cellular vulnerability and resilience to tauopathy and developing new mouse and cell models to understand the earliest stages in tau pathogenesis. Professor Duff has published 140 peer-reviewed research articles and received several prizes including the Potemkin Prize in 2006 and most recently the British Neuroscience Association award for Outstanding Contribution to Neuroscience in 2020 and Fellowship of the UK Academy of Medical Sciences in 2022.
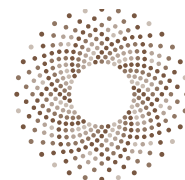
Brad O'Connor
CEO, Cogstate

Since 2005, I've served as CEO of Cogstate, helping lead our work to drive access and equity in brain health by building tools that help everyone measure and understand the health of their brain. Previously, I had a career in finance, which included a number of years in the Tax and Legal services group of PricewaterhouseCoopers, before accepting the role as CFO and Company Secretary of Cogstate in 2004. I originally joined Cogstate to help keep the company afloat–and the hard work and passion of my colleagues has kept me around for decades.

Dr Ivonne Suridjan
Director, Global Clinical Development & Neurology Indication Leader Roche

Ivonne Suridjan is an experienced clinical leader with 15 years of experience driving innovations and development of novel biomarkers and therapeutics in Psychiatry and Neurodegenerative disease. She is passionate about creating partnership and collaborating with people across functions and expertise to translate innovations from research concepts into routine clinical practice. She joined Roche 3 years ago and is leading the clinical development and disease area strategy for Neurology at Roche Diagnostics Ltd.

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

Charlotte Teunissen's drive is to improve care of patients with neurological diseases by developing body fluid biomarkers for diagnosis, stratification, prognosis and monitoring treatment responses. Studies of her research group span the entire spectrum of biomarker development, starting with biomarker identification, often by –omics methods, followed by biomarker assay development and analytical validation, and lastly, extensive clinical validation and implementation of novel biomarkers in clinical practice. She has extensive expertise with assay development on state of the art technologies, such as mass spectrometry and antibody-based arrays for biomarker discovery, ultrasensitive immunoassays, and in in implementation of vitro diagnostic technologies for clinical routine lab analysis. She is responsible for the large well-characterised biobank of the Amsterdam Dementia cohort, containing >5200 paired CSF and serum samples of individuals visiting the memory clinical of the Alzheimer Center Amsterdam (a.o. controls, patients with Alzheimer, Frontotemporal, Lewy Bodies).To ensure the quality of the biosamples, the group studies pre-analytical effects, which are key to implementation. Charlotte is leading several collaborative international biomarker networks, such as the Society for Neurochemistry and routine CSF analysis and the Alzheimer Association-Global Biomarker Standardization and Blood Based Biomarkers consortia. She is the coordinator of the Marie Curie MIRIADE project, aiming to train 15 novel researchers into innovative strategies to develop dementia biomarkers (10 academic centers + 10 non-academic centers), and the JPND bPRIDE project, that aims to develop targeted blood based biomarker panels for early differential diagnoses of specific dementias and is a collaborative project between seven European and one Australian centers.
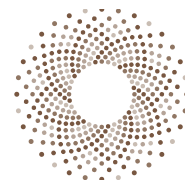
Discussion transcript

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Folks, we are going to resume this third session just before lunch. A very exciting session, I must say. I'm particularly conflicted myself because I've been really into biomarkers all my life. But I promise to do this very unbiased, to try to be unbiased at least.

So, we have a panel, originally five, but Art Toga's plane got cancelled yesterday. He is on his way here but right now will be landing at Heathrow. But despite that we have a very exciting and talented panel for you. So let me first introduce the panel to you. I'll ask them to come over.
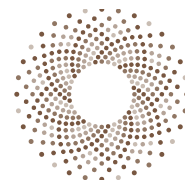
- **Professor Karen Duff**, for the Director of UK Dementia Research Institute

- We have **Brad O'Connor**, the Chief Executive of Cogstate. Welcome

- **Dr. Ivonne Suridjan**, Director of Global Clinical Development and Neurology Education Leader, Roche Diagnostics

- And **Professor Charlotte Teunissen,** the Head of the Neurology Lab, Neurochemistry Lab at the Amsterdam University Medical Centers

So the focus is for this particular session on the development of biomarkers. The other session this afternoon is about making a timely diagnosis and how biomarkers can actually fit into that. But here we are focusing on the biomarkers. We're talking about digital biomarkers, plasma biomarkers, imaging biomarkers in Alzheimer's disease and of course also other forms of dementia.

What are we able to do now and what will we be doing the next five or ten years? And if we know that, how do we get there? And I think some of the elements were already discussed in the previous two sessions not least the question of equity, having the biomarkers being affordable and available to everybody.

So as in the previous two sessions, I will just ask the panel members first to give a brief statement, without slides, on their thoughts, where we are, and what they think about the statement that I just gave. So, from left to right, let's start with you here Karen.

Professor Karen Duff, Director of UK Dementia Research Institute

Thank you very much for inviting me to this very thought-provoking session. So yes, the biomarker field really covers a gamut of different approaches, from biofluids and imaging, which is more used for diagnostics, to cognitive and behavioural biomarkers, to digital biomarkers, which we've already heard quite a lot about.

I come to this meeting as a l researcher running a molecular research lab, and I use a lot of mouse models and cell models to look at disease mechanisms. One of the things I'd like to touch on is the ability of biomarkers to inform on some of the mechanisms and the molecular underpinnings of these diseases. When you are thinking of biomarkers in this context, it can be any of those biomarkers I mentioned, from plasma, blood biomarkers, for example identifying tau levels or neurofilament levels to imaging markers looking at functional measures of the brain, cognitive and behavioural measures, and digital. How can we use these surrogate markers to understand the mechanisms of disease? Can we do better at using those biomarkers for feedback on mechanisms?

Importantly, can we use them to target the right drug to the right patient at the right time in their disease? I think this is a critical aspect of the biomarker field.

Can we use them to predict the progression and the trajectory of a disease? And for understanding which disease is which, can we separate diseases using these biomarkers?

To address some of those points, I would call on funders and policymakers to really try and help us take the field forward. We've done really amazing work in the last five to ten years in the biomarker field at all these levels. But we really need to do more, with a particular interest in how to use those biomarkers to understand disease mechanisms.

I would also ask for more work to be done on well characterised patient cohorts and use epidemiology and cohort data to identify what the biomarkers mean in those cohorts. We should use the biobanks for tissue and biofluids, use imaging studies, large imaging studies such as ADNI, for example, and particularly to call on the drug companies to work with policy makers to get the data from the clinical trials back into the hands of the researchers who can make so much use of it. So that's my charge to the funders and the policy makers to really help pull those resources together in a meaningful way globally so that we can actually use them to understand mechanisms better.

**Brad O'Connor**, Chief Executive of Cogstate

So, I wanted to focus on digital biomarkers and I really wanted to pick up on something that Lenny said at the start of the session today, talking about empowering people to manage their own health. And I just had some information I thought would be relevant for this group.

So, we've been developing a smartphone-based assessment where it uses Siri, or whatever digital assistant you happen to have on your phone, to essentially act as a doctor, in terms of asking questions. And that work is coming on very well, and the technology exists in terms of the voice-to-text and the ability to analyse answers from an individual.

But what I wanted to really talk about is some of the work that we've been doing with a digital advertising and market penetration group, going out to individuals and finding out to what extent people are interested in actually monitoring their own brain health. And some of the things that we found surprising; some things weren't.

So, people who use other digital health assessments, the smart watches and things like that, there was a really high correlation between those people in terms of the percentage of those people who wanted to monitor their brain health to the extent that they could. So that wasn't surprising.

What was really surprising was that people wanted to be able to do that with the information coming back to them and then they would decide what to do with it. That was really powerful. They didn't want that information being sent to their doctors, being sent to their family members. They wanted to have it themselves. They liked the fact that it was easy and accessible, so a smartphone app that they could use whenever they wanted. And they liked the idea of managing it themselves, people responded to messages about monitoring for decline, but they just wanted to understand
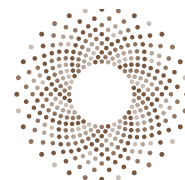
where they were. And it was really important that they understood where they were relative to age-matched peers. And then the idea of measuring change over time, because without a background in neuroscience, they come to this with an expectation of I expect to change over time, I want to do what I can to stop that, but I want to know that it's happening. And if you can empower me to do that, that would be amazing.

And then the final thing that was really surprising to us and remember that this is in respect of a product that hasn't been launched, it has no brand name and things like that. The click-through rates in advertising on things like Instagram were incredibly high. And not incredibly high in terms of a brain health monitoring assessment, they were just incredibly high. So, this marketing group that we were using were really surprised at the level of people who would click through to find out more information with no brand recognition and with no product at the end of it. And that they would share that, not only just click through, but then share it with others, say you should have a look at this as well, when there was really nothing there. So there's just a high demand for this.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Thank you, Brad, for this short comment. The meaning is that we have some short introductory comments, and then we'll ask the audience. But you're forgiven. Ivonne.
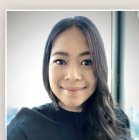
Dr. Ivonne Suridjan, Director of Global Clinical Development and Neurology Education Leader, Roche Diagnostics

That's a warning for me. I'll keep mine shorter. So, the question is kind of where can we expect biomarkers in the next five to ten years?

We've have advanced a lot in our field in terms of blood-based biomarkers. We can measure various forms of p-tau, AB42 and 40 in the blood. But I think we need to remember blood tests only address part of the problem, right? They address some of the barriers in our healthcare systems, but not all of them. Still the appropriate use criteria for blood tests is to use it as an adjunct to clinical examination.

What I observe in our field is that we often kind of get carried away in our conversation talking about which biomarker is better. I think we need to shift the conversations from biomarker to specific context of use. And even within that context of use, if we just focus on the context of use for detections of amyloid pathology, we need to start kind of unifying the field and thinking, okay, what is the acceptance criteria, the minimum clinical performance that we will accept as a physician, as a regulator, as payers, for a test to rule out, rule in, or to replace a PET or CSF.
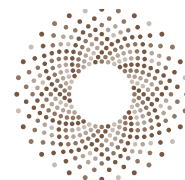
And then finally, all of these innovations will not reach patients unless we make some changes in terms of how we assess value of knowing, value of early detection. Because currently, the way the reimbursement decisions are really linking the value of diagnosis to effectiveness of therapy. So, there's I think we, the scientists need to work together also with governments and payers to change the way we think about value of early detection.

Professor Charlotte Teunissen, Head of the Neurology Lab, Neurochemistry Lab at the Amsterdam University Medical Centers

Okay, I'll try to be even shorter! Well, I think in one line: the plasma biomarkers are there, this train is rolling, and we can't stop it.

And I do think that the direction of the train, that we need to define carefully. We need to understand what the benefit is of the plasma biomarkers. For example, we can use them in memory clinics, that's the likely early implementation, because it's also part of the appropriate use recommendations, defined by a working group of the Alzheimer's Association. And we can use them in clinical trials. But that's to define amyloid positivity.

But we can talk about use of drugs, but I do think that the patients, they come to a doctor to know an answer to their problem. And then we should not only talk about Alzheimer's disease and amyloid positivity, but we need to have biomarkers or tests to discriminate the different types of dementias. So, we should not talk only about inclusion in trials. We can make definitions also on when to use, so the context of use also for diagnostic purposes. For example, we know very little about, or it's likely that, the sensitivity and specificity of the plasma biomarkers is worse in older populations, and similar as for CSF biomarkers. So maybe we should only individuals of a certain age and apply the blood test there in the years ahead.

But these are also things we will learn in the next years because we will start with implementation in a research setting, for example in Alzheimer's Center Amsterdam. And we will learn more about that and get answers to our questions.

But the blood biomarkers, they are there.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Yes. Thank you very much. So how about the audience? Well, there you go. John. And then, you.
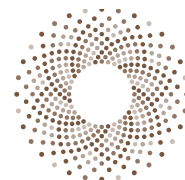
Participant | **Professor John Harrison**, Chief Scientific Officer at the Scottish Brain Sciences

Thanks, everybody. The theme I got from lots of that was that maybe we ought not to see screening with biomarkers, whether they be cognitive or blood-based, for specifically Alzheimer's disease, but maybe a broader campaign of being aware of your own health and if it happens to be the case that you have risk markers for Alzheimer's, then there's a track you can go down. So is the proposition to provide people with an understanding of their cognition and a means by which they can monitor it and once a year maybe a blood test and then build that as a project and then Alzheimer's drops out of that. Is that a better approach, would you say?

Professor Charlotte Teunissen, the Head of the Neurology Lab, Neurochemistry Lab at the Amsterdam University Medical Centers

Do you mean that we should first define and understand cognition?

Participant | **Professor John Harrison**, Chief Scientific Officer at the Scottish Brain Sciences

As well, yeah, that would be a good start. I find most people don't, so it'd be quite nice to educate and then give people the means.

Professor Charlotte Teunissen, Head of the Neurology Lab, Neurochemistry Lab at the Amsterdam University Medical Centers

Yeah, but also because the clinical tests are not well-performing, so that's why we now work so hard on the blood-based biomarkers. I'm convinced that we will get blood-based biomarkers for other dementias. We will find them. There are fantastic technologies nowadays to explain the cognitive changes. But I want to make the important point that today we should not use any plasma biomarker or digital biomarker without a cognitive test, because that's the framework we're in.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

But in a broader context, I mean, that's what you're saying, brain health sort of approach that you were mentioning, and then as a part of that, you could use a biomarker to give a risk profile.
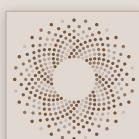
Participant | **Professor John Harrison**, Chief Scientific Officer at the Scottish Brain Sciences

Yeah, I mean, the analogy I used 30 years ago, if I was at lunch with my uncle and he clutched his arm and complained of pins and needles and a pain in his jaw, he'd write it off as indigestion.

Now he'd be straight to casualty. I think with cognition, we're sort of really behind the line in terms of people's understanding. And if we could fix that, then there may be more willingness to come forward.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Okay, good point.
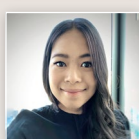
Dr. Ivonne Suridjan, Director of Global Clinical Development and Neurology Education Leader, Roche Diagnostics

I want to say something about that. I mean, if you look at this in terms of health system readiness, one of our main barriers is limited diagnostic capacity. And that's where we think blood-based biomarker could streamline patients who have low likelihood of having amyloid pathology and forward patient with high likelihood of amyloid pathology. And this way we can optimize the limited capacity we have with PET and CSF. So, we can see it from a health system point of view.
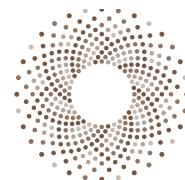
But then at the end of the day then comes down to like what's technically feasible in terms of where our science is today. This would be a really interesting discussions in terms of how good the blood-based biomarker needs to be as a triage test versus a test to replace PET and CSF.

So, what's technically feasible and then also what's actionable? Because when you talk about primary cares and many other professionals, it seems that it doesn't matter for them whether the blood test is positive or negative. They would still need to make decisions about forwarding these patients because it's not just Alzheimer's that's important it's also other types of dementia.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Very good. Karen, you had a comment?

Professor Karen Duff, Director of UK Dementia Research Institute

Yeah, I just wanted to reiterate the importance of the clinically meaningful insight that would come from these biomarkers. You know, a patient who's had an amyloid PET imaging or amyloid in the blood test doesn't really care if it shifts with the clinical trial, but they do care if they are better able to look after themselves or move around. So, I think it's very important to keep those two together, and we are very much behind on the cognitive testing.

And I wanted to bring up a point that somebody mentioned in an earlier session, that what's important to a patient is not whether they can deduct by seven on a mini mental test or other tests of cognition, what's often important to a patient is their social interactions. But cognitive abilities do underpin some of these behaviours that are more meaningful to patients. For example, my mother in the early stages of her Alzheimer's disease, she had the common symptom where she started to lose her orientation in space and so she wouldn't go out of her door because she didn't know how to get to the tube station to visit her friends. And she became very reclusive. So, I think we have to really understand the cognitive changes, and have tests for monitoring those cognitive changes, for example, your ability to navigate in space. And then they will feed back onto other sorts of measures that are perhaps more meaningful for the patients, such as their ability to meet with their friends and that sort of thing.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Very good. Hans you had a comment.

*Participant* | **Hans Moebius**, Chief Medical Officer of Athira Pharma

Thank you. I think an old conundrum in the drug development space for dementia, particularly for the smaller tier of companies, is the necessity to learn early about certain drugs. Whether they are promising or not. Any trial that is shorter than six months is likely not going to tell you anything. And then it also has to be large enough. So, I recall Keith Wessner's approach to that 30 years ago already.

But shouldn't we also discuss biomarkers in this context? How to enable and foster drug development. And next step would be to discuss it in the context of surrogate biomarkers for regulatory purposes. And there I would really like to hear more discussion beyond amyloid because in the last years there were important progress was made on the field of proteomics. And there are certain clusters that can describe Alzheimer's disease perhaps better than with good old-fashioned plugs and tangles.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Lots of questions, lots of comments. Who wants to respond? Brad, you first. I owe you.
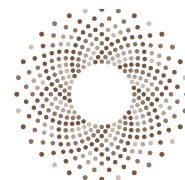
Brad O'Connor, Chief Executive of Cogstate

I agree. I think that I mean we get asked questions all the time about drug development in early phase and can I see an early efficacy signal…

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Or not.

Brad O'Connor, Chief Executive of Cogstate

Or the absence thereof. But in cognition, we try and advise people against it. What are you going to do with the answer? When it's positive you're going to say yeah that's great and when it's negative you're going to say well I didn't power it for effectiveness so we'll just ignore it and we'll move on. And that's why I think a targeted approach, especially in blood based biomarkers, bringing down the cost of that and actually understanding at least you are activating on the target will be a great advancement. I agree.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Charlotte, any comments?

Professor Charlotte Teunissen, Head of the Neurology Lab, Neurochemistry Lab at the Amsterdam University Medical Centers

Maybe I can comment on the clusters of proteins, because I think you were referencing the study that we published on clusters within CSF?

Yeah, that's true. We defined clusters in CSF within the Alzheimer population: patients that have an inflammatory profile and others have a synaptic profile and other blood-brain barrier profile, blood-brain barrier damage. And recently, we have been able to validate that and to extend it to five clusters. So, I think it's a very interesting approach because that will help you stratifying patients within a trial. For example, the inflammatory profile, you can expect that these are the patients that will react
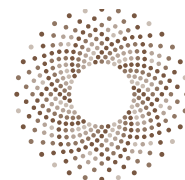
mostly and benefit mostly from anti-inflammatory treatments, if not all, but this group in particular, so you could reduce the cost of the trial by selecting that group.

And now we also have shown prognostic value. So, there is prognostic value within those clusters, different prognostic values. It's an interesting approach, but it's in CSF. The next step is to translate it to blood and also move away from mass spectrometry to immunoassays, because that will help the field also for monitoring treatment effects. But I do totally agree with your comment about the need for other biomarkers beyond amyloid, because that's part of the story, but for treatment monitoring, we need to have other biomarkers as well.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

So, to be honest Steve was first, but Howard has the microphone. That's the power of..

Participant | **Dr Howard Fillit**, Co-Founder & Chief Science Officer of the Alzheimer's Drug Discovery Foundation

I just wanted to follow up on what Karen was saying about clinical meaningfulness.

It occurred to me with the disease modifying agents that people will be going through a lot of neuroimaging and infusions and there's a burden of provision of care here. And if we look at the data at 18 months, even if people would be considered responders because they have a slower rate of decline, they're going to be worse. And so, when I see the patient in my office after 18 months of going through all of this burden of providing the drug, the family's going to come and say, yeah, but he's worse.

And so, I think we've talked a lot about cognition and function and all this, but the fact is they're going to be worse. And all I can say to them is, well, from clinical trials, it's likely that you might be a responder and you're having a 30% or 27% or whatever slow rate of decline than you would have also, which is kind of based on faith. And this goes to my point that I think biomarkers can be clinically meaningful. And the analogy that I get is cholesterol. And we know from translating population data to individual patients that a doctor has to treat about 150 people with a statin for five years to prevent one heart attack. So, most of the people who are taking statins are not really going to benefit. But how do we communicate this: cholesterol. The patient comes in and the clinician says, oh, your cholesterol is down to 140. Isn't that terrific? Yeah, it's great. That's clinically meaningful. The hope is that that will prevent the first heart attack.

So, I think that that's really kind of the argument for why biomarkers are going to be so important in clinical practice and translating the results of population data from the trials into the individual patient interaction.

Professor Charlotte Teunissen, Head of the Neurology Lab, Neurochemistry Lab at the Amsterdam University Medical Centers

Can I comment on that? So I do think that there are two messages that I take from what you just said. That we need to collaborate and drug companies need to share their data so that we can find unifying patterns showing the surrogacy, or not, of the drugs. This is similar to meta-analysis of amyloid PET, that gave us some indication the level of reduction of amyloid PET is predictive for a cognitive effect or beneficial outcome.

I think we can look in that way also at the fluid biomarkers and look at their rate of change. And not just at the end of the trials, because many trials show a positive effect at the end points, which could mean that either they're all positive and we have a glorious future, but it could also mean that we have to look in a more granulated way in the earlier time points and maybe look at the slope of the changes in those earlier stages. But that's the second point. We need to have more early monitoring also of the effects, so more regular blood and yeah, CSF sampling you do it only probably once or twice, but yeah, so there again we have to look into blood, but also at other measures.
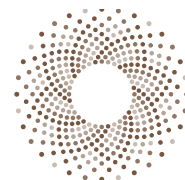
Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Karen, you want to?
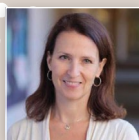
Professor Karen Duff, Director of UK Dementia Research Institute

Yeah, I mean, those numbers are frightening, one in five hundred, you know, actually respond to the treatment. But I think what that tells me, and I think where we're now, is we've really got a surge of new biomarkers coming through, but we don't really understand why they reflect the disease. What part of the disease molecular underpinning do they actually reflect?

For example, in Alzheimer's disease, you have certain p-tau epitopes in the blood that are used for monitoring. But we don't see those in tauopathies, FTD and so on. Why is that? Is it the amyloid that's the difference? Is that actually pushing those tau biomarkers? So, we really need to understand this. And this will allow us to stratify, which I think is really critical going forward to make these clinical trials more manageable.

But I think we also need to understand it so that we can identify new targets, the synapse loss, not just the amyloid and tau, the protein markers, but new targets that will come from understanding the molecular course of the disease.

And for that, I think we really need to do a better job of translating the human biomarkers which are coming through with how we can understand and tease apart the disease course through, for example, the use of mouse models where we can tweak and adjust and look at genetics and understand why only one in five hundred people responds. We can start to tease that apart.

And I would, for the next five to ten years, really like to see a focus on translating, back translating almost, from human studies to how we can develop models that will allow us to understand the dynamics of how those biomarkers are changing and what they reflect in the brain.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Ivonne, you had a comment to Howard or not?
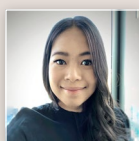
Dr. Ivonne Suridjan, Director of Global Clinical Development and Neurology Education Leader, Roche Diagnostics

Yeah, one perspective I want to add is that it actually takes a lot of effort and money to develop biomarkers from approval to clinical use. So, I would really encourage you to also look at the biomarkers that we already have today. They're really good already.

They're good for some context of use, certainly for detections of amyloid pathology. For example, many of the p-tau variants have been shown to reflect both amyloid and tau pathology in the brain and they're really good to be used as a pre-screener in clinical trials. Now, what I would do is to take the same biomarkers and see whether we can also use it as a treatment response predictor, so treatment monitoring.

And then in the context of clinical meaningfulness, I heard some of the interesting conversations about if you're just have a drug that only targets amyloid pathology, how much can we expect the reductions and the slowing of disease progression. So there I think we still need, there's still quite a bit of progress needed, to identify biomarkers that measure other proteinopathies, like TDP43 and alpha-synuclein. So, there I see kind of midterm focus as where we should be going.
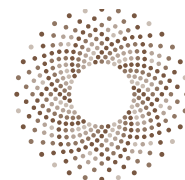
Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

We'll keep that in mind. Tetsu.
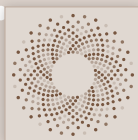
Participant | **Tetsu Maruyama**, Executive Director Alzheimer's Disease Data Initiative (ADDI)

So, I'd like to expand a bit on what's been said before in a plea again for data sharing, particularly around biomarkers and diagnostics for a number of reasons that we come up with here. One of them is the validation against a particular disease population will be important. Another, we've heard that it's going to be really important for anyone who runs a trial on a new mechanism to develop a biomarker specific for that. As an incentive for that, it ought to be realised that by sharing those data, not just the results but the data themselves about that, that biomarker that you put the effort into for a specific purpose can become more general. Ultimately, I suspect, in diagnosis and stratification are going to be fingerprints, and they're going to come from multiple different modalities, multiple different assays. Having all of those available for people to use the data is the way for us to discover their utility. And I know, Ivonne, you're a believer.

Professor Karen Duff, Director of UK Dementia Research Institute

I absolutely agree. And I think that this is something to be forced through. I think this is something that policymakers could put into requirements for a drugs passing approval. It's that they have to feed the data back to the science community. And I think that should be something going forward so that we should be able to implement better.
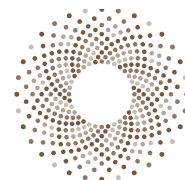
Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund
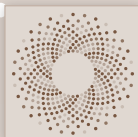
They're keeping the microphone over there.

Participant | **Rhoda Au**, Professor of Anatomy & Neurobiology, Neurology and Epidemiology at Boston University Schools of Medicine and Public. She also serves as Director of Neuropsychology at the Framingham Heart Study

I grabbed it from Tetsu hand.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Then you give it to Lauren. You go and then Steve.

Participant | **Rhoda Au**, Professor of Anatomy & Neurobiology, Neurology and Epidemiology at Boston University Schools of Medicine and Public. She also serves as Director of Neuropsychology at the Framingham Heart Study

All right. So, I just want to remind everybody that because we have very biased data, we actually don't know the distribution of amyloid and tau in the general population. We certainly know from neuropath studies that people can have a fair amount of amyloid and tau and remain asymptomatic. And this goes back to the issue of clinically meaningful. What we pay attention to is changes in behaviour, function, et cetera. And getting to the issue of cognition, just to remind everybody, everything we do, we do through our brain. So everything, function, behaviour, are all driven by cognition. It's pretty arbitrary that we separate them out, because they're really all the underlaying, right?

And so now what I want to do is toss this back to Brad because I want to remind everybody the possibility of digital. And I want everybody to think about this and Miia, this is a little shout out to you. Digital is the new blood. We can collect digital in its raw native format. We can analyse it for everything that we know, and it's not limited to just cognitive-related behaviours, by the way, right? We can measure it for what we know, and then we can store and save it and share it. That's right. Importantly, share it. Most importantly, share it, in order to get to this new reality of what digital can actually do. And so I will ask you, Brad, to comment on that.

Brad O'Connor, Chief Executive of Cogstate

And so, look, I agree, obviously, but I think the opportunity is to put technologies in the hands of people, right? So, to take it out of our selective hands and put it out into the community, I think that's where you find the answers. I think it's the goal of large data sets and what we can learn from that.

And it was spoken about in the first session about the promise of AI and how you could look at those large data sets. And then really, the goal should be to move from what we're talking about at the moment is very active measurement to passive measurement, or the combination thereof. So the collection of other data and analysing that in the context of looking at cognitive change, comparing that with blood-based biomarkers or other biomarkers and learning from that. You've got to collect that information, we've got to put it in the hands of the community before we're going to get any power out of that. It's great to talk about AI, but you need really big datasets and the way to do that is really cheap digital assessments.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

I have the sense that somebody who owns large datasets actually wants to comment. John Gallagher.
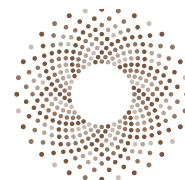
Participant | **Professor John Gallacher**, Professor of Cognitive Health at Oxford University and Director of Dementias Platform UK

So I own no datasets.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

You work with them.

Participant | **Professor John Gallacher**, Professor of Cognitive Health at Oxford University and Director of Dementias Platform UK

I work with them and one of the biggest issues we face are actually structural. People having a basis for sharing their data. Because if you like the ownership rules of them are unclear. For privately funded data, the ownership rules are very clear. But for publicly funded data, who grants access on what basis? And I'd like to suggest a principle that it's who can ever use the data to the best advantage should have a right of access.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Okay, any comments from the panel? Or are you just agreeing?

Professor Charlotte Teunissen, Head of the Neurology Lab, Neurochemistry Lab at the Amsterdam University Medical Centers

Yeah, I agree. And I think there are also instruments now that we have to publish our data. For example, our proteomics data sets, they are freely accessible because we publish them. So, I see that there are still barriers also for data sharing. It's good to have some unified databases. You need to structure and make a template for different types of data.

And so, for genetics they are more advanced with that than for proteomics, for example. It needs investment, and maybe there can be some common database or common platform where everyone can share the data and we have some access instruments as well. There are European rules of course. Here in Europe we have to do, well not here in Europe, but...

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

I warn you not to use the word.

Professor Charlotte Teunissen, Head of the Neurology Lab, Neurochemistry Lab at the Amsterdam University Medical Centers

Sorry, sorry ...We have to deal with also, and the ownership is something to deal with. But I think it's moving slowly, but in the right direction.
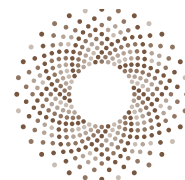
Participant | **Steve Salloway**, Associate Director of the Brown Center for Alzheimer's Disease Research, the founding Director of the Memory and Aging Program (MAP) at the Butler Hospital, a Professor of Neurology and the Martin M Zucker Professor of Psychiatry and Human Behavior at the Warren Alpert Medical School of Brown University, Providence, RI

So WCD is, in effect, an advisory body to policy makers, to regulators, to payers, and others. I think we should communicate a sense of urgency across the board, but especially in this area. Now that we've made so much progress in the plasma biomarkers, start using them in clinical practice. If I were a payer and I saw that monoclonal antibodies were coming into clinical practice and how much a PET scan costs and how inaccessible they are, I would want to get these plasma biomarkers into play ASAP. That should be a priority and we should communicate that as recommendations and implementation strategy.

The same as others have been talking about for monitoring treatment response. We have p-Tau, which is in an early stage, we need to do more. So, we need to bring it. But the urgency is to bring it into clinical practice so that we can validate it and it can guide treatment. We don't know how long to give these antibodies for, who's responding, who's not responding. And I think we have the potential, I think you guys will agree, some of the biomarkers we have and maybe others that we will develop soon can do that.

And the third thing, this is the hardest one in which people have been talking about is data sharing. I'm sorry Art Toga is not here because he really has pioneered through ADNI data sharing, and the NIA now mandates data sharing for trials that do not involve medication. But the trials that do involve medication are just or more informative than the observational trials. Somehow, we need to mandate that data. It's so critical to the field, as we all agree, but we just haven't gone over that barrier of intellectual property, to understand about how to do that. But there needs to be a mandate from regulators just as there is now for observational studies and Art has demonstrated that a platform can be created and investigators from all around the world can use it. We have the technology, so we need really the force of will and working through the legal barriers.
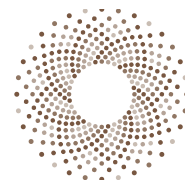
Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Thank you for that.

Participant | **Professor Simon Lovestone**, Global Lead Neuroscience Discovery and Translation Janssen

I could not agree more with the call for data sharing. It's super important. I do, though, just want to take time to say we are already doing it, we are making great progress. So just to give you three quick examples, very quick examples, the study that Charlotte was just talking about came from the data sharing and sample sharing initiative IMI-EMIF which then spawned another one currently sharing samples from industry and academia all over Europe called IMI-EPND. The call for sharing of samples and data from clinical trials is happening. So Janssen has made not just the data from our Alzheimer clinical trials, but the samples from our Alzheimer clinical trials available to the scientific community. You can access them through the ADDF initiative, biomarker accelerator initiative. And I'm delighted that a couple of other companies have joined with us in making those samples available. And I can give you a sneak preview of something that we'll be talking about more at ADPD and AAIC. Janssen, working with Gates Foundation, has put together a collaboration, partly funded by those two bodies, of over a hundred million protein assays in relation to Alzheimer's disease. We'll make these available and Tetsu's organization, ADDI, is hosting that data with a platform for data interoperability and data sharing. I actually think if you look across medicine, you could make the case that there is more sample sharing and more data sharing in our area than in most areas of medicine. So, it's really important we should be proud collectively of a field of what we've already achieved. It's quite remarkable.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Hear hear. Your neighbour next.
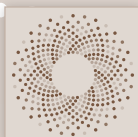
Participant | **Professor Derek Hill**, Chair of Digital Health at University College London and is CEO of Panoramic Digital Health

I wanted to revisit the digital versus non-digital biomarker issue and I get the sense that some in the room are arguing that perhaps the digital is going to be quick and easy. I'm not quite convinced it is. I know Brad has real experience of trying to do this for years. But the FDA recognized, I think, its first ever consensus standard related to AI and machine learning in December. And it has this quote in it: the amplification of errors in an AI system has the potential to create large-scale harm to patients.

There's a sense that regulators are concerned about the risk in AI, the biases, the difficulties in some issues around trust. And I think that perhaps to think of digital as the next blood is perhaps realistic. It wasn't quick to produce a blood biomarker. I think we've got to think quite carefully about the digital. And I think there's a need to be a bit more aware of some of the risks and challenges in that. Data has phenomenal value, but there's also, I think, some considerable challenges in having a pathway to actually impact and getting devices that really can be of high value for patient management.

**Brad O'Connor**, Chief Executive of Cogstate

So, thank you, Derek. I think it's really well-made comments. I don't think it's easy, and I think there are significant risks associated with AI. The quick thing I'd say is that we've got to be very careful not to let perfection get in the way of progress. We've got to get out there and try some stuff. The first panel this morning talked about why we're still doing these things. Because we're scared! The fear of doing something wrong can't stop us from moving forward. Your comments are really well made.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Yeah you, but I had John first, then Cornelia, and then you.
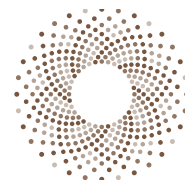
Participant | **John R. Dwyer, Jr.,** President of the Global Alzheimer's Platform Foundation (GAP)

Two very quick questions. One for you, Brad, and then for the biomarker team. We are conducting studies now with a number of the digital markers, and what we hear from pharma, and their FDA surrogates, is show us the through line back to the MMSE or show us the through line back to the MoCA. However crazy that is, we can't get purchase for the digital markers if we don't tell them what your device says is that a 21 on the MMSE. And in the absence of that kind of crosswalk, they are going to be regulators that can't get out of their own way with accepting that. So I'd love to hear you comment on that.

And for the blood marker folks, we are very concerned about early data showing that the blood plasma markers are showing some different cutoffs by race and ethnicity that we have already seen in CSF. And now there's concern that PET imaging also may be susceptible to this, and I'd like to hear what the equity is there.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Very good comments.

Brad O'Connor, Chief Executive of Cogstate

So really quick response. In relation to correlation amongst tests such as the MMSE, I think that whilst a valid question as a general statement, in the specifics, we must ask if the MMSE is a valid test to assess early Alzheimer's disease. And if people want to talk about relationship between early Alzheimer's disease and MMSE, I'll probably direct them to Dr. Harrison to give his thoughts on those sort of things.

Dr. Ivonne Suridjan, Director of Global Clinical Development and Neurology Education Leader, Roche Diagnostics

I want to echo some of the comment that's already been made. We talk about implementation strategy, but a step before that is really adopting appropriate measure to validate the blood-based biomarkers to address the medical comorbidity and the heterogeneity that you just said there. And I think there we can also be proud because there are lots of research and effort underway right now with global clinical trial platform to reduce costs and also to come up with these prospective validation samples that really takes into account the heterogeneities of where the tests we want to use in primary care. So, we need to make sure it's validated in a patient population that reflects where the test is going to be used in real world. So, I think a lot of us in the room, I can see are already working towards that. Now the implementation strategy piece, I think that's still quite new. And I think that's probably something that we have to figure out together as a field on how and how to do that. And how to make sure that we generate data that can convince the payers and the policymakers to make some changes as needed.
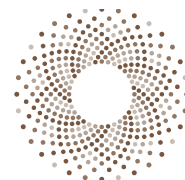
Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Okay. Cornelia. Over there.

Participant | **Cornelia van Duijn**, full professor of Genetic Epidemiology at the Nuffield Department of Population Health, University of Oxford

Thank you. I'm very convinced about the blood-based biomarkers, but I think the argument that has been made already, there's a lot of people with a high cholesterol who doesn't have a cardiovascular disease. There's lots of people with high blood pressure who doesn't have any pathology right? So,

what is keeping us really from implementing this now? Is it that the biomarkers are not specific enough? What is keeping us for implementing it for instance at the GP level or any other level that could help our health care so much and make the problem more manageable and cheaper?

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Yeah that's a call, what's keeping us?

Professor Charlotte Teunissen, Head of the Neurology Lab, Neurochemistry Lab at the Amsterdam University Medical Centers

Yeah, now we don't know yet how the blood-based biomarkers behave in a primary care population. We barely have any information about it. So, I would love to start with primary care, but there are a couple of issues that we need to solve.

For example, there is a worry that there will be over-testing. And what does a primary care physician have to do with the answer? They are not familiar with dementia or Alzheimer's and the different biological definitions, and what to do next with a positive answer? Or what if there is a positive result on the blood biomarkers, but not a cognitive effect, because amyloids can change years before we see the clinical symptoms. So maybe we need to enrich with prognostic biomarkers, but for a primary care physician, that's a dilemma on how to solve that. There are also barriers in funding, refunding. In the Netherlands, for example, care is organised more or less in silos between the different types of care. So, we need to break those walls.

So, there are issues we need to address, but it's so positive that we are discussing it because it's so new and that we are already thinking about those kinds of questions. And so there is still a lot of work to be done, but the rate of research, how it's ongoing currently, it's very encouraging. So, we will be able to solve all the challenges and all the questions in the next five or ten years. I think we need to slow down a little bit in primary care.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Hopefully. No, sorry I have to be strict. There's a question over there. You. Yes. No, no, no, no, the one behind you. Sorry. Yeah, sorry. The one with the microphone. Yeah, thank you.

Participant | **Sudhir Sivakumaran**, PhD, serves as the Vice President of the Neuroscience Program, Executive Director for the Critical Path for Alzheimer's Disease (CPAD) consortium

I think this topic of biomarkers can go on for a full conference, not just one day, but three, four days. But I want to share a few thoughts. I've been listening very carefully on all these topics, and I just came from a National Academies biomarker workshop in Washington, D.C. earlier this week.

I would like to start with what Dr. Ivonne actually mentioned, ultimately, it's all about the context of use. And as those who know critical patterns, we work in the regulatory landscape and together with industry sponsors as well. But the context of use is very, very important. And I would like to point out to Dr. Charlotte's actual paper, I think from a year ago, where there was a big review on the different context of use for the biomarkers. So I think it's very important to keep that in mind because ultimately defining the clinical meaningfulness will go back to the context of use and what does it mean all the way from tracking changes in the biomarker over time, but also being able to predict treatment effects down the line.

The other thing I just quickly wanted to mention is, you know, the Critical Path Institute, so we are, the Alzheimer's Consortium particularly, we have collected massive amounts of data.
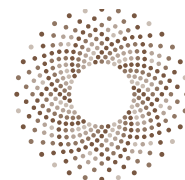
As of today, we have 97,527 individual patient-level records from Alzheimer's disease studies, spanning more than 70 studies. This includes industry sponsors, but also other observational studies, and we work with our colleagues from the Association, Dr. Heather Snyder, who is here, and also Dr. Art Toga. And I just wanted to share with this audience today, and I don't know if Dr. Mark McClellan is still here, I was talking with him earlier today.

At CPAD we are actually launching a formal working group for exploring the readiness of Tau PET as a surrogate marker, together with the sponsors, the regulatory agencies and the academic experts as well. But ultimately, that's a very long process.

The final message I want to share from a regulatory perspective, I don't want to speak for the FDA, but what we have heard from them is that, going back to what Dr. Ivonne mentioned, that we already have biomarkers. There's lots coming down the line, and Dr. Charlotte was very hopeful we will have them down the line, but the sponsors are encouraged to collect the data on every biomarker that's available, even as an exploratory measure or a secondary measure. The more we generate, the more useful it's going to be. So, I just wanted to share some of those perspectives and the regulatory agencies are fully in support of that actually. They encourage everyone to do that. So I'll stop with that, thank you.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Thank you very much. So, I'm going to wrap up because it's also lunchtime in a way. I mean, yeah, that's also a biomarker that needs to be addressed. So anyway, so I'm going to ask the panel for some final short comments. Charlotte, you first.

Professor Charlotte Teunissen, Head of the Neurology Lab, Neurochemistry Lab at the Amsterdam University Medical Centers

I'm really satisfied because, yeah, I think the points that have been raised are very important. So, data sharing, further development, we need to invest in this because it's such a fruitful and hopeful movement.
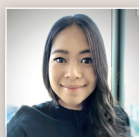
Dr. Ivonne Suridjan, Director of Global Clinical Development and Neurology Education Leader, Roche Diagnostics

I want to highlight that all these for blood-based biomarkers, or even digital, to really make an impact on patients, changes need to be made at the government and policymaking level.

I think payers have to recognise kind of the unique natures of Alzheimer's disease and start adopting a broader approach in assessing value and make reimbursement decisions that take into account kind of the holistic value of early detections. So, without those changes, all the blood-based biomarkers will stay in research practice and will never be adopted and implemented for clinical use.

Brad O'Connor, Chief Executive of Cogstate

Widespread use of biomarkers is what's necessary for earlier identification and the possibility of prevention rather than just slowing of decline.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Wow.
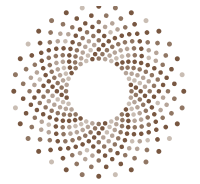
Professor Karen Duff, Director of UK Dementia Research Institute

We're now at the stage where we have a reasonable tool belt of therapeutic approaches, but we need heavy investment to increase the number and the specificity of our biomarkers at all of the levels. And we need to encourage and almost enforce sharing through perhaps regulatory mechanisms so that we can get that information back into the hands of researchers who can use it.

Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Thank you very much. Just remember, digital is the new blood and I wish you a very, very good lunch and we'll be back.

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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