

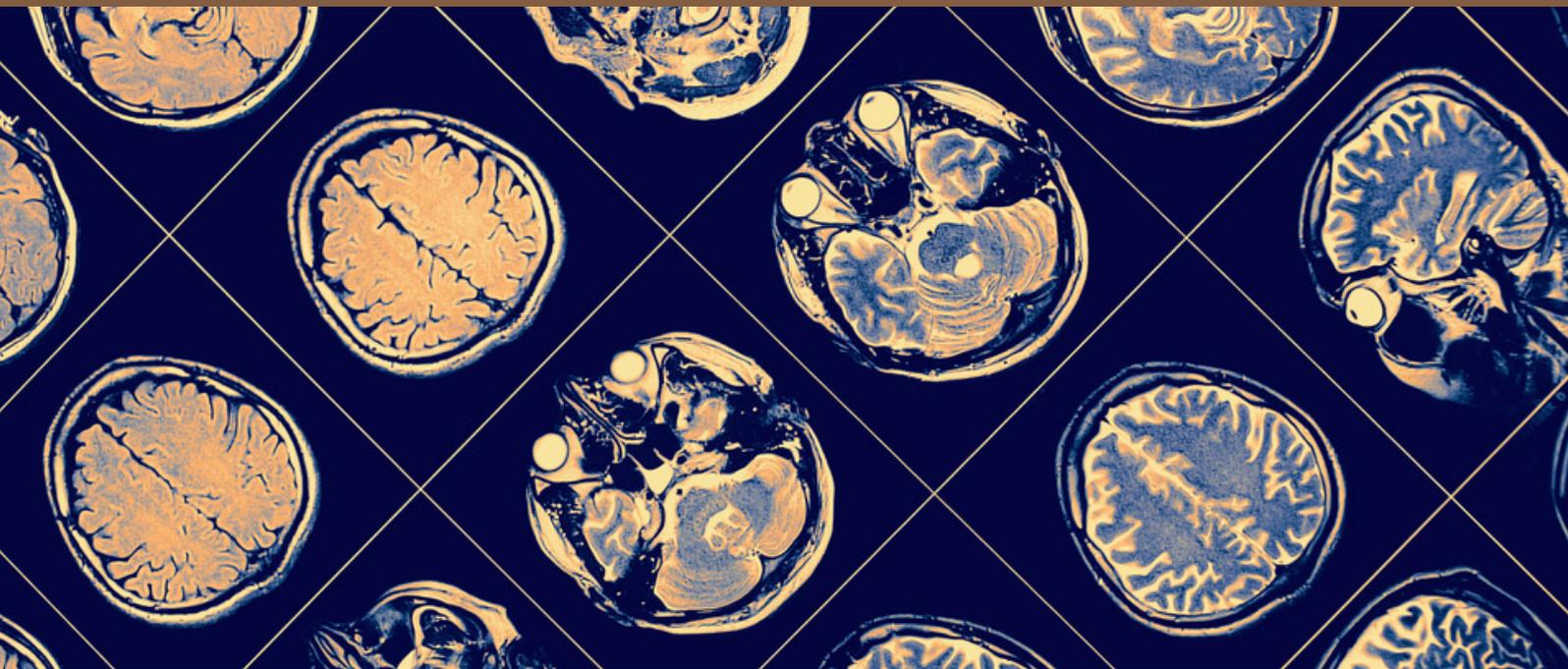


**World Dementia
Council** Leading the Global Action
Against Dementia

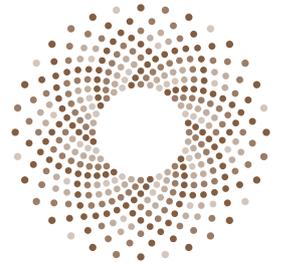
Research workshop: Transcript

The dementia landscape
project

18 November 2020



Co-chairs



Dr Maria Carrillo

Maria Carrillo is chief scientific officer at the Alzheimer’s Association (US), setting the strategic vision for the Association’s global research program. Dr Carrillo has published extensively on early diagnosis and biomarker standardization efforts, as well as on the global challenges to progress for research in Alzheimer’s and dementia. She is a co-author of the “Appropriate Use Criteria for Amyloid Imaging,” published by the Society of Nuclear Medicine and Molecular Imaging and the Alzheimer’s Association. Dr Carrillo earned her PhD from Northwestern University’s Institute for Neuroscience and completed a postdoctoral fellowship focused on Alzheimer’s brain imaging and risk factors at Rush University Medical Center in Chicago.

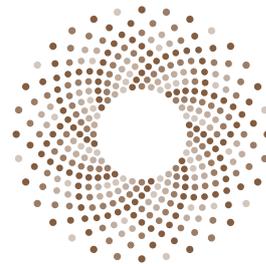


Professor Philip Scheltens

Philip Scheltens is professor of cognitive neurology and director of the Alzheimer Center, Amsterdam University Medical Centers (The Netherlands) and member of the World Dementia Council. His main clinical and research interests are Alzheimer’s disease, vascular dementia, frontotemporal dementia, magnetic resonance imaging, PET imaging and fluid biomarkers. He is active in the field of biomarkers and clinical trials and has been the national principal investigator for many studies, including phase 1-3 multicenter clinical trials. He founded and directs the Alzheimer Center since 2000, from which over 70 PhD theses have appeared since. In 2013, he co-founded the Dutch national plan against dementia (Deltaplan Dementie) and serves as the chair of its board.



Speakers



Professor Oskar Hansson

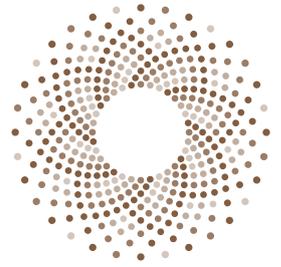
Oskar Hansson is a Professor of Neurology at Lund University and serves as a consulting neurologist at Skåne University Hospital (Sweden). During the last 20 years, Professor Hansson has conducted clinical and translational research focusing on the earliest phases of Alzheimer's. He has built a creative and multi-disciplinary research team and leads the Swedish BioFINDER study. His research combines the study of well characterized patient cohorts with state-of-the-art biomedical and biophysical techniques, most notably in brain imaging. Professor Hansson earned his doctorate in neurobiology, his medical degree, and additional training as a neurology specialist at Lund University.



Dr Cath Mummery

Cath Mummery is a consultant neurologist, and leads the Cognitive Disorders Service at the National Hospital for Neurology and Neurosurgery. She is head of clinical trials at the Dementia Research Centre, University College London and has been chief investigator on over 20 early phase drug trials of potential disease modifying agents, including the ground-breaking platform trial DIAN-TU in presymptomatic individuals at risk of familial AD, and a first-in-human antisense oligonucleotide study, targeting MAPT to reduce tau in AD. She has a particular interest in early phase studies and genetic therapies, and in the psychological impact of trial participation. She sits on a number of advisory boards for potential disease modifying agents and for dementia service development. She is deputy director for the Leonard Wolfson Experimental Neurology Centre at NHNN, a unit dedicated to the conduct of early phase trials in neurodegeneration.





Dr Eric Siemers

Eric Siemers has over 25 years of experience in clinical trials of neurodegenerative disease. His research focus is on the use of biomarkers in investigational drug research, the development of trial designs that fully characterize the effects of investigational drugs on chronic diseases, and more specifically, the development of strategies for treating individuals before the onset of symptoms of neurodegenerative diseases. Dr Siemers most recently served as a distinguished medical fellow for Eli Lilly and Company's Alzheimer's Disease Global Development Team, where he was responsible for the design and implementation of five large phase III clinical studies, in addition to playing a major collaborative role in two public-private partnership studies. Dr Siemers earned his medical degree from the Indiana University School of Medicine (US).



Professor Reisa Sperling

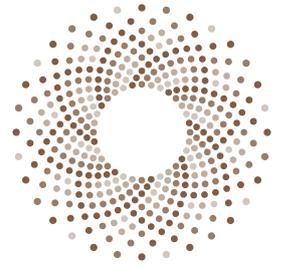
Reisa Sperling is co-principal investigator of the Harvard Aging Brain Study in Boston (US). She is a neurologist focused on the detection and treatment of Alzheimer's disease, even before clinical symptoms are evident. Her research uses neuroimaging and cognitive tests to understand the aging brain and the earliest changes associated with Alzheimer's disease. She is a professor in neurology at Harvard Medical School, director of the Center for Alzheimer Research and Treatment at Brigham and Women's Hospital, and director of neuroimaging for the Massachusetts ADRC at Massachusetts General Hospital.



Lenny Shallcross

Lenny Shallcross is executive director at the World Dementia Council. Prior to that he was Head of Community Engagement leading programmes across the UK to establish Dementia Friendly Communities. This includes the Dementia Friends programme which is the biggest health social movement campaign delivered by 10,000 volunteers that have recruited 2 million individuals through a community, digital and corporate offer. Before working for Alzheimer's Society he worked in the UK government as a political adviser at DCMS and the DoH, as well as working in Parliament and for the Labour Party.





Overview: A time for reflections

Professor Philip Scheltens

Professor of cognitive neurology and director,
Alzheimer Center, Amsterdam University Medical Centers
and member of the WDC



Optimism and Alzheimer's are not natural bedfellows. Daily, weekly – as clinicians – we are confronted with the frustration of being unable to offer our patients anything other than symptomatic drugs, care and support. The drum beat of trial failure accompanies us. And yet, despite this, now is the most optimistic. It is the most exciting time in my thirty years working in the field.

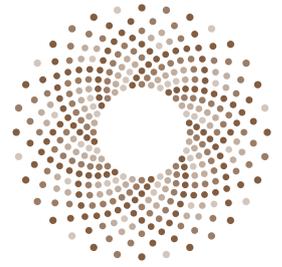
For so many people around the world, this has been a terrible year because of the Covid-19 pandemic. However, this year our field has seen exciting announcements in both treatments and biomarkers. But my case for optimism is not based on individual announcements, welcome that they are, rather on the fundamental building blocks that are now in place.

We know more about the basic science of the brain than ever before. The mechanisms that underlie Alzheimer's disease and other forms of dementia are unlikely to be more complex – or at least much more complex – than cardiovascular disease. We just know less about the biology of the brain than we do about the vascular system. Though that is changing. The steady accumulation of knowledge has not yet translated into therapeutics. But it does mean today we have a range of potential targets for disease modifying treatments. And this will lead to new treatments.

We are on the trajectory that cancer has been on for many years. The first treatments will have some benefit to some people. But new generations of therapeutics will bring greater benefit. Whatever happens with Aducanumab's regulatory approval, over the next decade we will see disease modifying treatments.

Our understanding of the underlying biology of the disease means not just hope for therapeutics but also lifestyle interventions to prevent, or slow, the development of the disease. We have a much better understanding of genetics and the risk profile of developing dementia and patients who might benefit from interventions before the clinical manifestation of disease. As has been seen with cardiovascular disease and cancer, preventing the development of pathology is a viable and successful public health strategy.

Alongside these improvements in understanding of disease, in the near future we will be much better able to accurately diagnose it. Thanks to CSF and imaging we are already better able to stratify patients. Blood and digital biomarkers will soon have a huge



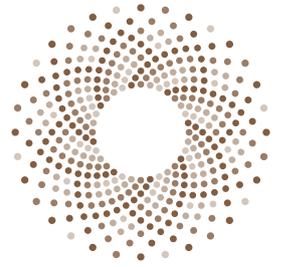
impact. We already understand more about the underlying genetic risk factors of disease, and genetic tests will become much more routine.

The benefits for clinical trials are obvious. With trials costing several hundred million dollars we are only going to have so many shots on goal. The potential to have trial ready cohorts that have biomarker profiles offers more flexibility in designing trials and the potential for delivering them both faster and cheaper.

Even without therapeutics, blood and digital biomarkers will benefit patients through the improved precision and timeliness of the diagnostic experience. Whether it prompts more patients to seek medical help earlier remains to be seen. The reason for patients presenting late are various, such as cultural factors or social and health system responsiveness. It may be that better diagnosis alone will not change behaviour.

Taken together, this means we should be confident that not only are we on the right trajectory, but that the pace of progress is increasing. Sustained funding increases along with well-developed funding strategies – from governments, not-for-profit organizations, philanthropy and the for-profit sector – have helped build capacity and knowledge in the field. Dementia remains relatively underfunded when compared to other disease areas. Maintaining and growing that funding, well developed and well executed funding strategies will be key. We will of course never have ‘enough’ funding. Over the last decade the sector showed how it can, with government and non-governmental partners, reduce financial risk through funding models. We need to continue to incentivize for-profit investment in the field. Utilizing big data offers plentiful opportunities to accelerate research but data sharing remains problematic. This is not a challenge we face alone as there are regulatory barriers right across scientific research, but other disease areas have done more to overcome it. Diagnosis, clinical trial recruitment and the cost of trials all, for different reasons, remain challenging.

But these are problems of pace and not direction. We are on the right trajectory. Over the last decade we have made huge progress. We can up the pace. This is a time to be optimistic.



Blood-based biomarkers for Alzheimer's Disease



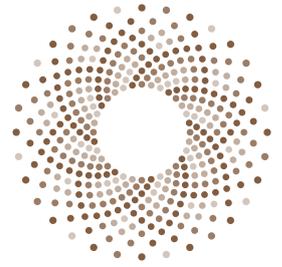
Professor Henrik Zetterberg
Professor of Neurochemistry, University of Gothenburg

Blood-based biomarkers have been described as the holy grail of biomarker AD research, because the promise of a simple, inexpensive, non-invasive test for AD is needed to accelerate observational and clinical trial research, diagnostics in the clinic and, when specific AD treatments are developed, allow appropriate identification of patients who would benefit. Recent AD blood biomarker discoveries have enabled both sensitive and specific measures of amyloid pathology, tau pathology and neurodegeneration.

Highly precise blood amyloid biomarkers were recently reported to have high concordance with both amyloid PET scans and CSF A β 42/A β 40 ratio (Ovod V, Ramsey KN, Mawuenyega KG, et al. Amyloid beta concentrations and stable isotope labeling kinetics of human plasma specific to central nervous system amyloidosis. *Alzheimers Dement* 2017; 13(8): 841-9; Nakamura A, Kaneko N, Villemagne VL, et al. High performance plasma amyloid- β biomarkers for Alzheimer's disease. *Nature* 2018), the gold standard biomarkers for amyloid plaques. These recent developments were enabled by highly specific and precise measures of A β in plasma by mass spectrometry with the data from several hundred participants with high concordance of plasma A β 42/A β 40 with amyloid PET and CSF A β 42/A β 40. Independent work done in parallel also utilized mass spectrometry to measure A β 42/A β 40 and other fragments to demonstrate high concordance with amyloid PET and CSF A β 42.

With accuracies of greater than 80% and receiver operating characteristics (ROC) area under the curve (AUC) of >0.85, the precision of blood A β now matches that of CSF or PET with each other (Ovod V, Ramsey KN, Mawuenyega KG, et al. Amyloid beta concentrations and stable isotope labeling kinetics of human plasma specific to central nervous system amyloidosis. *Alzheimers Dement* 2017; 13(8): 841-9; Nakamura A, Kaneko N, Villemagne VL, et al. High performance plasma amyloid- β biomarkers for Alzheimer's disease. *Nature* 2018). The robustness of the plasma test however, still remains a challenge; in CSF, the ratio is decreased by around 50% in amyloid-positive individuals, whilst the corresponding reduction is only 15% in plasma, which makes the test highly vulnerable to pre-analytical or analytical confounders.

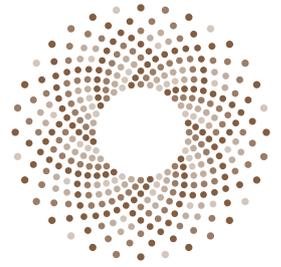
Similar to CSF, phosphorylated tau species in plasma, such as P-tau181 and P-tau217, increase with disease progression in those with A β aggregates (PMID: 32333900; PMID: 33106600; PMID: 32123385; PMID: 32722745). These blood biomarkers seem to increase already at the onset of A β pathology and may represent a neuronal reaction to A β pathology, which precedes tau tangle pathology. There are now several immunoassays



and mass spectrometry-based assays for phosphorylated tau species, showing high diagnostic accuracy for pre-dementia AD, available, and hopefully we will soon see automated high throughput clinical chemistry tests for this biomarker.

Neurofilament light chain protein (NfL) is a well described blood biomarker in multiple neurologic diseases, including multiple sclerosis, stroke, traumatic brain injury, Parkinson's disease, PSP, and AD (PMID: 30967444). Plasma NfL correlates well with CSF NfL and is a promising biomarker supporting AD progression correlating with cognitive and imaging decline (PMID: 30967444). Recent studies suggest that plasma NfL increases around 10 years before symptom onset in autosomal dominant AD and predicts neurodegeneration and clinical progression (PMID: 29070659; PMID: 30664784). NfL is a promising blood biomarker to detect and quantify degeneration in AD but it is important to keep in mind that it is a general biomarker for any type of neuronal injury, which is important to keep in mind when interpreting its result.

The impact of very high accuracy blood tests for AD are enormous and promise to revolutionize clinical trial design, accelerating discoveries of novel interventions, enable historic cohorts to provide deep understanding of the start and progression of AD, and transform AD from an often misdiagnosed (and misunderstood) entity into an objectively diagnosed disease. For clinical trials, the ability to pre-screen thousands to hundreds of thousands of potential participants will improve the ability to decrease enrolment periods, shorten trial durations, and enable the launch and testing of more potential therapeutics. This will accelerate the discovery of new treatments. When we have access to disease-modifying treatments, the blood tests will enable primary care physicians to rapidly identify those patients who should be referred to a memory clinic to be evaluated regarding if they are available for active treatment.



Reasons for optimism: The state of Alzheimer's Disease research in 2020



Dr Husseini Manji

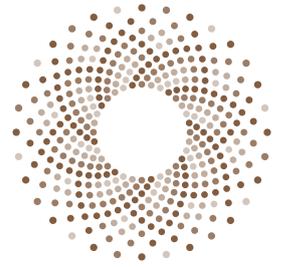
Global Head, Science for Minds, Johnson & Johnson

There is reason to be optimistic for the future of Alzheimer's disease (AD) research, despite the recent trial failures with compounds developed for AD disease modification. This optimism is firmly grounded in the potential of tau as an effective target, the growing diversity of drugs in clinical trials including those targeting the immune system, and the continued development and use of biomarkers.

If we are to hit the ambitious goal of having a disease modifying therapy (DMT) by 2030, a great deal rests on whether tau will prove a better target than – in the broadest sense – amyloid. On this front, there is reason for optimism, namely the clear relationship between tau pathology and AD, and genetic evidence that tau is a driver of neurodegeneration and, therefore, an effective target for therapeutic developments. This optimism is supported by the previous decades of research leading to the breakthrough in understanding that the characteristic spread of pathology may be a consequence of the interneuron seeding of pathological tau. This breakthrough has led to the development of tau-directed immunotherapies and it is with these molecules that the greatest hope for a DMT by 2030 resides.

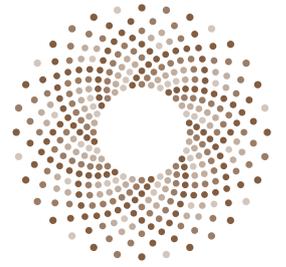
As a result of the inherent challenges in treating AD, potentially the most essential development is the continued growth in diversity of targets within the landscape of drug development. A strong diversity of targets is necessitated by the complexities of the brain and difficulty accessing it, along with the need to understand the disease's biology in order to create effective targeted interventions. The recent setbacks with drugs targeting amyloid plaque further underscores this need. The ability of genetics to provide answers to questions regarding the immune systems role in AD, such as whether immune dysfunction is a driver of the disease or simply a response and which of the multitude of targets is likely to prove most effective, has led to an increase in the number of immune targets in development. Questions remain, namely which pathway of immunity to target and given the significant possibility that the immune system could have both protective and deleterious effects at different stages of the disease, when to target it. Yet, the rapid increase of immune targets in development, including compounds that modulate neuroimmune regulation, is a very positive sign.

If the field is to see eventual success in the development of an effective DMT, biomarkers are likely to continue to play an essential role in the improvement of clinical trials. The combination of increasingly sophisticated biomarkers and the continued recognition of the heterogeneity of pathological process in people with AD is enabling trials in which



participants are defined on entry by pathological measures. Additionally, one of the challenges of having cognition as the primary outcome measure for disease modification trials is the inherent daily fluctuations that occur in individuals' cognitions. Biomarkers have the opportunity to reduce some of that variability leading to more rapid decision making for futility or acceleration in phase two trials, along with proof-of-concept studies.

The coming decade will invariably bring failures with it, requiring companies and governments alike to stay steadfast in their commitment to creating an effective treatment for this difficult and growing disease. Yet, that commitment is already evident in the continued research and increasing diversity of targets. The potentially significant developments within tau pathology and in biomarkers allows for improvements in clinical trials when it comes to screening, selection and increasingly proof of concept. It is essential that we remain optimistic and learn from our past mistakes as we continue to work towards developing an effective treatment for AD.



Research workshop

Wednesday 18 November 2020

08:00 - 09:30 CST	Chicago
09:00 - 10:30 EST	New York
14:00 - 15:30 GMT	London
15:00 - 16:30 CET	Central Europe
19:30 - 21:00 IST	New Delhi
23:00 - 00:30 JST	Tokyo



Discussion transcript



Lenny Shallcross
Executive director, World Dementia Council

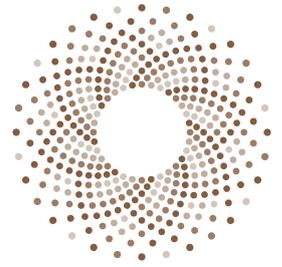
Welcome everyone. I am Lenny Shallcross, Executive Director of the World Dementia Council. I realise many of you have participated in a Council meeting before but for those of you who have not the World Dementia Council was established following the London dementia summit in 2013 hosted by the UK government as part of their G8 presidency.

The Council is chaired by Harry Johns, President and CEO of Alzheimer's Association (US). There are 24 members of the Council. Alongside the members there are a number of government members OECD and WHO are also members. At the London summit the international community committed to make progress in research, care, awareness and risk reduction.

The Council was established after the meeting with the purpose of supporting and challenging the international community to deliver on those goals.

At the Council's [virtual] meeting this July Council members agreed to produce a report evaluating the progress that has been made and identifying how that can be accelerated. They determined to hold a number of workshops, this being the first, to get the input of international experts on where we have come from, where we are, where we need to get to, and how we get there.

After this meeting we will write up a discussion paper, based on the contributions from you all today, which we will circulate to you and would very much welcome your comments.



I would like to introduce the co-chairs of today's workshop, Dr Maria Carrillo and Professor Philip Scheltens. I am grateful to them for not just agreeing to chair the meeting but shape the agenda, suggest speakers and participants.

As you will have seen from the agenda we have two introductory conversations: one on biomarkers and the second on diagnosis and early treatment before having an opportunity for a dialogue.

We are going to start with biomarkers and in doing so I would like to hand over to Maria.



Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

Thanks Lenny and I want to thank Philip, my co-chair, and Lenny, for all of the assistance in organizing the programme. And thanks to all of you for coming online in whatever timezone you are in. I know some of us may be more uncomfortable than others because of the timezones.

What an interesting time we live in across many spheres. Interesting times indeed across a lot of science including in our field with the possibility for a treatment. Very interesting times indeed so it is going to be great to have this conversation.

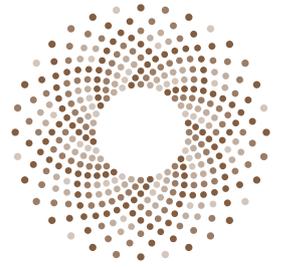
The first topic that Philip and I wanted to touch on was early detection and biomarkers. One of the biggest reasons why, and I know Harry Johns says this a lot coming from fifteen years at the American Cancer Society, is biomarkers drives a lot of what we think of as drug development.

Because being able to detect underlying disease and tie that to early identification first and then a treatment and perhaps have treatment that are effective therapeutics as they are called.

It is really changing the game. It has changed the game for other diseases but is changing the game for Alzheimer's as well.

We have two experts that can talk to this. And I think it is important at the end of this that all of us to have a discussion on where these technologies, these new discoveries, and innovations can take up. Because I think right now we are looking at the possibility of a treatment with a very expensive and harder to perhaps administer on a countrywide basis maybe a global basis if we can on the basis of a PET scan.

So I will ask Dr Oskar Hansson to speak and he is professor of neurology at Lund and he is going to talk to us about blood-based biomarkers and following that I will ask Reisa to speak and then will hand over to Philip to introduce the next two speakers.



Professor Oskar Hansson
Professor of Neurology, Lund University

As Maria said I will focus on blood-based biomarkers but also give some general introduction to AD diagnostics.

 **Disclosures**

Consultant-related activities or research support:

- Eli Lilly
- Hoffmann-La Roche
- GE Healthcare
- AVID Radiopharmaceuticals
- Biogen
- Cerveau Technologies
- AlzPath

 **Alzheimer diagnostics – a multidisciplinary approach**

Clinical assessments

- Cognitive tests
- Psychiatric & neurological assessments
- ADL function






MRI or CT

- Exclude other pathologies
- Regional atrophy patterns
- Cerebrovascular disease (Microbleeds)



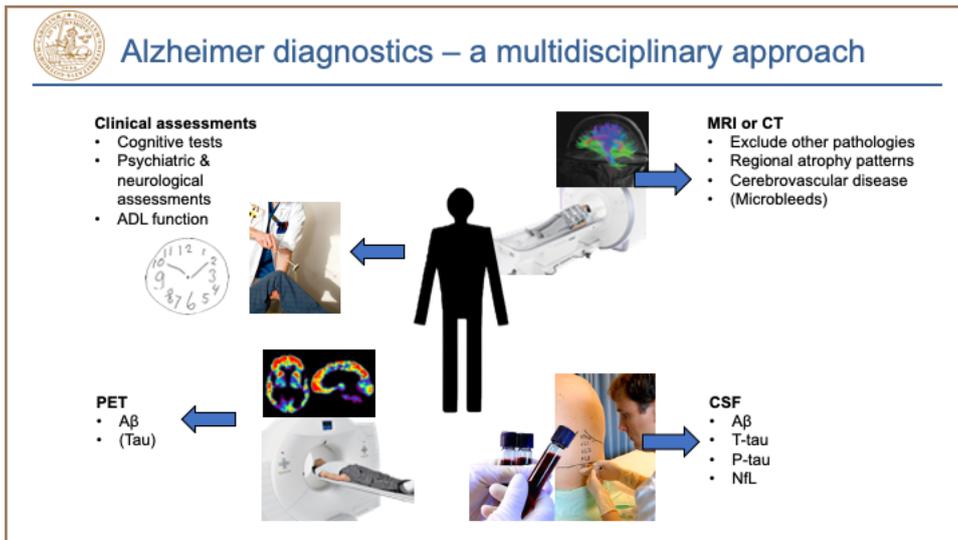
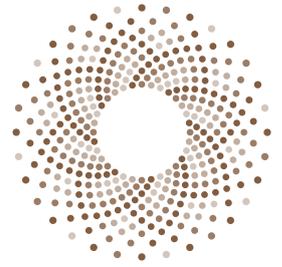
Concordance between clinical diagnosis of AD dementia and neuropathology is not that great (sensitivity 70-80% and specificity 50-70%)*

Even lower diagnostic accuracy in cases with MCI (and not dementia)

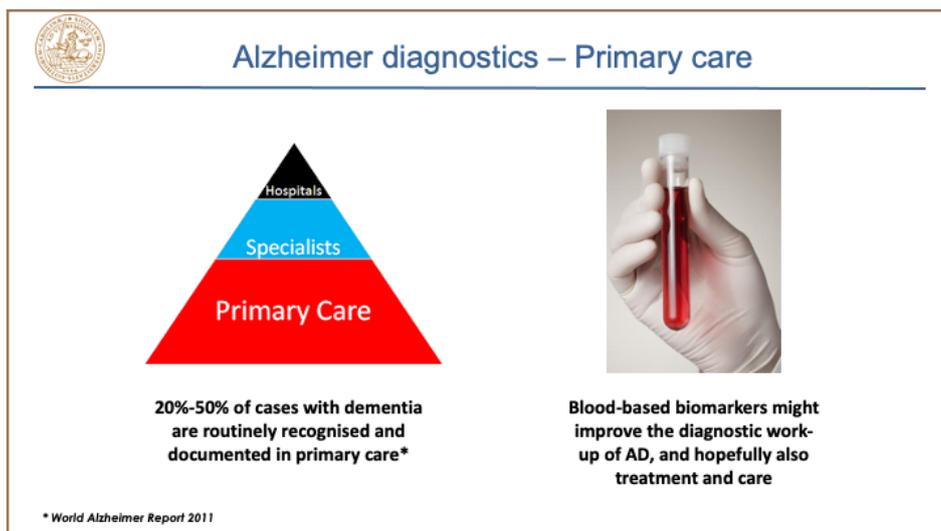
Beach et al., JNEN, 2012
Knopman et al., Neurology, 2001

As you all know, even if you are not clinicians, you know the traditional way of diagnosing Alzheimer’s disease is to do clinical assessments including psychiatric and neurological assessment, cognitive testing and determining the activity of daily living of the individuals. We also do and MRI or CT scan depending on where you are in the world, mainly to exclude other pathologies but also to look at the regional atrophy patterns and the presence of cerebrovascular disease and so on.

The problem of this way of doing the diagnostics is it is not very accurate when compared to neuropathology. So different studies have looked at this and the numbers are varying but the sensitivity is around 70-80% of an AD diagnosis and specificity is lower when it is done only using these types of tools. And it is even more difficult if the patient is at MCI stage to determine if the MCI condition is due to AD or some other aetiology.

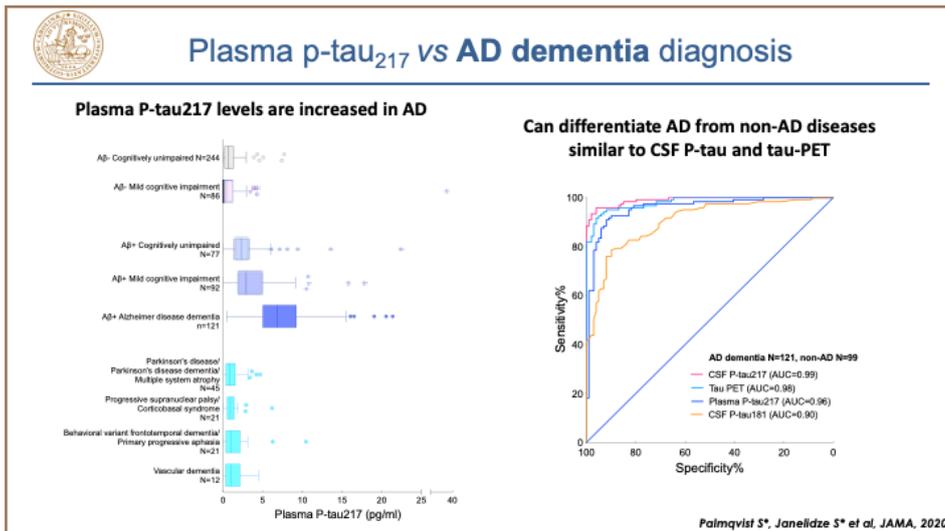
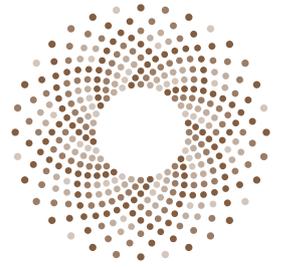


So that is why many centres in the world also perform PET imaging of the brain to determine whether there is AB pathology or doing CSF measures of AB, T-tau, P-Tau and maybe also NFL. This of course improves the diagnostics quite a lot. But this can only be done in specialist memory clinics and not in all such clinics around the world.

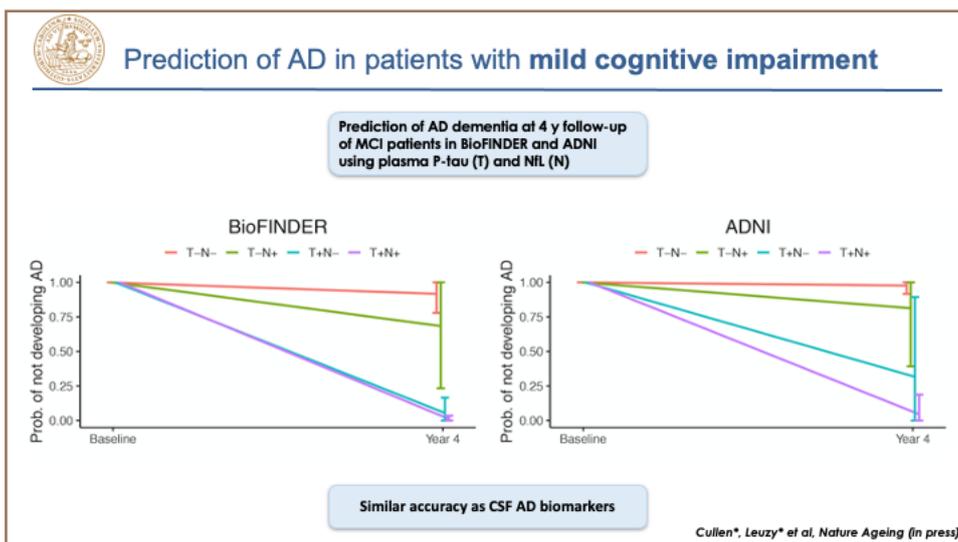


In primary care it is more difficult to make a diagnosis. There are studies showing that many people with dementia are not routinely recognised and diagnosed. There are even some numbers showing the majority of people have no mention of dementia diagnosis in their medical record. No dementia diagnosis means they might not get the symptomatic treatment and care that they should.

So that is one reason why we and others have focussed on the development of blood-based biomarkers so we can improve diagnosis and hopefully by doing that treatment and care. This is important even if we don't have disease modifying therapy or treatment, just symptomatic treatments. But it will become even more relevant if we do have so.

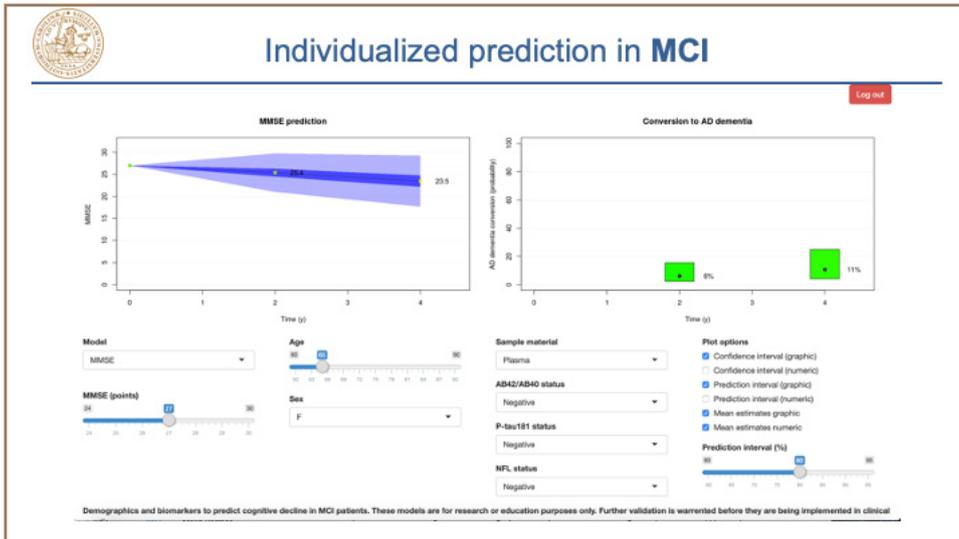
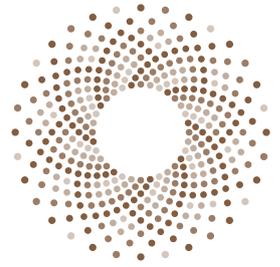


This was then very similar to measuring p-tau in CSF or when performing tau PET imaging. So, we now have a biomarker that is very good at differentiating AD dementia from other neurodegenerative diseases and it can be measured in blood.



However, it is much more difficult to diagnosis AD in patients with MCI and predict who will develop AD dementia in the future.

So here is one study that I haven't yet published where we measured P-tau and NfL in plasma and you see that those are T+ meaning they have increased p-tau at baseline there you can predict the development of AD dementia 4 years later with very high accuracy in bioFinder. In ADNI we found the best accuracy was when combining P-tau with NfL. But combining these two quite simple blood-based biomarkers we have a good way of predicting future development of AD dementia in patients with MCI. It is important that it has a similar accuracy when compared to CSF biomarkers.

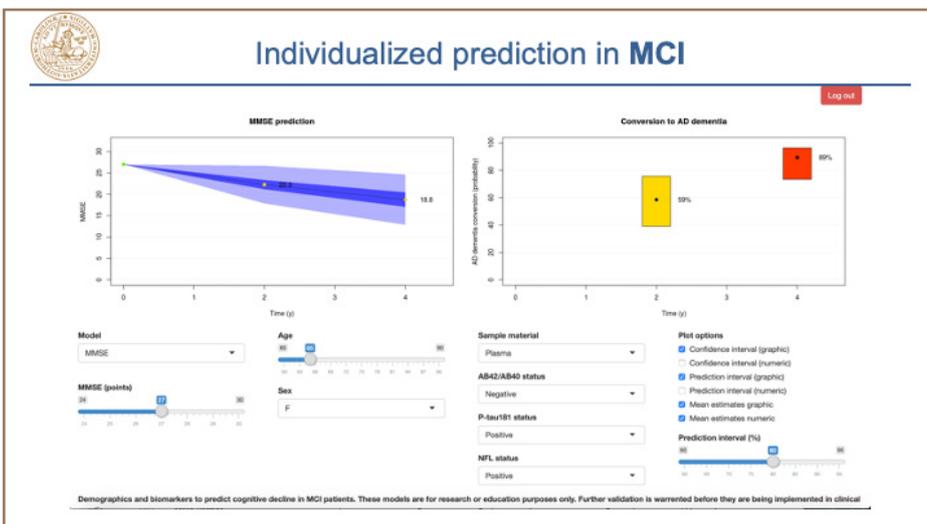


What is important here for the future is the individualised prediction. Because that is what the patient is interested in not group level data.

This is what we will see in the future both in specialist memory clinics and primary care. There will be different type of software where you add cognitive status here MMSE of 27 and here 65 years of age and gender here female. And then the biomarker status and for this individual all the plasma biomarker statuses were negative – AB42/40, P-tau and NfL. And then you see here the predictive change in MMSE over time in this individual. There is some decline over time with age. And you can see the individual has a 6% risk of developing AD dementia over two years and a 11% over four.

Chat function

The chat function was available throughout the workshop for participants to ask questions of presenters and to hold discussion amongst each other. It began just under 15 minutes into the event and is displayed below. It does not necessarily correspond with the adjacent transcript in this document.



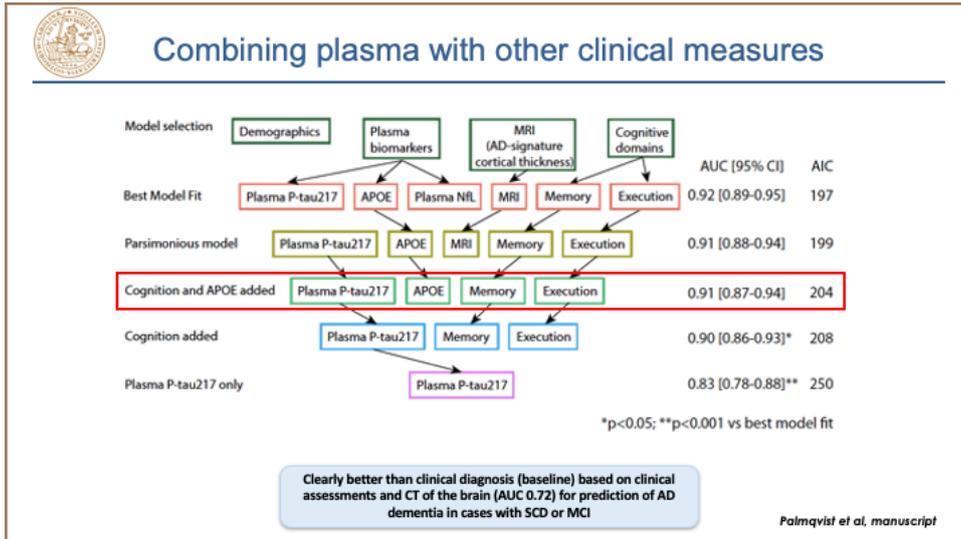
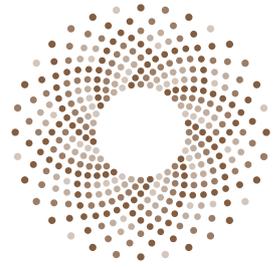
However if the plasma biomarkers had been different in the same individual that is P-tau had been positive and NfL positive the MMSE change would be more clear – a predictive change down to 18 points but also the change in the development of AD dementia. There is a risk of 60% after 2 years and 90% after 4 years. This type of algorithms will be improved in the future.



Dr Cath Mummery
Oskar, does the predictive value hold in presymptomatic individuals?



Professor Todd Golde
What is the conversion to the 42:40 in folks tau positive who then convert. Does the 42:40 go positive?



Then of course it is important to combine it with other measures because we should not only measure things in blood, but we should also do cognitive tests and MRI. This is a bit of a complex slide but what I wanted to show was what we are doing at the moment is seeing which of all these measures are actually helping in predicting AD dementia in patients with MCI. We looked at demographics, plasma biomarkers, MRI and cognitive domains. We found that an algorithm based only on P-tau in blood, APOE genotype, memory and executive function have a very high AUC of 0.91 of predicting AD dementia in patients with either subjective cognitive decline or MCI.

But most importantly this was much better than the clinical prediction of specialist who saw this patient at baseline. Their prediction after first visit when they had met the patient for 1.5 hr and did cognitive tests and looked at CT of the brain had only an AUC 0.72. So these biomarkers combined are much more accurate than the clinical predictions here. I should say I was one of the medical doctors doing this prediction which might explain why it was so poor!

 **Professor Reisa Sperling**

Oskar, I have a question about the beautiful MCI predictor. In the 2nd example, it looked like the Ab42/20 plasma ratio was negative but the p-tau predicted 80% likelihood of AD dementia. Is that common with negative Ab markers?

 **Ivan Koychev**

I wonder if you included cardiovascular risk factors in the MCI prediction models?

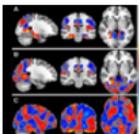
 **Professor Jeffrey Cummings**

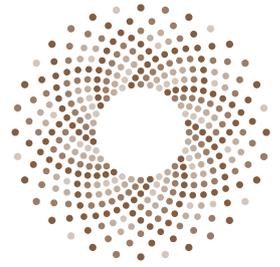
Would you require an amyloid marker of some type for the dx of AD?

Summary – diagnosis of MCI or dementia due to AD

- Plasma P-ta217 is a very accurate biomarker for both “MCI due to AD” and “dementia due to AD”
- Cognitive tests (incl memory & executive function)
 - Digital technologies (smartphones, tablets, digital pens)
- MRI (or CT?) of the brain
 - Automatic segmentation for detection of regional atrophy







What I believe for the future is that when it comes to diagnosis of AD in MCI and dementia we will probably combine P-tau, it could be other than P-tau217, with other cognitive tests including memory and executive function.

And here there is now very interesting developments in digital technology including smart phones which can be repeatedly done at home which will probably result in more consistent and reliable findings. But also doing it on tablets; for example, it will be very important in primary care to have cognitive test more standardised than today. And digital pens of course if you do drawings. Also, we need to do imaging of the brain MRI or maybe CT scan and here of course there is the development of automated segmentation to detect regional atrophy patterns.

Combining these quite simple tools will probably result in the future in much high accuracy both in clinical practice and in clinical trials in the MCI and dementia space.



**Professor
Clive
Ballard**

Contribution of cognitive testing could probably be enhanced with computerized neuropsychology - some validated for repeat self testing at home.



**Professor
Henrik
Zetterberg**

Regarding Reisa's comment: I think w/s plasma Aβ42/40 positivity in the algorithm would not change the prediction much.



**Dr
Christopher
Chen**

Would MRI markers of cerebrovascular disease such as WMH or strokes improve prediction of dementia?



**Dr
Eric
Siemers**

Rather than MCI to AD, how do the predictors work for subjective complaints to MCI?



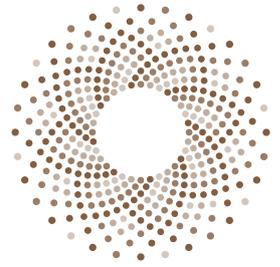
What needs to be done for blood-based biomarkers?

- Development of high-precision methods for measurement in blood
 - Fully automated platforms available in most clinical chemistry laboratories
- Develop a protocol for handling of blood before biomarker analyses
- Establish "appropriate use criteria" to avoid misuse and misinterpretations of biomarkers

However, we need to do a lot of things before we can implement in clinical practice. We need to develop high-precision methods for the measurement of blood-based biomarkers. The best is to establish them on fully automated platforms which are available in clinical chemistry laboratories around the world so it can be done in most countries around the world in most hospitals.

We need to develop a protocol, so we know how to handle the blood, so we don't get false positives or negatives.

But very importantly we need to establish appropriate use criteria, just as has been done for PET and CSF, to avoid misuse and misinterpretation. In Sweden we have been using CSF for 20 years. In the beginning it was not used optimally. It was done in patients who should never have been diagnosed. Although the biomarkers were positive, they never developed AD dementia in a 10-year period because they never had cognitive impairment at baseline and so on. So, it is a very important thing to develop these appropriate use criteria.



Improved AD diagnostics in primary care

- We need to perform large-scale prospective studies, with consecutive recruitment, in primary care
 - Population and setting is different compared to Memory clinics:
 - More heterogenous populations
 - Lower prevalence of AD
 - Personnel is less specialized on dementia disorders
 - Establish whether new diagnostic tools results in relevant change in
 - Diagnosis
 - Treatment
 - Care
- Such studies must have an accurate standard of truth
 - (Neuropathology)
 - Diagnostic work-up at memory disorder clinic (including CSF or PET)

If we now talk about primary care which I personally think is very important because more patients never meet a dementia specialist and will never do that. I don't know if many will have the resources in many countries for all patients with a memory disorder to meet a specialist.

To improve diagnosis we can't use studies that have been done in specialist clinics and just transfer that data into primary care. We need to do large scale prospective studies, with consecutive recruitment in primary care. Because the populations are different: much more heterogenous populations and the prevalence of AD is much less in these populations. And the personnel doing cognitive tests taking blood samples and so on are not specialised in dementia disorders.

Further, if we improve the diagnosis in primary care we need to show not just that the diagnosis actually becomes better but the treatment is changed in a better way and the care of the patient is also changed. It is not only that the diagnosis becomes better but that it results in better care of the patients. And of course, in such studies there needs to be an accurate standard of truth. Neuropathology is difficult but at least these individuals should be diagnosed in a memory disorder clinic using CSF or PET to have a standard of truth.



**Professor
Henrik
Zetterberg**

If p-tau is positive. But most individuals would be concordantly Abeta and p-tau positive.



**Professor
Reisa
Sperling**

How common is it though that the p-tau is very high with negative Ab markers - and still predicts dementia?



**Professor
Ricardo
Allegri**

For clinical purposes, could we think in use first NfL in order to detect degeneration, and after that other biomarkers?

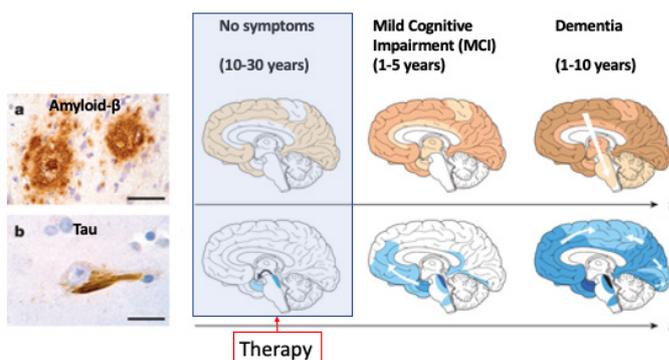


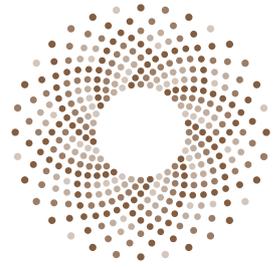
**Professor
Paul
Matthews**

Can you comment on potential added value of genotype-based PRS, particularly for the early, lower prevalence primary care populations?

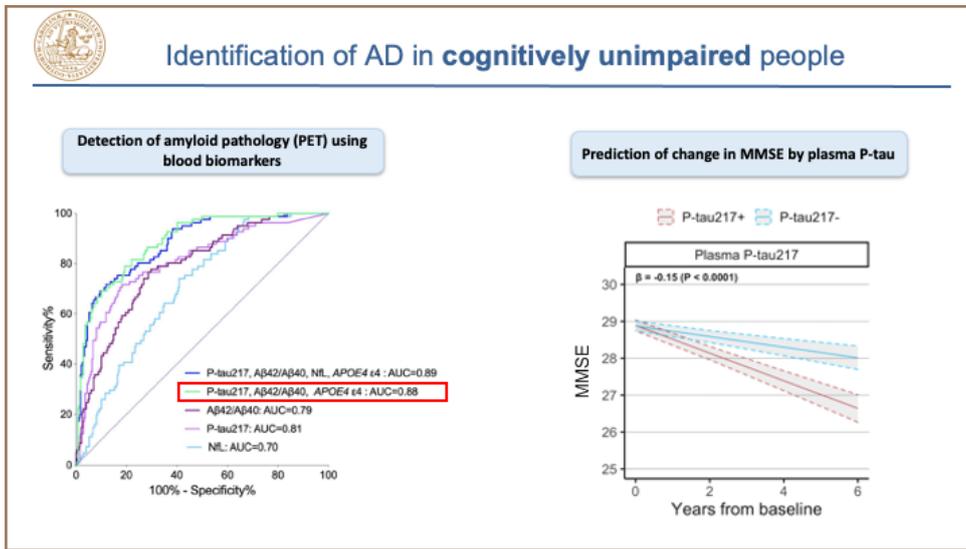


Trials in preclinical Alzheimer's disease





Professor Sperling will talk more about preclinical AD and prevention trials. I will just mention that trials are moving into the preclinical AD space.

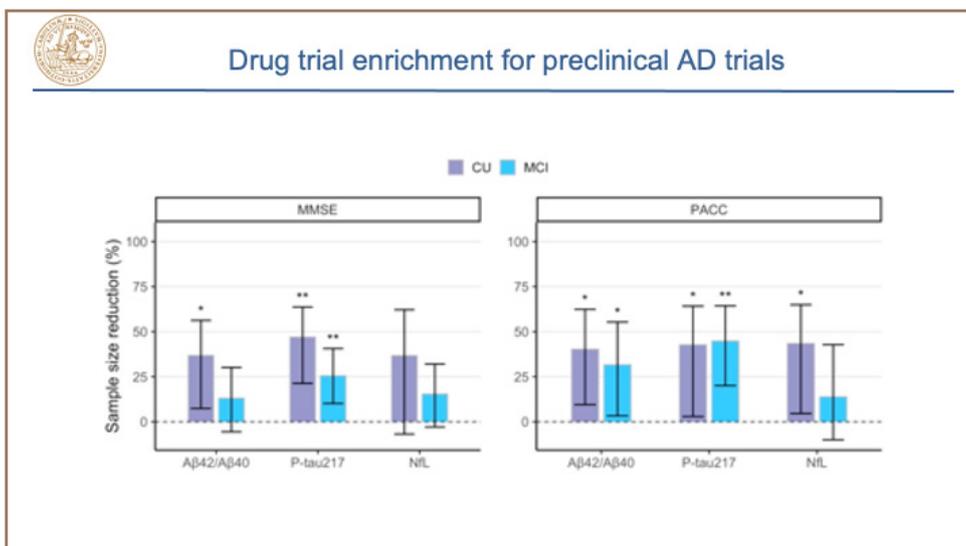


Can plasma biomarkers be used for that? I guess so. Here is one unpublished result in cognitive unimpaired people. If you combine P-tau217, AB42/AB40, APOE e4 genotype you have an AUC=0.88 for detecting if an individual is amyloid PET positive or not.

It is of course much more difficult to predict cognitive decline in cognitive unimpaired people but with P-tau just here alone, it is better of course if you combine it, you can see those that are positive deteriorate on MMSE to a higher degree compared to those that are negatives in this cognitively unimpaired population.



Amyloid-beta 42/40 changes first, and then some years later, p-tau217 and p-tau181 increase, then 10-15 years later tau tangles increase. Once tangles are increasing in the cortex by tau PET, p-tau217 and p-tau181 have reached maximum phosphorylation, but the total tau then increases.



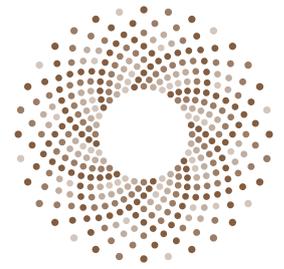
Meaning that you can use the biomarkers to enrich your population and thereby reduce your sample size and have the same power to detect a change in cognition over time.

So here for example is just one study where they investigate it using P-tau and NfL how much you can reduce sample size of the trial. So here for example with p-tau217 you can



In principle yes, but difficult marker due to non-specificity (and NfL also changes relatively late in AD compared with p-tau and Abeta42/40).

reduce it by 50% if you MMSE and similar in PACC. These types of studies will need to be done in larger samples later on.



THE SWEDISH BIOFINDER STUDY

Clinical Memory Research Unit, Lund University
 Head of research: Oskar Hansson

Senior researchers
 Dr. Erik Stomrud
 Doc. Joana Pereira
 Doc. Katarina Nigga
 Doc. Niklas Mattsson
 Dr. Rik Ossenkoppele
 Doc. Ruben Smith
 Doc. Sebastian Palmqvist
 Dr. Shorena Janelidze

Post docs
 Dr. Anna-Märta Gustavsson
 Dr. Antoine Lezay
 Dr. Claudia Cicognola
 Dr. David Berron
 Dr. Khazar Ahmadi
 Dr. Nicola Spoto
 Dr. Olof Strandberg
 Dr. Sara Hall
 Dr. Victoria Larsson

Laboratory technicians
 Pilar Lorenzo
 Camilla Orbjörn

Other researchers
 Prof. Elisabet Londos
 Doc. Christer Nilsson
 Doc. Håkan Toresson
 Doc. Malin Wennström

PhD students
 Anna Sveningsson
 Daria Pawlik
 Emma Borland
 Emelie Johansson
 Eske Gerjtz
 Mattis Jafakaz
 Maurits Johansson
 Nicholas Cullen
 Philip Insel
 Roman Sattarov

Research nurses
 Catrin Enstedt
 Cecilia Dahl
 Christine Karremo
 Emma Pettersson
 Elin Sjödin
 Katarina Johansson
 Marie Persson

Junior Doctors
 Anna Callmer
 Nils Ekström
 Felix Andersson
 Isabelle Glans

Administration
 Anne-Marie Rohrstock
 Joanna Grzegorska
 Tone Brorsson

Collaborators and funding

Academic collaborators

Lund University, MRI
 Doc. Danielle van Westen
 Doc. Markus Nilsson

Lund University, PET
 Doc. Jonas Jögi
 Doc. Tomas Ohlsson

University of Gothenburg
 Prof. Kaj Blennow
 Prof. Henrik Zetterberg

UCSF
 Gil Rabinovici

Gangnam Severeance Hospital
 Chul H. Lyoo

Banner Alzheimer's Institute
 Eric Reiman
 Thomas Beach

Universidad de Antioquia
 Yakeel Quiroz
 Francisco Lopera

Industrial collaborators

Eli Lilly
 Jeffrey L. Dage
 Nicholas K. Proctor
 Xiyun Chai

Roche/Genentech
 Udo Eichenlaub
 Tobias Bittner
 Gregory Klein
 Edilio Borroni

AVID Radiopharmaceuticals
 Michael Devous
 Michael Pontecorvo

Janssen
 Hartmuth Kolb

Funding
 European Research Council
 Swedish Research Council
 Knut and Alice Wallenberg
 Swedish Brain Foundation
 Swedish Alzheimer Foundation
 Swedish Parkinson Foundation
 ALF
 Region Skåne



Professor Gil Rabinovici

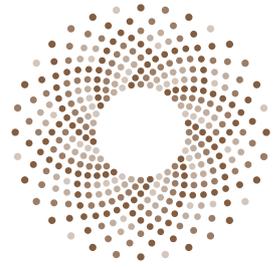
Given the high prevalence of AD pathology in older adults, expert clinical assessment is important for interpreting the clinical relevance of biomarker changes for the individual patient. One concern is that the clinical relevance of biomarker changes will be misinterpreted when used in primary care setting with minimal clinical assessments. That is why scalable clinical and cognitive tools are so critical to correct scaling of biomarker use.

So that was just an overview. Here are a lot of my friends and colleagues that have been helping in my lab but also of course many others. So with that I will return to Maria.



Dr Maria Carrillo
 Chief scientific officer, Alzheimer's Association

Thanks really appreciate that Oskar. We are going a little over time a tiny but that is ok. We will save discussion until after Reisa has given her talk. There are a lot of good questions in the chat so feel free Oskar to take a look at that; you really engendered a good discussion there. And now Dr Sperling who will of course be talking about PET.



Professor Reisa Sperling
Co-principal investigator, Harvard Aging Brain Study

That was fabulous Oskar and I cannot wait to have some more discussion. I am going to be talking about PET imaging



Professor Howard Bergman

Agree on importance of studies in primary care. In Canada, dementia care is anchored in primary care. The diabetes model vs the cancer model. There will never be enough specialists to meet the potential demand.



Professor Henrik Zetterberg

Yes, primary care and also diverse populations.



Dr Michael Devous

Randy, can you elaborate on the time scale you mention? The data I've seen in MCI/AD suggests that tau PET is positive about the same time as plasma p-tau. I think you were suggesting a 10-15 gap between these two. Did I misunderstand?



Disclosures

Consultant-related activities or research support:

- Eli Lilly
- Hoffmann-La Roche
- GE Healthcare
- AVID Radiopharmaceuticals
- Biogen
- Cerveau Technologies
- AlzPath

Here are my disclosures and I want to acknowledge my funding.



Alzheimer diagnostics – a multidisciplinary approach

Clinical assessments

- Cognitive tests
- Psychiatric & neurological assessments
- ADL function





MRI or CT

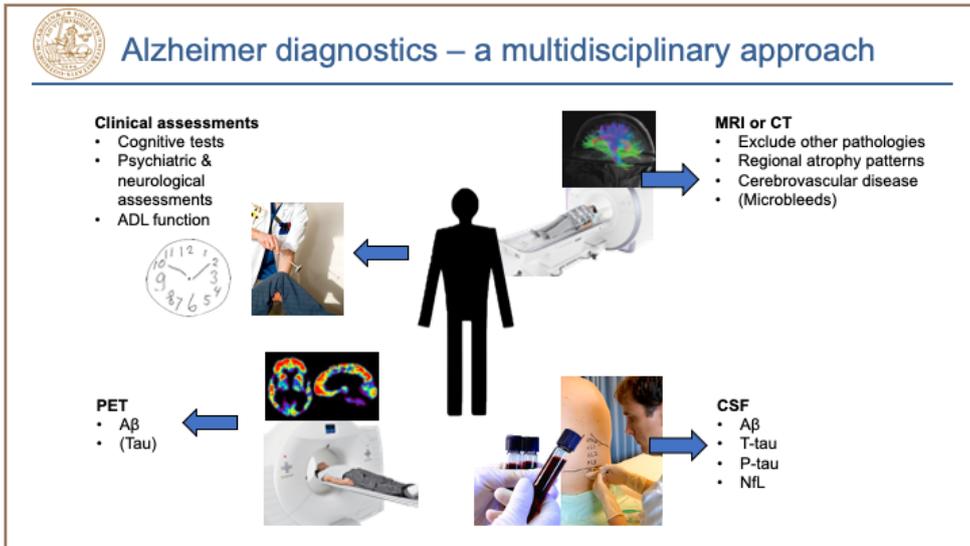
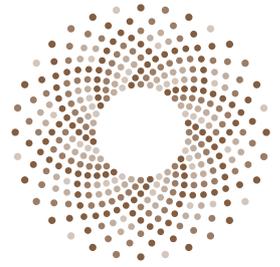
- Exclude other pathologies
- Regional atrophy patterns
- Cerebrovascular disease (Microbleeds)



Concordance between clinical diagnosis of AD dementia and neuropathology is not that great (sensitivity 70-80% and specificity 50-70%)*
Even lower diagnostic accuracy in cases with MCI (and not dementia)

Beach et al., JNEN, 2012
Knopman et al., Neurology, 2001

I want to put this in the same context that Oskar did because I think this is critically important as we move way back up this trajectory to preclinical, and hopefully even earlier one day. Many of you on this group have already contributed to this the NIA-AA framework redefining AD as a biological construct and then these biomarkers become critical for how we identify people and treat them.



I am going to be focussing on imaging and I am really going to focus right now on the relationship between amyloid and tau in the preclinical space because I think one of the important findings, as was just discussed a lot just now in the chat, is the relationship between AB and tau, how these evolve and importantly what this means when we want to intervene

I am especially going to look at this middle group. Individuals who are clinically normal who have elevated amyloid and looking at whether they or not they have abnormal tau and in particular tau spreading beyond the medial temporal lobe into the surrounding neo-cortex.

 **Professor Randall Bateman**

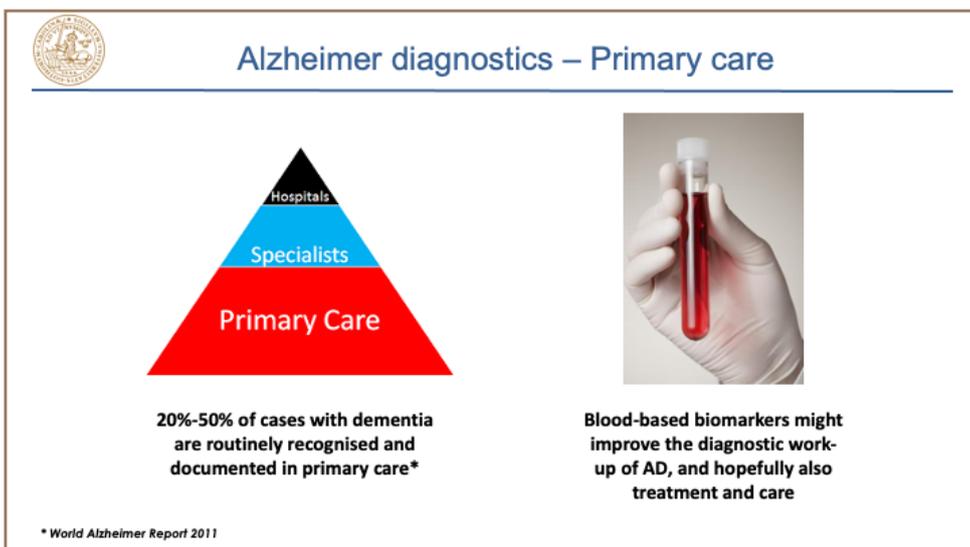
That's correct Michael - see the DIAN publication in Nature Medicine 2020: <https://www.nature.com/articles/s41591-020-0781-z>

 **Professor Gil Rabinovici**

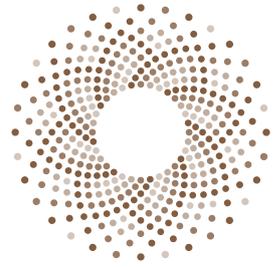
In Oskar's case, could it be that the negative plasma Abeta42/20 has more to do with sensitivity of the assay (ie p-tau assay more sensitive) than true absence of amyloid? Plasma p-tau elevations very strongly predict changes in amyloid PET.

 **Dr Michael Devous**

Thanks Randy!



We referred to this locally as the “ca-tau-strophe”. This came out of the tau pow-wow in the Human Amyloid Imaging meetings but increasingly we see this evidence that there may be a critical level of amyloidosis at least in amyloid imaging and I think also in some of our plasma biomarker work as well after which tau seems to accelerate and particularly spread out into the neo-cortex.



And you can see this cross-sectionally in data here. We have known this for a while that once you get passed a certain level of amyloidosis individuals actually accumulate more tau that you would expect from a linear regression, suggesting there is some kind of acceleration at some point, maybe the clearance mechanism is failing at that point, but there is a rapid spread.

Again you can see it cross sectionally on the left and on the right what you can see is some newer data showing this explosion of tau that occurs once you get past in this case about 50 centiloids of amyloid in PET imaging. I also do want to bring up as it came up this empty left upper hand quadrant. That is why I was asking Oskar in the chat, and we should discuss this, but we very rarely ever see these very high level of neo-cortical tau on tau PET imaging with either F-AV or MK in people who don't have elevated amyloid so I am very interested in seeing whether this happens more with blood-based biomarkers.

 **Professor Randall Bateman**

There is a 15 year gap between when soluble CSF p-tau217 and p-tau181 increase and when tangles increase. P-tau217 and p-tau181 seem to be a soluble tau response to amyloid plaques long before tauopathy in the brain develops. Also, the tau in CSF (the first 2/3 of the protein) is completely different than the tau in aggregation and tangles (the last 1/3 of the protein).

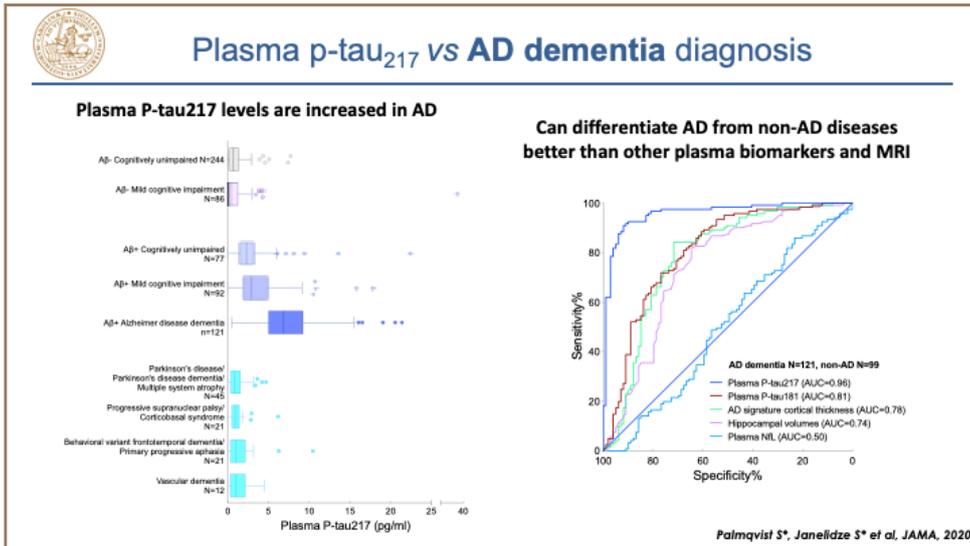
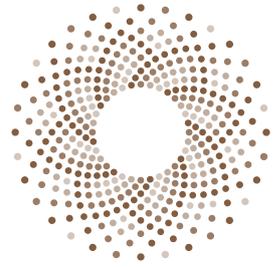
 **Professor Todd Golde**

And why that is is a mystery that needs to be solved... why does abeta increase extracellular tau and what happens to the other end?

 **Professor Randall Bateman**

Completely agree Todd.

So more recently we have been really focussing on how much tau PET accumulation we can detect, how early we can go and ask whether we can change this with drug treatment. This is some new data looking at this group of high amyloid CN. Here the threshold is actually down below 20 centiloids but it goes up if you even if you pick people with 40 and 50 centiloids. But even as low as 20 centiloids you can see this acceleration of tau accumulation and in particular in the regions you would expect: medial, lateral and inferior temporal lobe. It is certainly not up at the rates you see in MCI and AD dementia but it approaches 0.1 SUVR per year in these somewhat elevated amyloid individuals who are still clinically normal and that is enough to power trials looking at whether we can delay that in secondary prevention.



 **Professor
Henrik
Zetterberg**

Yes, agree as well. A key question.

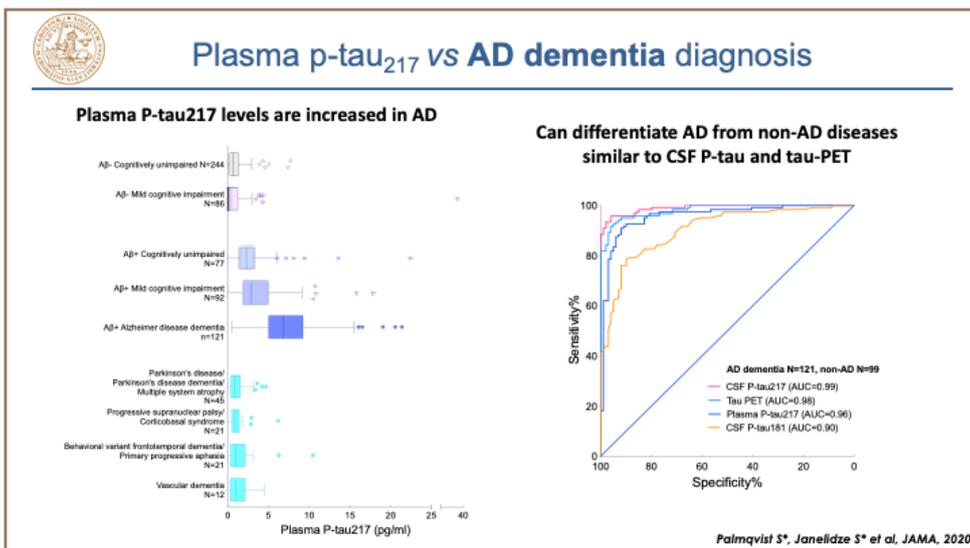
 **Professor
Todd
Golde**

Question for Oskar and Henrik.

That turns to how we are using these drugs in prevention trials. I am going to focus on how we are using imaging in these studies right now.

 **Dr
Maria
Carrillo**

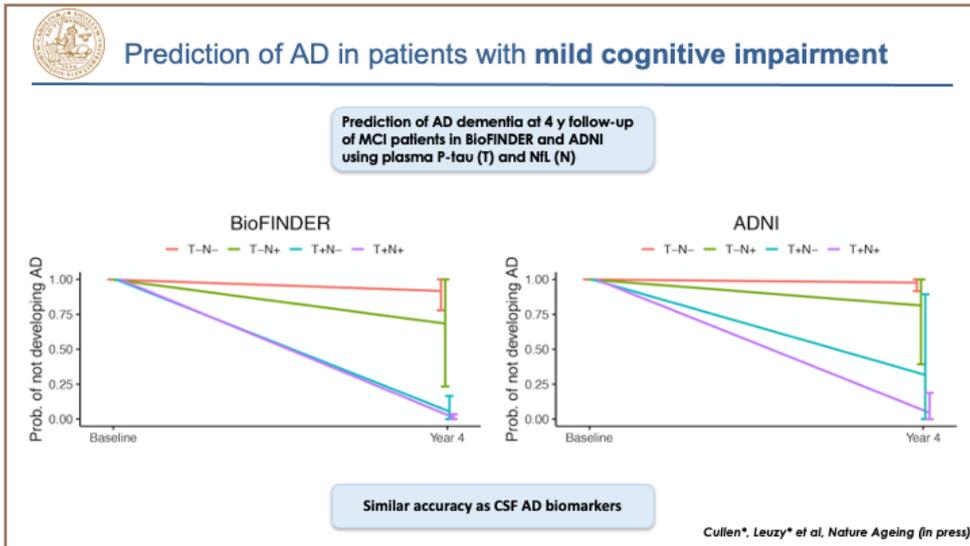
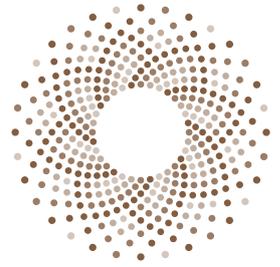
Todd, I will call on you next.



 **Professor
Cornelia van
Duijn**

There is an urgency to determine the AUC's up to 20 years before MCI for preventive research and trials. Cohorts studies up till now suggests abeta will be important.

So the A4 study which I think everyone is aware of. We were screening for a certain level of amyloidosis in these individuals. And here we were used 1.15 Suvr which is about 24/25cl.

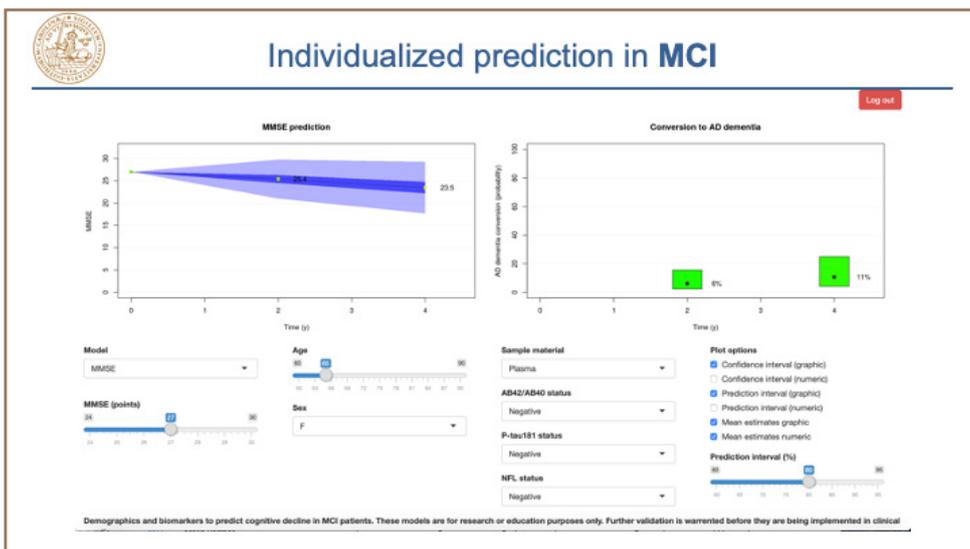


So here just to show you in practice how this worked. We ended up doing florbetapir PET on about 4486. We predicted about 30% of them would meet our criteria for amyloid positivity and it was 29.5% so that prediction was really right on. Those individuals with high amyloid went forward in screening and a subset who were not eligible went into the LEARN study funded by Alzheimer’s Association to be able to have a comparison group.

And I do want to remind everyone that the A4 and LEARN screening data is publicly available on LONI and GAAN and we have granted access to about 500 groups so far.

Dr Michael Devous

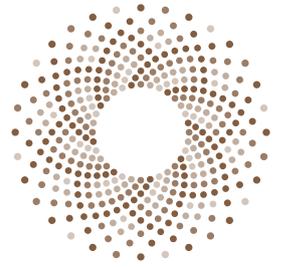
So it may be that when you study the DIAN population you are able to see the earliest changes, while when you study patients for clinical trials you are already well done the road and the concurrence between plasma p-tau and tau PET seems closer in time. Perhaps AHEAD, A3 and A4 will clarify this timeline.



One of the slight surprises related to this, because we had a very narrow cognitive range, they all had to be CDR=0, all had to be not super normal and nor impaired in any way but we still did see on the PACC even at screening baseline these individuals perform less well.

Ivan Koychev

Agree with Cornelia. We need to look at people with comorbidities associating with AD (eg diabetes, HTN) as a population to monitor with blood/digital biomarkers to identify preclinical caseness 20 years before symptoms.



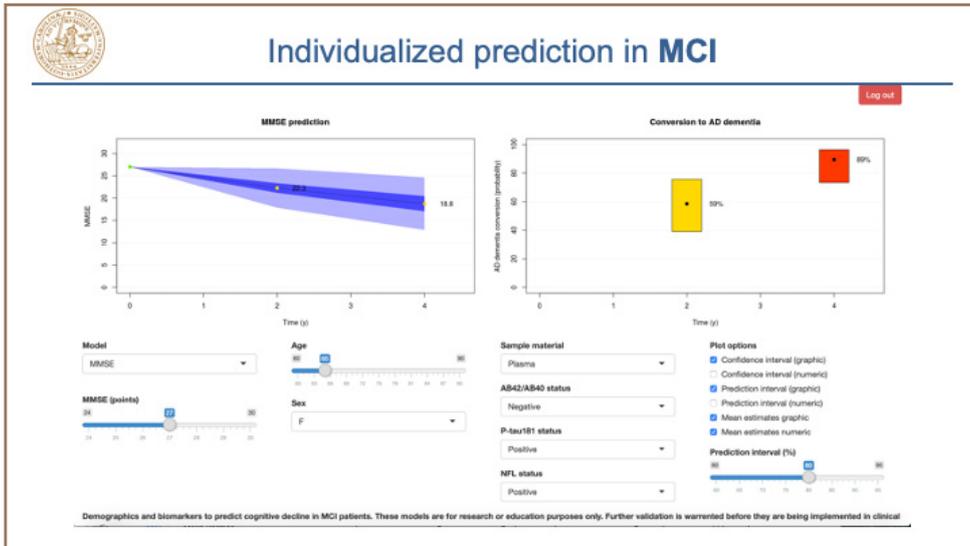
**Professor
Todd
Golde**

But what was the long-term follow up on the folks from the phase 1b? Can we justify use in symptomatic phase, is the long term outlook really done not change if the long-term outlook does not change?

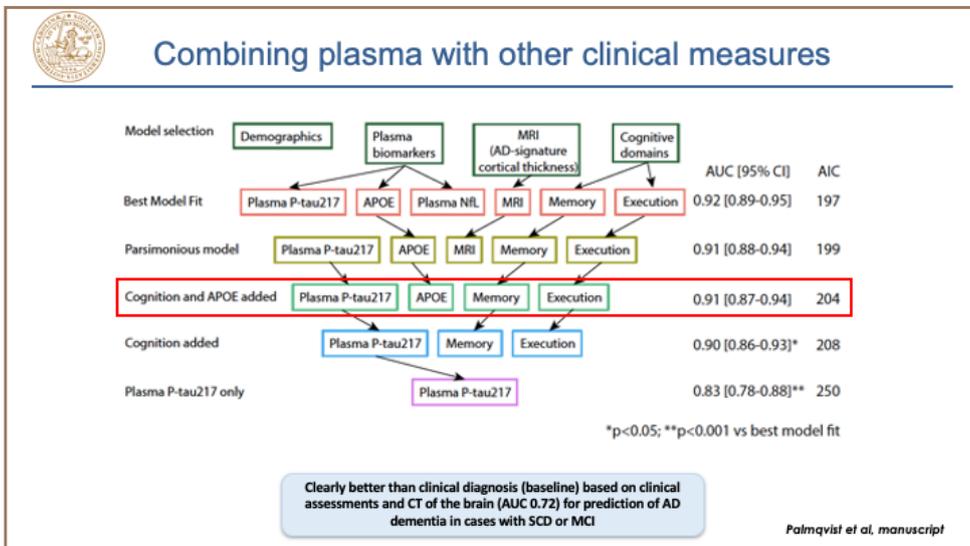


**Professor
Linda Van
Eldik**

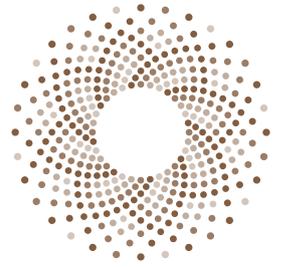
Completely agree with Eric that combination therapy will be critical for such a complex disease. We will need therapies that likely include an anti-amyloid/abeta agent, but we also have to go beyond amyloid to include other disease progression mechanisms.



We also saw that they were more likely to have demonstrated change in cognitive function over the last year even though they were all CDR zero and all normal but the self-report were much more likely to say they had noticed decline even though they were still independent. Then this one at the bottom blew me away: the study partner was more likely to say they had been much more likely to be repeating questions. These are the odds ratio of being AB+ on the basis of this simple questionnaire.

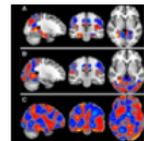


Oskar mentioned the computerised testing and maybe we will come back to this. But actually, the iPad testing here was almost the same effect size as the PACC on the C3 and we are now reporting this to smart phones as well.



Summary – diagnosis of MCI or dementia due to AD

- Plasma P-ta217 is a very accurate biomarker for both “MCI due to AD” and “dementia due to AD”
- Cognitive tests (incl memory & executive function)
 - Digital technologies (smartphones, tablets, digital pens)
- MRI (or CT?) of the brain
 - Automatic segmentation for detection of regional atrophy



 **Professor Clive Ballard**

Maybe it's about mapping clinical trial design/enrichment to the treatment target. Which may be different for example if targeting amyloid or tau compared to targeting concurrent cerebrovascular disease?

So back to the tau PET these data we looked at 390 individuals in the tau PET subset. On the right here are the regions of higher tau levels associated with higher amyloid levels in the A4 cohort. All of these individuals are already amyloid positive, all of them are normal. Yet you still see the relationship between amyloid and tau including in the entorhinal cortex which often still gets referred to as normal ageing tau. It may be ageing. It may be in normal people. But it is strongly related to amyloid.



What needs to be done for blood-based biomarkers?

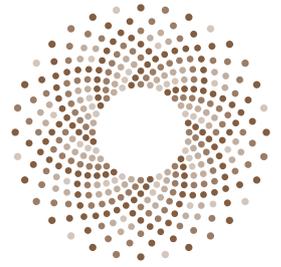
- Development of high-precision methods for measurement in blood
 - Fully automated platforms available in most clinical chemistry laboratories
- Develop a protocol for handling of blood before biomarker analyses
- Establish “appropriate use criteria” to avoid misuse and misinterpretations of biomarkers

 **Professor Cornelia van Duijn**

Agree that combination therapy will be crucial and that inflammation needs to be tackled ASAP in polytherapy. Can we study this as a secondary analysis of current/ongoing trials and design smart ADAPTIVE trials targeting this?

So that data right there was what kept me awake at night. That maybe even A4 was too late to completely stop the “ca-tau-strophe” because about 56% of the A4 sample already had some neo-cortical tau.

So we started working on how we can go earlier. This is data across ADNI, AIBL and Mayo clinic showing that right before people get to the level of amyloid positivity and have this kind of long point where they are accumulating at a pretty substantial and steady rate through preclinical and often into early MCI, it starts to drop off at early dementia. We can see this rapid acceleration of amyloid accumulation and that is what we wanted to target in our next study.



Improved AD diagnostics in primary care

- We need to perform large-scale prospective studies, with consecutive recruitment, in primary care
 - Population and setting is different compared to Memory clinics:
 - More heterogenous populations
 - Lower prevalence of AD
 - Personnel is less specialized on dementia disorders
 - Establish whether new diagnostic tools results in relevant change in
 - Diagnosis
 - Treatment
 - Care
- Such studies must have an accurate standard of truth
 - (Neuropathology)
 - Diagnostic work-up at memory disorder clinic (including CSF or PET)

So that leads to the AHEAD Study - A3 and A45 trials. This is based on some modelling we have done. As you can see this early subthreshold level of amyloidosis is a very strong predictor of who has the acceleration in amyloid and as I showed you this is associated with this acceleration of tau change. So in A3 study we are going subthreshold trying to catch these people preventing them becoming amyloid positive or at least having very levels. In A45 we are taking people who already have very high levels – above 40 centiloids - and trying to prevent cognitive decline.

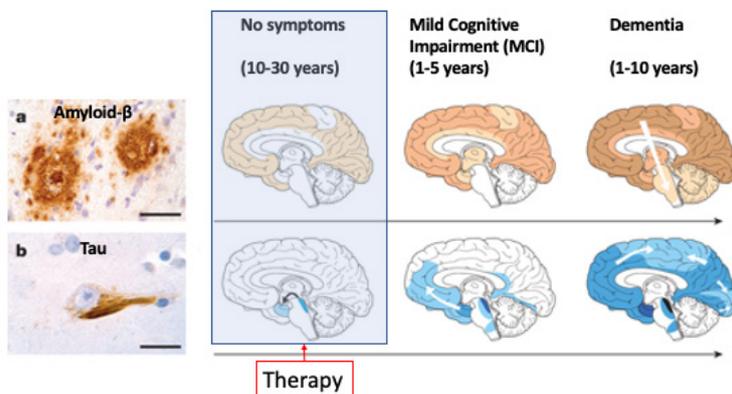


Professor Reisa Sperling

Cath: excellent points! I actually think the blood-based biomarkers might help us with increasing diversity in our trials. If we can build relationships in the community with blood test registries, we might make a dent. We are planning this for AHEAD 3-45.



Trials in preclinical Alzheimer's disease



I will just show you this snapshot. This is two other things on imaging and A3 and A45. We made the decision to use the Navidia tracer this is closer to pib we can especially look with more sensitivity and specificity in the low range and we are using the Merck tracer for tau. So using the ADNI data in this case with the simulation I showed you where you want to be for the A3 between 20-40 centiloids, here is the forecast for the first 48 people based on the ADNI data from 5 or 6 years ago and Florbetapir and here are the first 48 who now with PET scans in the US which really seems to be as we predict they would be.



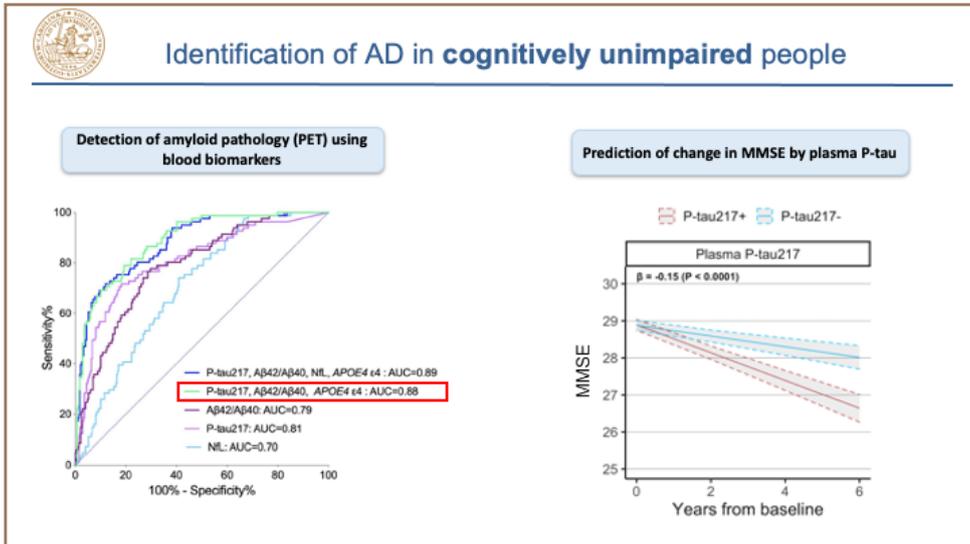
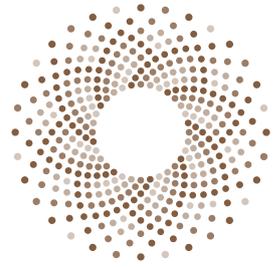
Professor Jeffrey Cummings

Are we ready for a trial where the participants are defined with blood biomarkers and not imaging?



Professor Howard Bergman

Key issue trial vs clinical populations. Related to issue Oskar brought up about primary care.



I just want to acknowledge my amazing collaborators and turn it back over to Maria.



**Professor
Bart De
Strooper**

Need to be careful with "inflammation", I see it more as a glia reaction. We know that classical immune/inflammation therapies have little effect.



Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

Thank you so much Reisa I really appreciate it. I know we already have a larger time for discussion. We already have a lot of great conversation in the chat and in particular Todd Golde's million-dollar question: why is an increase in extracellular tau happening with AB and what happens at the other end. All great questions. Right now, for Oskar and Reisa can I ask for clarifying questions and we will leave the hypothetical meaty discussion for the end after our next two speakers. Any clarifying questions?



**Professor
Randall
Bateman**

Monotherapy in prevention has much better chance of having a large effect because the co-pathologies seem to develop at later stages.



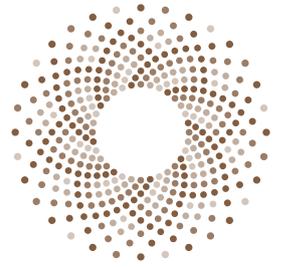
Professor Reisa Sperling
Co-principal investigator, Harvard Aging Brain Study

I have a clarifying question which I asked in the chat I don't know if Oskar saw. In your great example the second one where the MCI predictor you had very high p-tau predicting AD dementia predicting 80% over a few years. But they were AB- but that rarely happens with imaging and I wonder how often it happens there and I wonder if they would still be AD dementia if they didn't have AB markers even eight years down the road.



**Professor
Todd
Golde**

As I have stated before, unless we have rigorous preclinical data to justify the combo we likely end up with a failed combination therapy.



Professor Oskar Hansson
Professor of Neurology, Lund University

So it is hard to make individual predictions using this algorithm so that was only one case stimulating it. There we see, it was AB42/40 in plasma not CSF based on immunoassay. What we have been seeing in the symptomatic phase of the disease, here MCI, P-tau is really the great predictor of future development. In those few individuals where you have increased P-tau but not AB, probably the plasma measurement is not correct. In plasma there is only a decrease of 10-15% on average in AB42/40, in CSF a change of 50%. Meaning that it is much more difficult to accurately divide + from - using AB42/40 in plasma. There are other methods that may be better than the one we used. In this particular case this is probably a AB+ person but the plasma measure is not correct.



Professor Rudolph Tanzi

Timing is so important. We need to hit amyloid and tangles early - preferably presymptomatically. But, resilient brain data would suggest reducing neuroinflammation - reactive microglia and astrocytes would appear to have a chance to help symptomatic patients. Our neuroprotective drug combination at Amylyx (AMX0035) was successful in ALS and now being tried in AD (phase 2 reads out this year). It protects against oxidative stress induced by neuroinflammation.



Professor Todd Golde
Director, Evelyn F. and William L. McKnight Brain Institute (MBI), University of Florida

We have different p-tau antibody assays, and do we think it is really a biologic difference or simply a difference in the assay characteristics that gives them a difference in the sensitivity and specificity.



Professor Oskar Hansson
Professor of Neurology, Lund University

The majority of difference when it comes to certain p-tau variants like 181, 217, 231 they actually perform quite similar if you would optimize them a lot. But what typically you see if you use the same total tau antibody, the same platform, and so on, is that the 217 increases relatively more with the disease, so there is a much higher fold-change compared to 181 and 231. And the main reasons are the levels are very low with people without the AD for 217.



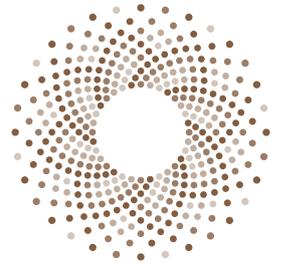
Professor Philip Scheltens
Professor of cognitive neurology and director, Alzheimer Center, Amsterdam University Medical Centers and member of the WDC

It is a very exciting discussion if you look at the chat function. But we have to move on because we have a second exciting topic: the therapeutic landscape. The reason we do all these biomarkers the reason we are interested in early diagnosis is because we think early treatment is of paramount importance. We have two speakers talking about the research landscape on therapy at the moment which is Eric Seimers and Cath Mummery.



Professor Howard Bergman

Will be carefully looked at by payers. In Canada, that means government health insurance.



Just to save time I won't launch into lengthy biographies of them. You know them both very well. Eric can I ask you to start.



Dr Eric Siemers

Former distinguished medical fellow,
Eli Lilly and Company's Alzheimer's Disease Global Development Team

I was asked to spend five minutes or so to summarize the state of where are with therapeutics in AD. So easy task!



For this esteemed group there is probably less misunderstanding where we are. But I think it is worth laying this out. There is lot of word on the street that Alzheimer's is really tough and there are all these negative studies and what are we going to do about this. But if you start to dissect it out a little bit the story becomes a little different.

If you start off with just protease inhibitors whether gamma or BACE inhibitors. I think everyone here knows gamma-secretase inhibitors probably as a class cause a bit of cognitive worsening. The one thing I'd say about semagacestat that was the first potential DMT is that it didn't do nothing. It went in the wrong direction.

Then there was a lot of enthusiasm in the field for BACE inhibitors when these ran out – and by the way the Alzheimer's Association did a great job in getting the companies together and making it clear that we were seeing what are probably class effects here. This was a big disappointment. A big surprise. But again, and this is all with hindsight, these proteases don't have one substrate. Gamma-secretase probably has a lot more than BACE. But BACE doesn't only have APP as a substrate. What we have run into with protease inhibitors is if you non-specifically inhibit those things can go the wrong direction. And remember that with the Icelandic mutation that is on APP it is not on BACE.



Professor Reisa Sperling

I think combination is key in symptomatic disease - but monotherapy easier in prevention.



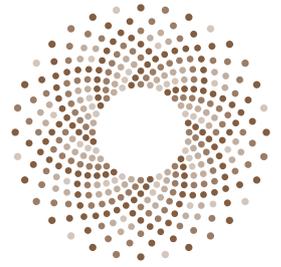
Professor Bart De Strooper

First mono to demonstrate mechanistic effects, then combination.



Ivan Koychev

Representativeness can be boosted through blood biomarker monitoring of cardiovascular conditions at risk for AD: these are often over-represented in non-white populations and a way of taking dementia to primary care.



I think in this timeframe when the BACE inhibitors were reading out there was pretty interesting work on monoclonal antibodies that probably was a little bit underappreciated because the BACE story was so dramatic. First was bapineuzumab but here the dose was so low I don't think it is surprising that you didn't see anything. Solanezumab in the EXPEDITION-1, -2 and -3 caused numeric improvement – I will come back to that. But directionally it was the right direction. BAN2401, phase 2 study, but again the right direction. Gantenezumab the jury is still out on. Crenezumab we haven't seen all the data. Then of course there is aducanumab. Which everyone on the call will be pretty familiar with. Those are showing movement in the right direction. At CTAD I saw two different meta-analysis by two different statisticians both came to the same conclusion that the monoclonals are moving the needle in the right direction.



Professor Rudolph Tanzi
Problem is FDA insist we improve cognition in symptomatic patients with amyloid-targeted drugs, we will never have an early intervention.



Dr José Molinuevo
I fully agree with this, how to move forward a compound that have shown proof of mechanism in preclinical AD to a phase 3 may be complex, due to regulatory requirements.



Dr Christopher Chen
Given that there are multiple risk factors for dementia, surely prevention has to be a combination approach too?



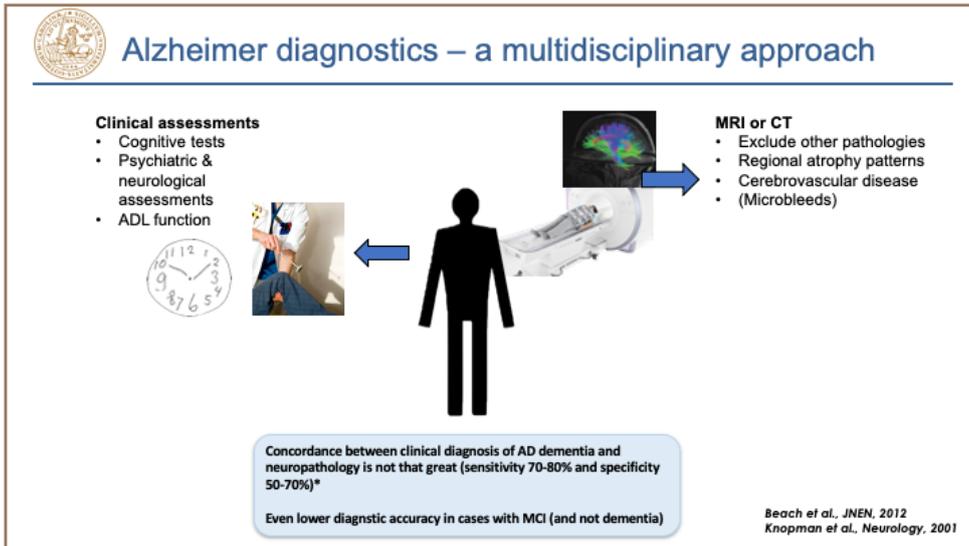
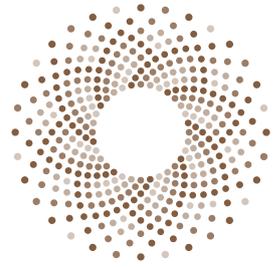
Disclosures

Consultant-related activities or research support:

- Eli Lilly
- Hoffmann-La Roche
- GE Healthcare
- AVID Radiopharmaceuticals
- Biogen
- Cerveau Technologies
- AlzPath

So just to dive into that a little bit more. This is the EXPEDITION 3 study. A very consistent but small effect size. It is very small but also very consistent. BAN2401 all the caveats of phase 2 studies but nonetheless the data lines up pretty well.

Aducanumab, and this is purely my opinion, and I'll be brief about it as I am sure we can talk about it for a long long time. Two phase three studies one of which was positive one of which was negative. The advisory committee meeting for FDA was overall relatively negative. We don't know what the FDA will actually do about it. If you look at it in a traditionalist frequentist statistics approach if you have one positive and one negative than you have to go and do another study. But if you think about it in a more Bayesian approach, what is your prior probability. You have a class of drugs that seems to be moving the needle, different antibody obviously, and then you also got the 103 study that was a 1b study with all the caveats around that. But that in my mind increases the probability you are seeing a drug effect. You have one positive and one negative and in a Bayesian way it is a little different thing. I think it is unfortunate thing that the advisory committee never got to the question which is: what is the probability of aducanumab having zero efficacy. My personal opinion is the probability of that is pretty low. Now is it big enough, how does the risk- benefit compare, these are different questions. But the probability that it does nothing is quite low.



So here are a number of different targets that everyone is familiar with. We have already talked about some of them. Tau is on here. There are some interesting molecules that work on synaptic function that are starting to come out. Inflammation isn't on here and it needs to be. All of us probably agree that in the end it will be combination therapies where we will make real headway with the disease. But these are the ones that have been looked at so far. Early days for tau but obviously a great target.



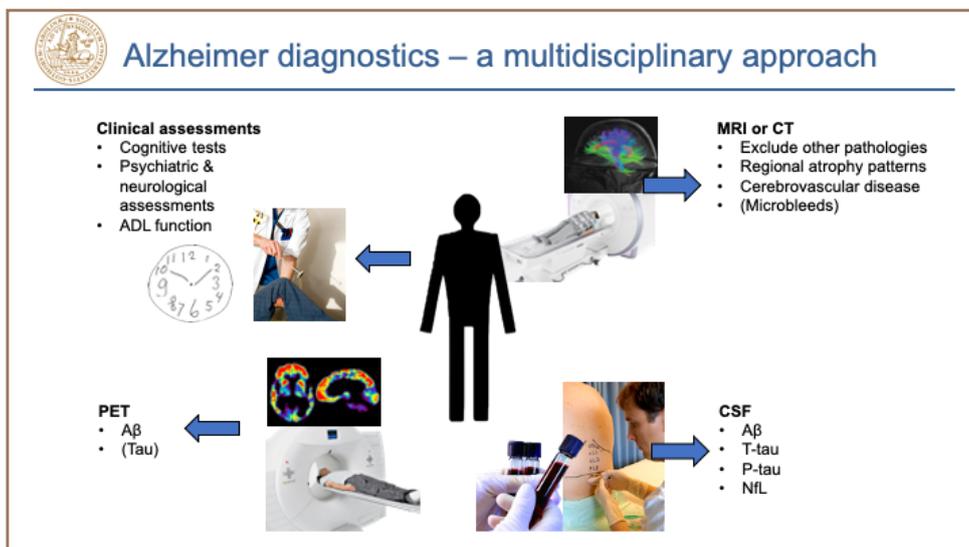
In other diseases, the FDA has shown some willingness to embrace broader interpretations relevant to the context of use, as long as they are accompanied by evidence of clinical meaningfulness.



Do they not consider the slowing or arrest of progression? I had thought so.

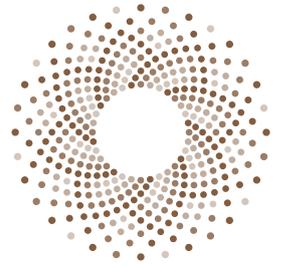


Yes, I do think vascular risk prevention is very important. We have published a series of papers showing vascular risk interaction with amyloid, increasing tau and cognitive decline in preclinical AD. But the vascular prevention may need to be mid-life!



Let me finish up then to go back to the point about monoclonals that are more related to AB and amyloid. Unfortunately, perhaps not for people on this call, but more broadly in the field, people tend to be pretty monolithic about AB and amyloid. What we really don't know at this point is what is the best target.

You see the various antibodies on here and they have been developed to target different things and they have different amounts of specificity. To take solanezumab since I worked on it a long time. It is actually fairly specific. It doesn't have much binding to anything else. Which is good or bad depending on how you look at it. I think there is some appreciation in the field – this might be part of a discussions – that the most toxic



species is certainly not monomers and it might not be plaques but oligomers. All of these things are in equilibrium with each other so you may not move one without the other. Maybe that is where a bit of efficacy came with solanezumab because you pulled down enough monomers that you disassociated some oligomers.

As we refine understanding which targets will give you the most efficacy then you can build on the toehold you have right now with these relatively small effect sizes and make them better. And that is just with a drug that targets AB or amyloid or AB-oligomers. Combination therapy once we have tau and targets in inflammation that is when we really start to make headway.

I think where we are right now is like the early days of HIV. Some of the first protease inhibitors were having an effect on biomarkers and on the disease but it took years before combination therapy turned it into a manageable disease.

And with that Philip I will turn it back over to you.



Professor Philip Scheltens

Professor of cognitive neurology and director, Alzheimer Center, Amsterdam University Medical Centers and member of the WDC

Thank you very much Eric. I agree completely we are on a turning point and the resemblance with HIV period is actually quite striking. We will quickly move on to Cath Mummery who is consultant neurologist in the national hospital in London and is a clinical trialist over there. She will share her thoughts without sharing slides. Which is also refreshing. But it has a particular reason because she is recovering from a shoulder operation. Cath can we invite you to share your thoughts.



Dr Cath Mummery

Consultant neurologist leading the Cognitive Disorders Service, National Hospital for Neurology and Neurosurgery

Thank you, Philip. Thank you for those kind words. I am delighted to be here even if I have one wing and not the other at the moment. Eric just laid out beautifully the state of where we are now and some of the exciting things that are happening. When I was thinking about what to say today, I thought about the last time we met which was 2018, which for many reasons feels like a lifetime ago. Since then, there has been a lot that has happened.

The changes that you described Eric in terms of aducanumab, regardless of the FDA outcome, showing for the first time a positive clinical correlate with a biomarker correlate has to be an event that really changes things moving forward. Not just in terms of the amyloid hypothesis but in terms of trials as a whole. I also think, from the point of view of what has happened since 2018, completion of the first part of DIAN-TU adaptive platform, being able to put together that global effort, being able to look at that rare



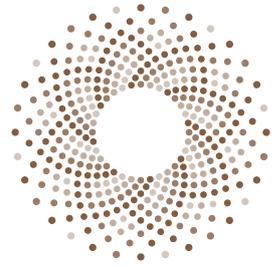
Professor Paul Matthews

An added benefit of platform trials is that it helps the community join in prioritisation, recognising the opportunity costs of any trial in this disease.



Dr Maria Carrillo

The SPRINT MIND trial shows this promise, and the PREVENTABLE trial that goes earlier than anti hypertensives, with statins, in 20K people in the USA may show us answer to that.



disease group was a huge achievement. There was a positive biological result that will be explored further, which I think was really important. But we can achieve that sort of study which we couldn't before. So that for me was a major plus in the past couple of years.

Eric mentioned BACE inhibitors, so I won't go through them again; but what about the positives? We have expanded our portfolio. We are now seeing large numbers of tau studies looking at different methodologies and different targets – which I will come back to in a second – and we are also looking at other targets such as inflammation, which Eric mentioned.

Methodologies have exploded, especially in genetic therapies. We have drugs licenced in some neurodegenerative diseases, not ours, but in others. And we are now trialling genetic therapies in genetic dementias but also in sporadic AD. And the fact that I can say we are using a gene silencing treatment in sporadic AD is to me really exciting and something to look forward to.

In terms of how we can build on where we are at the moment, and I agree with Philip that it is a tipping point, these are really just my personal reflections to get the discussion going.

We have made huge progress – biomarkers you've heard about already – I won't go through them as Reisa and Oskar have given beautiful presentations. But we still have a way to go.

We understand better the relationship between amyloid and tau deposition thanks to the experiments such as the one Reisa showed us. But we don't understand the things that Todd has just mentioned for example, the mystery about why amyloid creates this. We don't understand which forms of tau are toxic. We don't know when it would be beneficial to give a microglia activator and when it would be detrimental. There are so many different things that we are not yet certain of. There is a lot of work to do.

And what is really important, and I see Bart is on the call, is that we work hand-in-hand really closely from the lab to the clinic and back again. So it is not just understanding the drug going into the clinic it is also going back from, for example, a failed drug to the lab so we understand exactly what has happened from a PKPD point of view and all the rest of it. I think that is really important: sometimes we get so excited about the next new drug that we forget to look at what we have got already. We have huge amounts of data.

Turning to the population, we have got so much better at enriching our population, but we need more work. What is happening in the rapid progressives? We have some information about that, but we need to get better. Stratification of subjects in our trials, again, there is a lot of information on how to improve but we are still learning. Again, keeping that information coming out is really important.

We need to consider what we are aiming for with our population. At the moment we are aiming for a homogenous population so that we maximise the opportunities of getting a positive result. But the chance that that looks like our clinical population are vanishingly small. Our clinical population has multiple co-pathologies and co-morbidities. So there



**Professor
Rudolph
Tanzi**

In the Feb 2018 guidelines, the FDA said if the field "agreed" on biomarkers for early presymptomatic pathology (amyloid and tangles), they would be more likely to allow trials on therapies targeting early pathology and tracking biomarkers for them. If the drug is safe, they would consider conditional approve and look at subsequent real world evidence for reducing incidence of AD. Why are we not pushing this agenda as a field?



**Professor
Bart De
Strooper**

Agree Rudy.



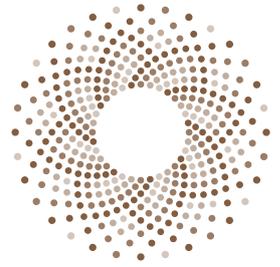
**Dr
José
Molinuevo**

Me too, and get EMA also on board.



**Professor
Ricardo
Allegri**

I agree Rudy.



is a mismatch. And somehow, we need to keep that in mind when we are thinking about our treatment trials. Parallel pragmatic trials would be a ridiculous thing to suggest but it is a possibility.

So we have also moved earlier in the course of the disease. Reisa mentioned we are not only doing secondary prevention but also primary prevention. We are looking at pre-preclinical AD which is very exciting but has many new challenges and I am sure those will come up in the discussion. But just think about if we are starting to put together combination treatments and we are starting to time these treatments, we need to time them differently for amyloid treatments, tau treatments, and how to time the combinations and finesse our understanding of what will work when. It sounds like we have great work starting to look at this, but again we need to continue this focus.

Something we don't talk about often is post-mortem studies in relation to drug studies. I think this is hugely important. We do this in some studies, but we need a robust way of collaborative working where we make this default in all our studies. These are the most valuable brains imaginable, so we need to consider how best to use this precious resource.

Coming back to the patient or the participant. Recruitment has always been one of the biggest challenges and we have got better at it. We have registries now which will accelerate, hopefully, that recruitment. And we have the blood-biomarkers which we have just been hearing about which will revolutionise screening into trials. If they do predict decline in pre-symptomatic that will make a huge difference. But we need to continue to think about how we enhance access for those under-represented. Our trials population have 100% or 90% white in many trials and that does not represent the population that needs treatment. So how do we engage with those who don't really know and don't have access? And with that I will finish.

Thank you.



Professor Philip Scheltens

Professor of cognitive neurology and director, Alzheimer Center, Amsterdam University Medical Centers and member of the WDC

Thank you very much Cath. Very appreciative of your insight. I have a few people on the chats. The chat was a little bit quieter than the biomarkers. Not that it was less interesting or provocative I would say. Clive, I see you had a question about clinical trials design and enrichment to treatment target. Perhaps you can elaborate that.



Professor Clive Ballard

Pro-Vice-Chancellor and Executive Dean, College of Medicine and Health, University of Exeter

It was in response to what Cath was saying about how representative some of the trial populations are to the clinical populations. But I think the other dimension of this is



Dr Cath Mummery

Agree Rudy, need to keep pushing.



Dr Maria Carrillo

Will call on Ivan and then Gil.



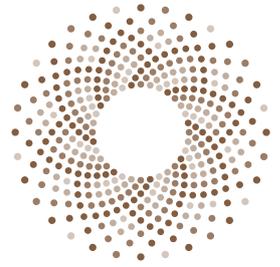
Professor Cornelia van Duijn

Agree Randy, we need large scale low-cost trials. The adaptive design and platform as was used in the Covid-19 recovery trial is feasible in dementia if blood-based biomarkers are used to reduce costs and screen people to be called in for PET.



Dr Margaret Hamburg

The blood-based biomarker is a game changer. I am confident that FDA and EMA will agree along with other major regulatory authorities.



what the treatment target of a particular therapy is. So my question is should we be more flexible in how we design trials? For example, if our target is an amyloid or tau the current biomarkers would seem an obvious way to enrich trials for that group. If we were targeting someone with concurrent cerebrovascular disease that might be a much older population a much different population and we might need a different clinical trial design to optimise that. So, I suppose the question is do we need a slightly more flexible approach to how we design the right trial for the right treatment target?



Professor Paul Matthews

Large prospective longitudinal population-based cohorts with participants reaching higher risk age groups offer a huge opportunity, given banked plasma and serum from decades earlier. Million woman study, UK Biobank and others in the UK are examples.



George Vradenburg

Davos Alzheimer's Collaborative is developing global biomarker-based clinical trial infrastructure. Welcome engagement from those interested.



Professor Philip Scheltens

Professor of cognitive neurology and director, Alzheimer Center, Amsterdam University Medical Centers and member of the WDC

Excellent points. I think everyone will agree with that. There are some comments on the chat on combination therapy. Eric you mentioned combination therapy, can you address the points mentioned?



Dr Eric Siemers

Former distinguished medical fellow, Eli Lilly and Company's Alzheimer's Disease Global Development Team

Well sure, I saw a couple of those. I don't think I saw anyone who disagreed with the idea of combination therapy.



Professor Philip Scheltens

Professor of cognitive neurology and director, Alzheimer Center, Amsterdam University Medical Centers and member of the WDC

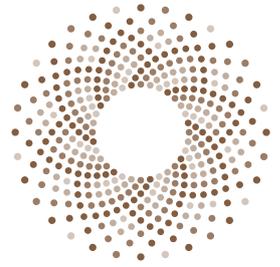
It will be difficult to test won't it, in terms of clinical trial design? How would you do that?



Dr Eric Siemers

Former distinguished medical fellow, Eli Lilly and Company's Alzheimer's Disease Global Development Team

In terms of clinical trial design that has come up. This is where you start talking about platform studies. But as part of the platform you may have a combination of two different drugs. It is challenging. And partly challenging if you have two different drugs from two different companies. Because you get into that aspect of it. It is doable. That is probably another thing that as a field we are going to have to get our heads around.



I think we have got better at data sharing. That is a topic that has evolved over a while. But if we can get into the habit of thinking about drug sharing so to speak. With companies working together to get these combinations out. It isn't easy but it is doable.

One other thing about the population which I meant to mention and one of the pluses. There was a worry that you had to be all the way in preclinical otherwise none of these drugs were going to work. But looking at preclinical with A4 or A45 that is still from a public health standpoint a great thing to do. But the fact that we are seeing these positive signals out of people with MCI or mild dementia due to AD I think is really important because we weren't sure whether even that was going to be too late. And based on these signals I think it is fair to say it is not too late.



Professor Philip Scheltens

Professor of cognitive neurology and director, Alzheimer Center, Amsterdam University Medical Centers and member of the WDC

Maria shall I give it back to you for more of a group conversation on all of the issues we have tackled?



Dr Maria Carrillo

Chief scientific officer, Alzheimer's Association

Thank you Philip. I think what we want to do next is really for the remaining time together is to have much more of that discussion that we were starting to see happen in the chat. But let me just make sure we are all on the same page in terms of what we would like to see from this discussion.

We are looking to you as leaders in the field. International experts that have visibility to all of this, clearly on a large scale but with specialities not only in your field but perhaps your country. And it is important for what we want to accomplish here, Philip and I along with the World Dementia Council with Lenny as leadership.

We want to hear from you: here is where we are today, where we have come from, where do we need to get to next with what we have and what do we need to actually get there. Is it something brand new? Is it the further development of what you have been hearing about? Especially right now when we are at such a point where we can see perhaps a treatment being approved and what that impact could have. Or if we are still on the hunt for additional treatments depending on what the EMA and FDA decide about the current treatment they are considering.

Who would like to start?



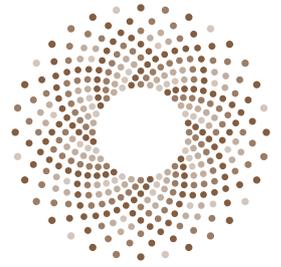
Dr Eric Siemers

The biomarkers are great, especially to ensure target engagement. But to know you have a good target, at some point you need cognitive measures. That might be a place to apply digital cognitive biomarkers.



Professor Rudolph Tanzi

Agree, Peggy. If we can agree on blood-based biomarkers for early pathology and then come up with safe drugs that can hit those biomarkers, we can be proactive and allow the Feb 2018 guidelines to help presymptomatic patients... and not just wait and be reactive with symptomatic patients.



Professor Todd Golde

Director, Evelyn F. and William L. McKnight Brain Institute (MBI),
University of Florida

I think there is reasonable evidence that BAN2401 and aducanumab engage target better than the other anti-amyloid agents. Maybe the Lilly P3; I don't know where that stands as well. But I think we have all said these need to be put into prevention studies if they are truly are engaging target and to really test their impact there. I think it is important we ensure as a field that, whatever happens with Bigoen's approval or not, that we recognise that is not moving the needle far enough in that setting.

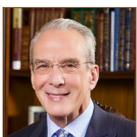
We have to be cautious. There are a lot of people who would like to see those drugs fail. But there is no one in the field who should want to see a drug fail. I don't care if there is no mechanism behind it. We should want to see something work. But it doesn't mean the hypothesis is wrong. It just means we didn't test it at the right time. Maybe. We also need to go to the distance. I said this eight years ago. I want to see autopsies from these people. Did they really clear amyloid and how much? And until we have that I might be hesitant to say put it into one of Randy's or Reisa's or Eric's prevention studies. Because if it is not doing that, we have missed something. And we need to know that. And we need to know it sooner rather than later. Every month we wait on that, these are long trials, and we waste everyone's time.



Dr Maria Carrillo

Chief scientific officer, Alzheimer's Association

I am in full agreement Todd. And we have often said at the Association we want to leave no stone left unchanged. We want every drug out there that has a possibility to see its day and have its chance. So thank you for that. Jeff?



Professor Jeffrey Cummings

Founding Director, Cleveland Clinic Lou Ruvo Center for Brain Health

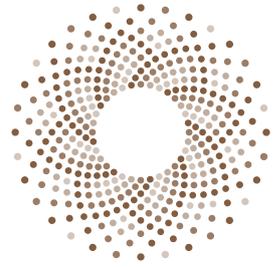
I will bring Randy into this conversation also. I think platform trials and the platform construction is an efficient way of advancing trials particularly at the phase 2 level and particular with these great biomarkers we heard about today.

One of the great disappointments in the recent past is the decision of IMI not to continue to support the EPAD. I think that was a very strong platform organisation. I know it had trouble getting compounds. But that is something the world, all of us, could come together to help more with it. I think that kind of platform trial is really important.



Dr Michael Devous

The FDA position regarding Aducanumab suggests they are ready to consider not only biomarkers but modest clinical change. As Eric said, the data imply that this particular drug was not awful. While we pursue a huge trial-ready cohort, and cocktails in addition to monotherapy, should we also be preparing to understand the clinical implementation of therapeutics with 15-20% effects?



Randy is doing it beautifully for ADAD. But it needs to be done for late onset AD so we can test drug and drug after drug without reconstructing the platform every time we need to do a trial.



Dr Randall Bateman

Charles F. and Joanne Knight Distinguished Professor of Neurology, Director of the Dominantly Inherited Alzheimer Network (DIAN), and Director of the DIAN Trials Unit

I just want to comment and thanks for the words Jeff. A few things about that. We have done it for amyloid and we are now doing it launching the tau next-gen arms to have three tau drugs run in parallel in the platform. There are definitely advantages in the platform and especially for this rare population.

One of the things for the field that we have not been able to do as well as other fields such as cancer and more recently Covid-19 is pull out the big guns and really launch dozens or hundreds of drugs and test them in parallel in a very significant way. And keeping in mind the audience here and the fact this is a World Dementia Council meeting, I think one of our big limitations is our trials take way too long to start, run, finish and analyze because of our disease.

That is going to fundamentally change with the blood-based biomarker implementation of screening and enrolment. But there are major limitations in our ability to enrol numbers of people needed to make it economical to do that. If I were to identify one thing that is really facing our field, it is embarrassing that we can't do what has been done in covid19 and cancer. I really think the consternation about does drug a and b and c and these individual targets, a lot of that would go away if we had real good clinical biomarker data.

As has been pointed out the final evaluation of the brain with the neuro-path data we have implemented that in the DIAN-TU trials. Everyone has been offered a brain donation. We have the majority of people doing it.

But I think this is a magnitude issue. Short of a breakthrough that happens by chance, we need numbers. I would ask the group to think about this a little bit. How do we build clinical trials to allow them to run much faster and much less expensively? The \$300-\$500m trials, ours are in the \$100m range, you can take only so many shots on goal and it is just not enough.



Dr Maria Carrillo

Chief scientific officer, Alzheimer's Association

Very true and I think biomarkers can change that right? Other diseases do that in much shorter time because they have much excellent markers of the disease.



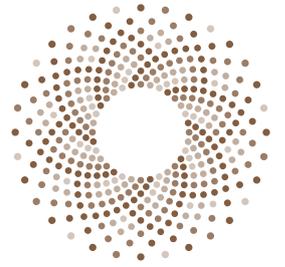
**Professor
Todd
Golde**

I would remind folks that the most commonly used drug that was approved based on a biomarker are statins, and need to be given to 20-25 high risk individuals to prevent 1 cardiovascular event. We would never see this effect in a typical AD prevention study. As Randy points out however, in famial hypercholestermia the effect is easily observed... the challenge is obvious for prevention we need to have much bigger effects and be as safe or safer than a statin.



**Professor
Henrik
Zetterberg**

Yes, from a biomarker perspective we need to scale up our capacity to analyse large numbers for available biomarkers and also develop better biomarkers for TDP-43 and a-syn.



Professor Reisa Sperling

Co-principal investigator, Harvard Aging Brain Study

I am thrilled Jeff you brought that up and Randy knows about this but we are working on a platform trial in sporadic AD that will come through ACTC hopefully led by Adam Boxer and Keith and biomarkers outcomes. So really building on what DIAN has done and saying can we do this is sporadic AD.

I will say that this issue of combination therapy is one of the first things has come up in this, because if we are in early symptomatic disease or even late preclinical the issue of can we do a tau platform trial without an amyloid part to it if there is an approved drug, and what if the drug is approved over the next who knows when what does that mean? I think there are some really complicated things. But it is time.

I agree with you Maria this will made so much easier by blood-based biomarkers. We can have this pre-screened trial ready cohort, hopefully work with groups across the world, to have hundreds of thousands of people ready to come into these studies who are pre-screened with blood-based biomarkers.



Dr Maria Carrillo

Chief scientific officer, Alzheimer's Association

We hope. I am going to call on Ivan next he has asked for an opportunity to speak.



Ivan Koychev

Clinical academic psychiatrist, University of Oxford

Thanks. I am Ivan I work at Oxford. Further on from Randy's point about making the clinical trials efficient, I think we have identified that we don't normally need to identify conversation in MCIs but we do need to identify people 15 to 20 years earlier. And also the second point was something that Cath mentioned which is how do we make it representative of people who do get the disease at the end?

And I think what we really need to be thinking about is how do we build an infrastructure that allows us to pick up people who are 15 to 20 years out. To this end I think the biomarker development that Oskar spoke about and Hendrick has been working on is a great equaliser. It does allow us, if you think about which are the groups we need to start monitoring with these scalable biomarkers, to actually start picking out the people who are at this inflection point, as Reisa spoke about. And that is something we have seen in NIH studies.



Dr Hussein Manji

Agree completely, Eric. Indeed, that (digital biomarkers) is one of the aspects that will be utilized in the Davos Alzheimer's Collaborative.



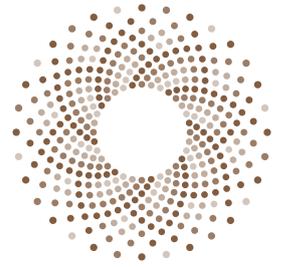
Dr Christopher Chen

A platform like recovery works because the outcomes can be measured early, hence the attraction of using biomarkers to identify interventions to move forward with.



Ivan Koychev

To Gil's point: longitudinal blood biomarker/digital cognitive run-in trajectories in trial-ready cohorts offer an option to decrease sample sizes based on change from expected individual trajectory.



This is something that I have put in the chat, but maybe we need to think about the conditions that we know are associated with AD like cardiovascular disease and hypertension. Think about creating large cohorts of these people who are monitored regularly with these scalable biomarkers, the blood biomarkers, but also the digital biomarkers that again we heard about. Then we start to pick up these people just on the inflection point. And we create an infrastructure which is ready to input these people into the clinical trials that everyone else has talked about. So that is something I want to bring up: how do we create this infrastructure?



**Dr
Eric
Siemers**

Gil, is there a platform study in the future for LEADS?



**Professor
Gil
Rabinovici**

Eric, yes, that is the vision for a future LEADS-TU.



**Professor
Bart De
Strooper**

I agree Reisa, biomarker people and basic scientists will have to work a bit harder to get more biomarkers for the other proteins in ND.



Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

It is a great question and I know we were trying to do some of that in the United States I put in the chat the PREVENTABLE study. It is 20,000 individuals in the US. That is a lot. We are on the executive scientific board for it which is why I know about it. They are following with the statin not just the cardiovascular risk but they include cognition. How maybe do we encourage that which is a combination of NHLBI, which is the blood institute, and NIA, and create something like that? I am going to noddle on that. It is a good challenge. Gil?



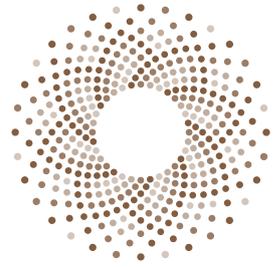
Professor Gil Rabinovici
Edward Fein and Pearl Landrith Distinguished Professor, Departments of Neurology and Radiology, University of California San Francisco (UCSF)

Another challenge that we haven't discussed much is the heterogeneity of patient trajectories and the course of disease. The EMERGE and ENGAGE studies really illuminated that because the placebo group behaved really different in the two trials.

We saw beautifully from Oskar and Reisa's presentations how if you take someone who is amyloid positive and add a tau biomarkers that can really dramatically change the prognosis and the individual trajectory.

I think that we have to also recognise that we are just scratching the surface. Even though we have made tremendous progress in biomarkers there are still a lot of very important neuro-pathologies we know are contributing significantly to cognitive impairment - TDP43, vascular disease, inflammation.

In parallel when we have better precision medicine approaches for prognosis that will really help our trails. Because we may need smaller trials if we can stratify patients more accurately. And also go for more targeted interventions for individuals instead of treating everyone as if they have the same course in a trial.



Professor Bart De Strooper

Director, UK Dementia Research institute,
Professor and VIB researcher, KULeuven, Belgium and UCL, London

From my perspective I don't think making bigger and bigger trials and trying to target more and more cases is the way forward. Smaller trials in stratified populations where you have clear hypothesis on mechanism is probably going to give us quickly the idea of a couple of drugs that will clearly be relevant and then maybe you can expand to larger studies. It is not the brutalism approach that will give us a lot of progress.

I am just thinking about anti amyloid therapy it is now used in people with TDP43 with all kinds of mixtures. There is a subgroup, I have been involved in a neuropathology study recently, with pure amyloid and tangles. So why don't we specify that only that type of patient is treated and look at what happens with amyloid and tau pathology? Instead of trying to include hundreds of thousands of people and have this mixture of confusing disorders and then coming up with the argument that only poly therapy is going to help.



Dr Randall Bateman

Charles F. and Joanne Knight Distinguished Professor of Neurology,
Director of the Dominantly Inherited Alzheimer Network (DIAN), and
Director of the DIAN Trials Unit

But Bart how would you identify those people?



Dr Maria Carrillo

Chief scientific officer, Alzheimer's Association

Randy you have the DIAN population, a unique population. Gil you want to talk about the early onset population that we are thinking about for LEADS.



Professor Gil Rabinovici

Edward Fein and Pearl Landrith Distinguished Professor, Departments of
Neurology and Radiology, University of California San Francisco (UCSF)

So just like autosomal dominant AD is a nice model for relatively pure disease. Similarly, we know that patients who develop sporadic AD at a young age have fewer co-pathologies and have a more pure form of disease. Amyloid and especially tau can account for or predict trajectories with much higher R-squared than in older populations.

The LEADS study which we hope to broaden to an international network and prepare for a trials unit is another population we should be thinking about for testing proof of



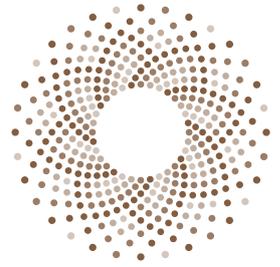
**Professor
Todd
Golde**

We also need renewed efforts to develop therapies and interventions that could have bigger impacts in the symptomatic phase. The bell curve for when we will have "prevention" in place in the general population is pretty large, we need to deal with the reality that many many folks will still get AD before we can prevent it.



**Professor
Linda Van
Eldik**

The ADRCs and the MARK-VCID programs are exploring blood-based biomarkers especially for vascular and inflammation profiles that could help with stratifying patient selection. One advantage of fluid biomarkers is that we can get a "profile", if we as a field decide what combination of markers is relevant.



concept certainly and maybe in the future for pivotal trials. Because they do have a more pure form of amyloid and tau related form of dementia.



Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

Bart go ahead. I agree with that.



Professor Bart De Strooper
Director, UK Dementia Research institute,
Professor and VIB researcher, KULeuven, Belgium and UCL, London

I am also thinking about genetics so polygenetic risk scores. Which need to be further developed I would agree. You can already do nice predictions if you go to the extreme +2/3 standard deviation -3. The type of prediction you have there is of the same level that you have with the full penetrant mutations almost. So if you take people who has an overload of risk genes that are in the inflammation pathway than all of a sudden testing your anti-inflammatory drugs in such a small group is so much more relevant than testing it in hundred thousand patients where whatever mechanism can be operational where your effects will disappear because of all the other factors. So, I think we should combined thinking big with clever and small.



Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

That's right. And actually, the FDA has suggested that. That we might do proof of concept in the smaller groups where we could find the evidence. And Gil is typing the answer to Eric's question that is in the planning. Reisa you are next.



Professor Reisa Sperling
Co-principal investigator, Harvard Aging Brain Study

I want to agree with Bart but say I don't think these aren't mutually exclusive. Platform studies should and can be done in proof of concept, smaller groups with short term biomarker outcomes, to make better decisions about what goes into these giant phase 3 trials. But we don't fully know other than in pure disease – and I think DIAN and LEADS is definitely the way to go – but in later sporadic disease we don't fully know how best to define these groups. If we are too narrow we may miss opportunities. So, I think these



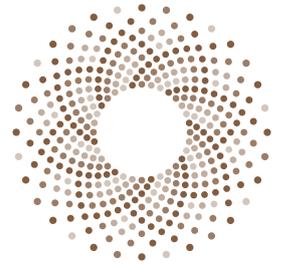
Dr Maria Carrillo

MARK VCID is a good example of basic science working with human trialists... in blood/vascular contributions.



Professor Clive Ballard

Also, if we are creating platforms how we combine commercial/industry compounds, academically developed compounds and re-purposed compounds and a big shift in clinical practice to adopt this in primary care – which would be the big advantage.



platforms should be adaptive partly on who is showing a response as well in these proof of concepts. So for example, you can say if you are past a certain level of tau, if you have evidence of vascular disease, is this still going to work?

But Randy did ask you an important question Bart. How do we define who has these co-pathologies? So TDP43 critical in that older group but we can't really see it other than saying the hippocampus is more shrunken than it should be for the amount of tau. Alpha-synuclein which is certain there in a number of people. Vascular, we are better at in risk profile but again the white matter hyperintensities we see are not all vascular, or at least not exactly caused by the same thing. So that is where we need some work. How do we better define these sub-groups?

But I agree with you: homogenous small groups, shorts trials, proof of concept. And at least that is what we will try at least in our first platform.



Professor Cornelia van Duijn

Professor of Genetic Epidemiology at the Nuffield Department of Population Health, University of Oxford

Thank you. Well we are naturally going to the idea we need them both probably. Large scale effective trials as well as well as the targeted trials.

What we are working on in Oxford together with Ivan and Martin Landray from Big Data Institute, who developed the REVEAL trial, is that evidence shows that given we now have promising drugs and we have the biomarkers we are quite sure these large scale trials will be feasible. That is the first thing they should be feasible. Of course, the question is how long before the onset of the disease. We don't know precisely is it 5 years or 10 years. What is going to happen when.

What is more importantly we did a lot of work in cardiovascular disease and the idea that these large scale trials are less effective and more costly is simply not true. It is not that they are more costly if you do a smart design. You can't do a PET every other month in every patient. You can forget about that. That would make it extremely costly. But if you can use biomarkers that are relatively cheap the cost of these trials is not higher. It remains to be proven whether they are as effective. We don't know. But the chances are good. If they work in covid19, if they work in cardiovascular disease, why would they not work in AD? Is Alzheimer's less complex than cardiovascular? I dare to doubt that.



Dr Niels Prins

Director, Brain Research Center

Thank you. I think that one other different important topic is how we can boost clinical drug development by improving recruitment. In Europe I think we have a marketing problem with Alzheimer's drugs trials. It seems almost to be a taboo. So pharma trials



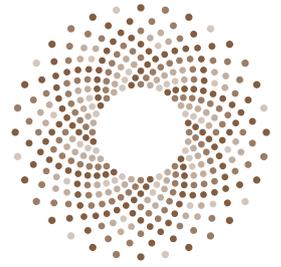
Dr Michael Devous

I agree Todd. One challenge that we have to tackle is the time frame for trials both in symptomatic and in asymptomatic populations. We seem to have settled on 18-24 months for symptomatic populations, but much of the recent trial data suggests that may be too short. While we can clearly see biomarker alterations, the subsequent clinical effect might take longer to observe (how long, 36 months, more?). This question likely gets substantially amplified in the asymptomatic population. A4 seemed long when it first started, but now I wonder if it is long enough!



Dr Martin Traber

There is still a large gap in adopting CSF testing in clinical routine.



are not well accepted. I think this is also something that we can improve. Now in covid19 you see it is totally accepted people are willing to participate in trials, journalists are positive. It is the same for cancer. In AD it is totally different. I think it also has to do with the fact patients are not vocal and caregivers are so tired. We as leaders in the field, particularly in Europe, I don't know whether it is the same in the US, but this is something we can improve.



Dr José Molinuevo

Vice President, Clinical Development Neurodegeneration, Lundbeck

I do agree, I think it was Gil who mentioned, to develop trials with very clear target populations so we can test proof of mechanism and proof of concept. And I fully agree with that. But if we go into a very selected population that the complexity is to move that to a larger more generalize population in phase 2 and phase 3 trials. And that is what we may be facing. I do agree that the first step has to be target population where we can enrich with many biomarkers to ensure success but then the challenge will be trying to reach a more generalized population in a larger trial. We have to balance both things somehow.



Fiona Carragher

Director of Research and Influencing, Alzheimer's Society (UK)

I want to go back to Oskar's excellent presentation on biomarkers. Particularly thinking about his final slide on what needs to happen next. Because I don't think we can underestimate how much time and effort and preparation there will need to be to get high precision measurements of these scaled up biomarkers into routine clinical practice. I am a clinical biochemist by background, and I have run big clinical chemistry labs, and this is going to take a long time. So I would suggest an action for us as an international community is to start working with groups such as the International Federation of Clinical Chemists working together with the international measurement system so that actually we can start to think about scaling up these biomarkers because it will take a very very long time.



Dr Maria Carrillo

Chief scientific officer, Alzheimer's Association

I don't know whether Oskar or Henrick would like to address this? We currently have FFAB for example the GBSE working on this on a global level. We have done this with CSF already and worked with those groups. Henrick is there anything you want to add because we did manage to I think be successful with CSF?



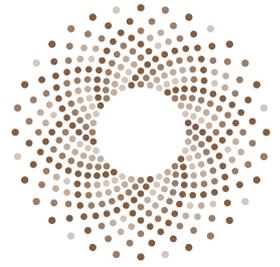
**Professor
Howard
Bergman**

We will have biomarkers and we will have effective therapies. So, we need now, in parallel to the biomarker and therapy research, to think of how this will land in our healthcare systems and the potential for the great numbers anchored in primary or specialty setting; care; complexity of Dx process; costs; resulting ethical and equity issues that will arise.



**Professor
Clive
Ballard**

And encouraging people with early cognitive impairment to present to their primary care doctor.



Professor Henrik Zetterberg
Professor of Neurochemistry, University of Gothenburg

Yes I think this is a very important comment but I think it will be much faster for the blood biomarkers actually Fiona. There is lots of work going on in the big clinical chemistry companies. Most of them are working with p-tau, AB and also NFL. We don't have good biomarkers yet for TDP43 and alpha-synuclein – that is a big problem and we need to solve that somehow. It is hard. Many people have tried but we shouldn't give up.

For p-tau, AB and NfL there I think we will see clinical chemistry assays appearing in the next year or two. There is a network of people to work on getting these standardised. It might be one or another company will be before the others. But we can use the network within the GBSE and AAB already created to get standardisation in place. So I am rather hopeful that it will not be a big hurdle but we need to work hard on it



Fiona Carragher
Director of Research and Influencing, Alzheimer's Society (UK)

From the UK perspective it will be the evaluation and adoption into clinical practice when we get there, that has to be done in parallel. Because we know from other diseases when we have had really good blood-based biomarkers, with great kits that have come out from the big diagnostic companies, and they have been NICE guidelines, they still haven't been adopted at scale. There is a final step we need to be thinking about there.



Professor Oskar Hansson
Professor of Neurology, Lund University

I fully agree with you. What I think is very important if we want to get it into primary care is we need to show that it really makes a difference for the patient. So that it is not just changing the diagnosis in the medical record but it is changing the treatment and care they get. I think that is crucial otherwise most physicians will not do it. They will think what is the point of just measuring something if it doesn't really help the patient.



Dr Randall Bateman
Charles F. and Joanne Knight Distinguished Professor of Neurology, Director of the Dominantly Inherited Alzheimer Network (DIAN), and Director of the DIAN Trials Unit

Does that equation change if a drug is approved...?



Dr Michael Devous

In response to Gil and Randy, should we consider an IDEAS-like study to understand how blood-based biomarkers might get used in the general population?



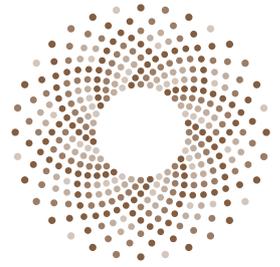
Professor Serge Gauthier

A note of caution about screening in asymptomatic persons with plasma biomarkers. We need a REVEAL-like study to assess psychological impact of disclosure.



Dr Maria Carrillo

We may need it, but waiting a bit for the companies to move their development along, it's going to be a year or so. But we are discussing this in the current effort to revisit/address the AUC for Amyloid and include TauPET.



Professor Oskar Hansson
Professor of Neurology, Lund University

It will definitely change because it will become more obvious. But already today in many countries 50% do not get cholinesterase inhibitor and so on even if they have AD.



Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

I think this is a really important discussion. We have already seen this happening with the IDEAS study because we are trying to convince Medicare and Medicaid that that intervention, in a very select population with appropriate use criteria that we develop of course, should have access to it and have it covered. We may not see such an uphill battle with blood. It is cheaper. But at the same time thinking about appropriate use criteria there Oskar as we have already discussed is very important. Gil, I think you had a comment about this?



Professor Gil Rabinovici
Edward Fein and Pearl Landrith Distinguished Professor, Departments of Neurology and Radiology, University of California San Francisco (UCSF)

This may be really cultural or societal dependent. But I actually have the opposite concern from you Oskar. Because I am worried that primary doctors, at least in the US, are going to over order blood test. Because it is much simpler to order a blood test than interview a patient and a caregiver and do cognitive testing. My worry is that anyone who comes in with a non-specific cognitive complaint may get these biomarkers and that will lead to misinterpretation without the appropriate clinical context. It may depend a lot on where you are practicing but that would be my concern with blood-based biomarkers in the US.



Professor Oskar Hansson
Professor of Neurology, Lund University

I fully agree with that.



Professor Randall Bateman

Yes, definitely. IDEAS has a sub-study, PARIS, to look at concordance to PET, and clinical utility of the measure. Psychological impact is being assessed for PET and may be translated for blood-based biomarkers.



Dr Eric Siemers

Agree, the trajectory of cognitive decline matters.



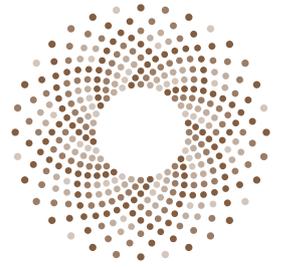
Professor Henrik Zetterberg

Yes, AUC for the blood biomarkers will be very important.



Professor Rudolph Tanzi

Can we get a transcript of this chat?



Dr Randall Bateman

Charles F. and Joanne Knight Distinguished Professor of Neurology, Director of the Dominantly Inherited Alzheimer Network (DIAN), and Director of the DIAN Trials Unit

Gil that is a concern I have as well. Especially using a single biomarker. But this is where the panel of biomarkers will be really helpful; if you have amyloid, tau, neurodegeneration. What needs to be done is the studies that look at what is the cause of the person’s cognitive complaint and impairment. That is really a clinical thing that needs to be done right now when comparing this to other biomarker standards like PET and CSF. But the question really is, what is that person’s cognitive complaint due to? And is it really due to the AD path? They may have AD pathology for example p-tau217 and Amyloid-beta abnormal a decade or more before someone becomes symptomatic. So that is not enough to say that their symptoms are due to AD. And we still need to emphasise the clinical issue of identifying the cause of primary concerns because other diseases are right now more treatable and we shouldn’t miss that.



Dr Cath Mummery

Consultant neurologist leading the Cognitive Disorders Service, National Hospital for Neurology and Neurosurgery

Coming back to Neils view on the difficulty with recruitment. I both agree and disagree. Yes recruitment is difficult but I don’t think that is due to reluctance if people understand what a trial is. Yes we have the converted that come in. The well-educated. The very healthy. These tend to be the people who come into studies. At least in the UK. But if you go out there and give people the information they need in the right way they want to be involved in trials. It is not that they don’t want to be involved in trials it is just they do not understand them and we are not accessing them. And I wonder if access, and Fiona and I were on a call about the pathway for future DMTs in the UK about how we need to use blood-biomarkers, how we need to outreach to primary care, and whether these things will improve access to people we think are reluctant when actually what they are is unaware.



Ivan Koychev

Clinical academic psychiatrist, University of Oxford

Just coming back to what was raised earlier about the danger of over diagnosing through cross-sectional use of blood biomarkers. I think that is a valid concern and that is why we should be thinking about trajectories rather than single point measurements. Going back to the idea that we know who the at risk groups are based on the co-morbidity. So we should be thinking about prospectively monitoring these people and looking for that inflection point that Reisa was talking about. We know roughly when it happens: so mid-50s moved slightly by APOE4. Cross sectional blood-based biomarkers have a lot of pit falls but at the same time trajectories would be very informative. And for the sample



Lenny Shallcross

Yes.



Dr Maria Carrillo

We are drafting a paper, we will send for your input and comment. So in essence yes Rudy.



Professor Rudolph Tanzi

Thanks. Wonderful discussion!



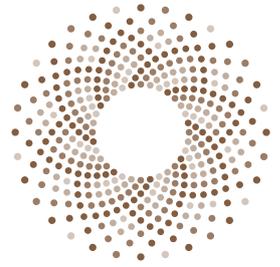
Professor Bart De Strooper

This was a great discussion, thank you for organizing this!



Dr Hussein Manji

Yes very good discussion, and fully agree that the pump is primed, and it behooves us to make a difference for our patients.



size of the trials otherwise if you are looking for a change in individual trajectory you are going to be looking at much smaller sample sizes. So there is a lot to be said for the prospective monitoring of risk.



Dr Maria Carrillo
Chief scientific officer, Alzheimer’s Association

I think that is very correct. Jeff I will call on you. One of the things we are very much thinking about it is how we will take all the appropriate use criteria for multiple biomarkers and put them together in a trajectory of sorts. It will certainly not be early enough. Not yet. We don’t have the data. But Jeff?



Professor Jeffrey Cummings
Founding Director, Cleveland Clinic Lou Ruvo Center for Brain Health

I want to build on Neils and Cath’s point. One of the things that “Professor Covid” has taught us recently is people can be interested in drug development. All of a sudden we are talking about testing and antibodies and clinical trials. I would love to see that sense of urgency and knowledge that is coming into the general population translated into Alzheimer’s disease care and clinical trial participation. The population is now more attuned to trial than it has ever been and the importance of trials and how they get FDA approval or regulatory approval in all countries. All of that is in the public domain now in a way it has never been before. We should try capture that momentum and that teaching moment we are having, to try get people involved in clinical trials more broadly.



Dr Maria Carrillo
Chief scientific officer, Alzheimer’s Association

The pump is primed you are absolutely right Jeff. It is a moment of inflection here for us. We have come close to end of time. I want my co-chair Philip to say a few words and about next steps for all of this because we are really grateful for your time and insight.



Professor Philip Scheltens
Professor of cognitive neurology and director, Alzheimer Center, Amsterdam University Medical Centers and member of the WDC

Thank you Maria. I think this was a really exciting discussion. And it is a real privilege to have all these thought leaders together at the same time enjoying the conversation.



Professor Randall Bateman

Michael, see the PARIS IDEAS study: <https://alz.org/ideas/overview.asp>



Dr Michael Devous

I agree. Very effective forum!



Professor Howard Bergman

Not too early to think of implementation research.



Dr Cath Mummery

Can we make this regular?



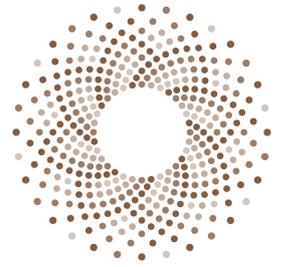
Professor Randall Bateman

Great discussion. Only wish we had more time!



Dr Maria Carrillo

Agree, we should revisit in 6 months and see where we are.



I think this has been really helpful. As Maria said at the outset, we had three elements here: where have we come from, where are we now, where are we heading to.

I think many of the elements especially regarding the biomarkers but also the therapeutics options we now have are unparalleled. And if we combine that with the enormous impetus we have in the general population that we are really changing the field by doing better trials having an enormous amount of new leads and targets that we can use and having the biomarkers and having the appropriate tools finally to measure the effect in selective patients and also to measure whether there was target engagement.

I think we are in a really good position to change the future. That has not been the case for a long time. Whatever the decision of the FDA, it will not change the fact that we are in a different era now. We can combine all the knowledge we have now – of course it is only AB and tau that we have the appropriate biomarkers for. But the speed that has been developed over such a short period of time we will be able to identify the other proteinopathies as has been mentioned. TDP43 was mentioned, alpha-syneuclein was. It is really crucial. For the time being since we don't have them, we can focus on homogenous groups. Small trials with dedicated drugs targeting one proteinopathy for instance and doing the appropriate trial in shorter timeframe than we have every done before because we have biomarkers will open up a better future for therapeutic development. It all comes together very nicely.

For the next steps Lenny will just ask you whether you willing to contribute your insight in every perspective that we have discussed to help draw together a paper that the World Dementia Council will publish in due course. So thank you Maria, thanks to Lenny and Josh for organizing this. It has been a really great experience. And Lenny famous last words for you.



**Professor
Todd
Golde**

Agree with Bart, the focus on unmet need, science and lack of dogma is essential



**Dr
Cath
Mummery**

Yes, Maria!



**Professor
Ricardo
Allegri**

Yes, I agree.



Lenny Shallcross
Executive director, World Dementia Council

Thank you Philip. As Philip said after this meeting we will be reaching out to you all as the Council develops the paper and we would welcome your insight and guidance. So look out for that! I just want in closing to thank once again Maria and Philip for chairing what has been a great conversation. To thank all our speakers for stimulating the rich discussion we have had and thank you all for participating. And, depending on your timezone, it only remains for me to wish you a good morning, afternoon, or night.

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.

worlddementiacouncil.org

© 2020 World Dementia Council
UK charity registration number: 1170743

Cover image editorial credit: Shutterstock.com

