World Dementia Council

Leading the Global Action Against Dementia

Global dialogue on clinical trials: Transcript

The dementia landscape project
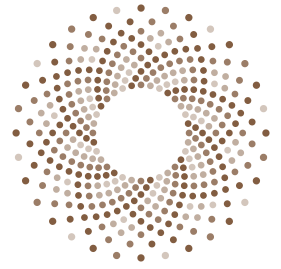
9 March 2021

Organized in partnership with

Alzheimercentrum Amsterdam
Amsterdam UMC

alzheimer's association

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 investigaror 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.
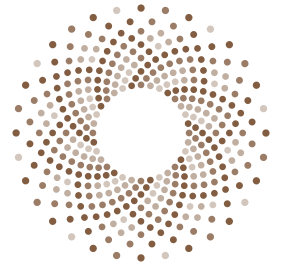
Speakers
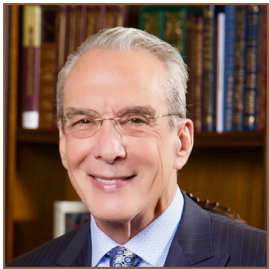
Professor Jeffrey Cummings

Jeffrey Cummings, MD, ScD, is Founding Director, Cleveland Clinic Lou Ruvo Center for Brain Health. He is the Joy Chambers- Grundy Professor of Brain Science, Vice Chair for Research, and Director of the Chambers- Gundy Center for Transformative Neuroscience, Department of Brain Health, School of Integrated Health Sciences, University of Nevada Las Vegas (UNLV). Dr Cummings is a world- renowned Alzheimer's researcher and leader of clinical trials. He has been recognized for his research and leadership contributions in the field of Alzheimer's disease through the Henderson Award of the American Geriatrics Society (2006), the Ronald and Nancy Reagan Research Award of the national Alzheimer's Association (2008), and the Lifetime Achievement Award of the Society for Behavioral and Cognitive Neurology (2017). In 2010, he was honored by the American Association of Geriatric Psychiatry with their Distinguished Scientist Award. In 2018, he was honored with the Leadership and Achievement Award by the International Society of CNS Drug Development, and he received the Bengt Winblad Lifetime Achievement Award from the national Alzheimer's Association. In 2019, the International Psychogeriatric Association awarded him with the Distinguished Service Award and he received the Alzheimer's Drug Discovery Foundation's Melvin R. Goodes Prize that honors an innovative researcher who has made a significant and lasting impact in the field.
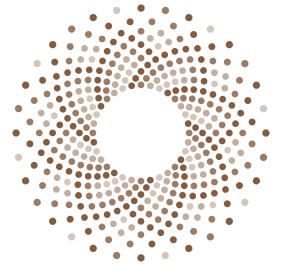
Dr Mark Mintun

Mark Mintun, M.D., has been the Vice-President of Pain and Neurodegeneration Research and Clinical Development since January of 2018. In 2010, Dr. Mintun joined Avid Radiopharmaceuticals, a wholly owned subsidiary of Eli Lilly & Company, as Chief Medical Officer and became its President in 2014. Prior to Avid, Dr. Mintun was Professor and Vice-Chair of Radiology at the Mallinckrodt Institute of Radiology at the Washington University School of Medicine, with joint appointments in Psychiatry, Neurology, Bioengineering, and the Anatomy and Neurobiology Departments. He earned a BS in Chemical Engineering from the Massachusetts Institute of Technology in 1977, received his medical degree in 1981 at Washington University School of Medicine and completed a research fellowship in neurology and residency training in nuclear medicine. Dr. Mintun has co-authored over 200 research publications that include reports of brain imaging to characterize flow/metabolism relationships, neurotransmitter systems, circuitry for processing affective stimuli and the pathology of neurodegenerative diseases. More recently he has led development programs for both amyloid and tau imaging of patients with neurodegenerative diseases.
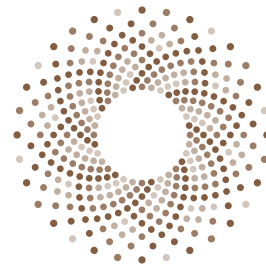
Lenny Shallcross

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.

Global dialogue on clinical trials

Tuesday 9 March 2021

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. Good morning, afternoon everyone. Thank you for joining us on what is a lovely sunny spring day here in London at least. Which contrasts with the cold winter day we last got together. For those of you who were not at the last meeting I am Lenny Shallcross, Executive Director of the World Dementia Council. This is the second meeting we are holding, the last one was at the back end of last year. You will have seen the transcript of the meeting as well as the essays reflecting on the conversation we had.

As I said at the last meeting, we will be producing a report later in the year evaluating the progress that has been made on the goals set by the G8 – as was – at the London dementia summit in 2013 and identifying how that progress can be accelerated. Since we met last November, we have had a number of workshops on different aspects of the global agenda. They have been on prevention, on technology, on care and later this week we have a meeting on trials in low and middle-income countries.

All these events are designed to get the input from international experts on where we have come from, where we are, where we need to get to and how we get there. After this discussion today we will produce a paper covering the conversation we had today and the one at the backend of last year. We would welcome your comments and the paper will form part of the report we produce later in the year.

Before I hand over to Philip just a reminder to mute and unmute yourself. We will be recording this meeting, like the last one, but that is for the purpose of producing a
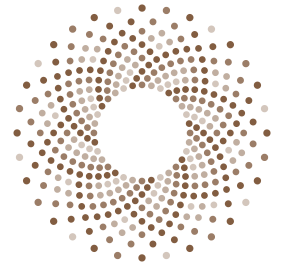
transcript. The chat function is again open, and I would encourage you to use it. If you want to participate in the meeting use the chat function to indicate you would like to speak, raise your hand or just wave. Maria who will be chairing the conversation will bring you in.

Having just mentioned her I would like to introduce the two co-chairs. Maria Carrillo, Chief Scientific Officer for Alzheimer's Association. Professor Philip Scheltens, Professor of Cognitive Neurology in the Netherlands. And with that I will hand to Philip.

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

Thanks Lenny. Thank you very much. Great that you are all here. Great turn out. Fifty or more people joining us today. At our last meeting we had excellent opening contributions from Oscar Hansson and Reisa Sperling on biomarkers and Eric Siemers and Cath Mummery on the development of therapeutics. It was a rich conversation and I think showed what an exciting time this is for our field especially how biomarkers have improved our understanding and how it will improve the development of clinical trials even further.

Because of that I think it is completely justified to start this session with an overview of where we are with clinical trials and we are very pleased that Jeff Cummings agreed to share his thoughts on the topic. As you will all know, at the Chambers-Grundy Center for Transformative Neuroscience at the University of Nevada, has kindly agreed to share his perspective.

After that we will have a bit of time for conversation on not just clinical trials but the research landscape: where we have come from, where we are now, where we are heading to. It is the last of those that for me – and for our patients, now and in the future – is the most important.

Can we make sure we make progress faster and how do we align policy makers, regulators, research funders help facilitate that? That is a debate we repeatedly touched on last time and we want to expand today.

As I said we're delighted to have Jeff share his thoughts on where the clinical trial field is today, and I am very happy to give him the floor now. Jeff.

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

Thank you, Philip. Great to see you all. It is terrific that we can get together in this way even if we are all isolated. It is great to be invited so thanks to Lenny and the Council and Maria and Philip. I am very happy to share my thoughts today. We have developed a Clinical Trial Observatory as part of the Center for Transformative Neuroscience at
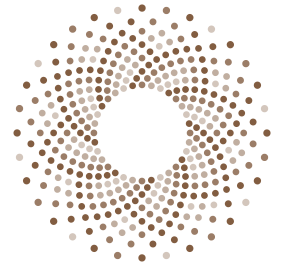
UNLV. We follow trials very carefully and we do an annual report. The information I am going to share with you today is brand new; it is all from the new report that has not been published yet. I hope you find it interesting. I have tried to provide information and also some identification of challenges and provocative observations that emerge from our work.

[Slides that were shared in the meeting are pre-publication and have not been included the transcript has been amended to reflect that.]

In the current clinical trial pipeline there are 126 agents in clinical trials for Alzheimer's disease. This would compare to about 3000 agents for cancer. To give you some perspective. It would be wonderful at some point in the future when we cannot put all the drugs in AD trials on one map. There are twenty-eight drugs in phase 3 – not that many. Phase 2 has seventy-four and this is the largest cohort that we have had in the six years since we have been doing the annual review. There are few drugs in phase 1, but out phase 1 observations underrepresent this phase of development – 24 is an underestimate because our information is derived from clinicaltrials.gov and not all Phase 1 trials are registered on the registry.

Disease modifying therapies (DMTs), or the desire to try intervening in the basic biologic process of Alzheimer's Disease, is the most common approach. 83% of the agents are in the DMT category – either biologics or small molecules. The symptomatic agents – either cognitive enhancers or drugs addressing neuropsychiatric symptoms make up the rest. Among DMTs: there are overall 31 biologics – that is an active area – and there are 73 small molecules.

Repurposed agents comprise 40% of all agents in the pipeline. This is a notable observation. These are drugs that have been approved for other purposes and now they are being studied for Alzheimer's Disease on the basis of mechanistic or epidemiological observations. There are thirteen cognitive enhancers in the pipeline and nine for the treatment of neuropsychiatric diseases. Although our only successful agents for the treatment of Alzheimer's Disease are cognitive enhancers, this is a relatively limited area of development.

One of the conventions we have adopted in the annual report now is the CADRO – the Common Alzheimer's Disease Research Ontology – which was developed by the NIA, the Alzheimer's Association, and a group of international funders. It identifies mechanisms of Alzheimer's disease that can be targeted therapeutically. They are: amyloid; tau; inflammation/infection/immunity; synaptic plasticity/neuroprotection; metabolism and bioenergetics; proteostasis/proteinopathies; vascular; growth factors/hormones; epigenetics; and where there are target areas with fewer than three active agents we have just classified these as "others".

There are a substantial number of amyloid-targeting agents but that is not the most common area in the pipeline. Inflammation/immunity is the most common followed by synaptic plasticity. Amyloid and tau do have a number of agents that are addressing those targets and there are a number of agents for amyloid in phase 2 as well as being the most represented of all targets in phase 3. Inflammation has quite a few agents in phase 1 and phase 2 but not very much in phase 3. Those are largely early-stage
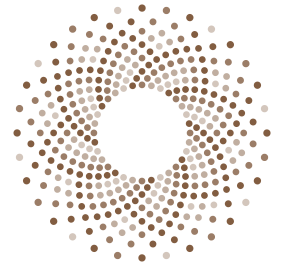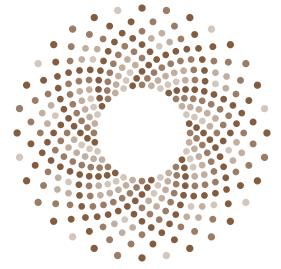
agents. You can see as our understanding of the disease progresses targets begin to be prosecuted and agents progress from the earlier phases to the later phases. In summary you can see where the action is in terms of AD drug development: synaptic plasticity, inflammation, tau and amyloid are the most active areas currently in the pipeline.

Our studies emphasize that trials are a global enterprise. If you look at phase 3 trails, about a third of the trials are done in North America, a third only outside North America, and a third in a combination of both. In phase 2 there tends to be an emphasis in North America only although some trials are carried out only outside North America and some in a combination of both. In phase 1 – and I am sceptical of our phase 1 numbers because so many trials are not on clinicaltrials.gov – you again see an emphasis on trials in North America. By the times the trials reach phase 3, the trials have to be large, and the emphasis is on global involvement.

One of the things that we see reflected in the pipeline is tour increasing understanding of the continuum of Alzheimer's disease from the preclinical to the prodromal and finally into the dementia phases; the clinical trials have expanded reflecting this continuum. There are five trials in the preclinical space, there is one trial including preclinical, MCI and mild AD dementia. There are 13 trials that are MCI or MCI/mild AD dementia. This is the most popular area in which to work right now --- a biologically very dynamic area. There are 11 trials in mild to moderate AD and 11 trials in mild to severe AD. In summary: 46% of trials currently involve predementia participants. That is, they are either preclinical or they are prodromal phase of the continuum. So, we have certainly seen a great movement towards earlier populations in the clinical trial space.

I have tried to emphasize in this brief review areas where I think improvements could occur and one of them is in the development of platform trials. I think these are highly productive. They allow the development of a continuous framework, so you are not constantly recreating the stadium in which the games of clinical trials are played. It is a stable network that can grow new sites, test multiple agents, have multiple biomarker readouts, apply adaptive design, have shared placebos that are highly conservative of patient experiences, introduce novel measures, and bring in patient and partner input into the trial design. Platforms for AD trials are extremely limited… The DIAN-TU for autosomal-dominant AD is a terrific example of the platform approach. EPAD was a great platform approach but is not continuing to receive funding from IMI; and that is a disappointment. This is an area that can be grown. There is some discussion now about a Tau platform that may be brought in through the Alzheimer's Clinical Trial Consortium (ACTC) in the United States but that is at an early stage. Platform trials represent a key initiative that the Council could discuss and encourage.

Recruitment continues to be an extremely important and limiting factor in clinical trials. Let's take the preclinical DMT space: the average length of a trial for a preclinical population is 150 weeks – three years. Some of course go on longer, as long as five years. But the average length of the five trials in that space is three years. It takes a little over twice as long to recruit for the trial than to expose the agent for the trial. So, a trial that is only three years for exposure is over six years to prosecute the entire trial. And then if you look at trials for neuropsychiatric symptoms. Here you see how difficult they are. If the patient has to have dementia and agitation or dementia and psychosis then those trials are extremely difficult to recruit for, with the recruitment period being about

tenfold longer than the exposure period. In between are fewer extreme examples of DMT trials with MCI or mild to moderate dementia and trials for cognitive enhancers. But in all trials the recruitment period is substantially longer than the exposure period. This is a major problem, and we have to fix it. This is what is slowing getting new drugs to our patients.

One of the calculations we did this year that was novel was look to at the number of participant weeks that our participants are giving to clinical trials. And this gave us some insight into how much we are asking of participants in clinical trials. Currently we need about 39,000 people to populate all of the currently registered trials. If you multiply that number by the number of weeks contributed in all the different types of trials, you conclude that participants for the currently registered trials will contribute 2,540,000 participants weeks for all of the currently registered trials. And each of those participants has a care partner and they are contributing 2,540,000 weeks to the clinical trials; in total over five million participant weeks by either the participant or their research partner. It is striking, really striking. And we are asking so much more of our participants these days: longer trials, more biomarkers, more procedures. And they have had to do it in the middle of a pandemic. It is a remarkable contribution our participants are making.

We are coming to the end. I want to emphasize one aspect: we have talked a lot about R&D. But R&D doesn't get the drugs to patients. It has to be research, development and dissemination and if the virus has taught us one thing it is the importance of dissemination. We want global equity when we have new treatments for Alzheimer's Disease. And we are going to have to plan to achieve that. There is an ecosystem that is required to advance these drugs and that includes foundational science and translational science such as biomarkers of course. It all has to be funded which is daunting a challenge. We have to have data science to understand the data that are generated and regulatory science to understand how to move the drugs from trials into market. We have to have dissemination science in order to get approved drugs to patients worldwide. A successful ecosystem of research, development and dissemination (RD&D) is what will eventually lead to better public health.

Tis ecosystem is not planned; it is uncoordinated. One aspect for the Council to consider would be to give more thought and more emphasis on the need to coordinate the R, D and D elements that are necessary to get new drugs to our patients.

I will just summarize the points that struck me as I was developing the data.

- Most programmes target disease modification, and the targets are increasingly diversified. That is all great although the numbers are still small.
- Late-stage trials are global, so this is something we are involved in throughout the whole world.
- I believe platform trial structures could accelerate phase 2.
- Recruitment is challenging. In every trial, recruitment is longer than exposure.
- Participants and research partners are making enormous contributions to research trials, and we have fully appreciated that.
- The research, development and dissemination ecosystem are not optimized for the co-ordinated delivery of science to improve public health.
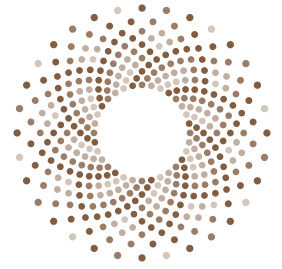
Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

Thanks Jeff. That was a great start there and great peak into the publication that is coming out so great that we will have access to all of that information. I think before we take questions generally and have a conversation, and this is an open conversation I would like to invite Mark Mintun to comment. One of the common threads that I heard in the conversation that is really relevant to the challenge Lenny at the top of the hour has tasked us with is to think about where we are, where we have come from, where we need to get to and how we get there.

And I saw especially in terms of the diversity in the field that is much greater than in comparison to where we were 10 years ago right Jeff? Certainly, AB trials are the most mature, because that is the ones we have invested in and started off on. As is our understanding of drugs against AB, like the recent donanemab which was reported out, and why I am asking Mark Mintun to start us off. We have had that top line report, which will follow with more details at ADPD coming up in a few days, and we will learn more. But it is great to see the diversification of the field through that graph and certainly the I-DROP and the CADRO which the NIA and the AA created with about 20 other funders. So that is fantastic to see.

I also want Mark to address the maturation of the field when it comes to the underlying biomarkers that we have available today that are being deployed to make patient selection much more accurate. So, I think, donanemab used that type of approach and Mark would you be able to share some of your thoughts and strategies on that.

Dr Mark Mintun
Vice-President of Pain and Neurodegeneration Research and Clinical Development, Avid Radiopharmaceuticals

Absolutely. Thank you, Maria. I think you are right it is a new type of trial. There are a couple of things probably worth mentioning.

The philosophy was we focussed on the brain pathology. The biomarkers are aimed towards the underlying pathology. In that way it affects several different elements of the trial. You have the effect on enrolment in the sense that you can focus on confirming the pathology as you screen for people and you bring them into the trial. In this case you screen for both pathologies: amyloid and tau.

The tau pathology now gives you a chance to stratify the level of the disease. That we think is going to be very important. I treat this a little bit like when people started developing oncology classification and staging techniques. Because different treatments might be for different levels or different extents of disease. Of course, some people ask "isn't that going to make it really hard to enrol because you narrow the window?" But in fact one of the consequences of this approach is you can actually widen the clinical window while you narrow the pathological stage. So, in other words an 80-year-old with
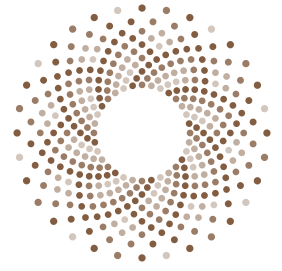
a level of tau may have an MMSE 21 while a sixty-year-old with that same level of tau might have an MMSE of 29. You might exclude one or the other if you decide you are going to enrol on a narrow clinical basis rather than a narrower pathology basis. It is a thought we are going to be able to explore with the types of data we are getting out of trials now including the TRAILBLAZER ALZ trial we are going to be talking about soon.

Another aspect, that is sort of obvious, is that if you are going after the pathology with your drug you can measure target engagement. Everyone has sort of noticed that it is great to see evidence of amyloid going down on our amyloid scales. So, using the biomarkers for that as well, I think it is really interesting and reflects on the great diversification of targets we just heard about because it unfortunately means we should also have diversification of biomarkers to see how well we are engaging the target. I think some of the perplexing ones are the ones in neuroinflammation where we would love ways of being able to monitor that but so far it is a work in progress.
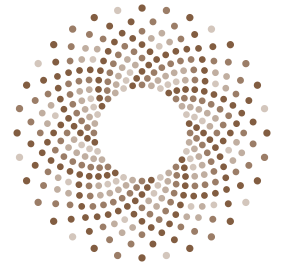
Another aspect of biomarkers is the continuing data we are getting that we hope we can establish something from as a proxy marker of treatment success. We have been looking for things like that for a while. It may not be amyloid reduction per se, but it could be slowing of tau or stopping of tau progression.

But I admit these sorts of biomarkers are complicated and hard to propagate in every country. We heard from Jeff about the importance of doing global trials. And so we are also looking as a field at what aspect of blood biomarkers can substitute for some of the more validated PET imaging biomarkers of pathology. That is a really exciting development over the last year where we are making progress and I am sure Oscar Hanson was talking about that before.

But those are one level but then some of the things that then become an interesting aspect is that when you are stratifying by pathology, if indeed it does work to make a more homogenous population, your trials by almost necessity become more powerful, more homogenous. A more homogenous population means fewer population variants and therefore more powerful. So, you can more quickly get to information about a treatment drug (a smaller trial therefore not recruiting as long or do a shorter trial - one or both of those).

And one final thing, a little more controversial. When you are much more certain about the types of patients you are bringing in and the way you are monitoring, I would say we should not be afraid of going into combination trial. We are getting so many good signs that we are starting to see efficacy. And of course that is fantastic. But that does not mean we should be happy with the progress. We should be open to doing combination trials where we are hitting the target even harder, or we are going after two targets. Going after amyloid and tau together is the most obvious one when you are in that business, so I imagine a lot of people are thinking about that. Again, it makes it a lot easier to do when you have carefully selected the population for that.

So those are my biggest ones so obviously you know we have other aspects of this trial like the composite measure, which we believe is a little more robust, like the iADRS. One of the things that isn't different is you still need to replicate them. So in that case we still have the standard aspect of being able to go after a very important proof of concept in phase 2 and then being able to replicate it.

That's my thinking Maria on the types of impacts the increasing levels of biomarkers in our field can make in our trials.

Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

Thanks Mark I appreciate that. I do think that is an important contribution because it sets us up towards nudging the field. moving to the next step in practice. We all have a lot of ideas and a lot of thoughts about the shoulds and woulds and coulds. What we want to talk about is what gets us into the next step where we are actually doing these trials with the knowledge that we have accumulated. What gets us to that next evolution? We have about 40 minutes for discussion. Open discussion so it would be great to hear thoughts from this group.
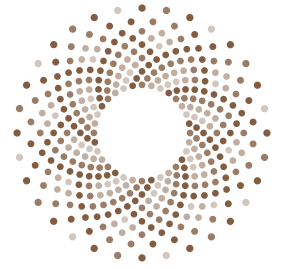
Professor Rudolph Tanzi
Director of the Genetics and Aging Research Unit and Professor of Neurology, Harvard Medical School

Two great talks thanks so much. My question is when we talk about disease modifiers, we talk about modifying disease symptoms and that is what the FDA expects us to do with an Alzheimer's drug – helping with cognition, learning and memory. But we all know this disease starts decades before in terms of pathology. So, when will we start seeing movement in trial and the FDA interested in modifications of disease at the pre-symptomatic stage? Removing amyloid and tau pathology a decade or two before symptoms. I know the February 2018 guidelines were moving in that direction. But does anyone here know if there is any prediction when we will start see the FDA inviting trials of that type using biomarkers.

Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

Well they already have actually Rudi. So Billy Dunn participated in that 2018 framework. And then just a few months after the framework was published, he actually published some draft guidelines that Rusty Katz had put out. They basically overlaid on the NIA-AA framework a staging system from 1, I think he identified it though to 4 but he presumed it went through to 5 and 6. So we can share that website, we can put it in the chat, but it does actually call out the pre-symptomatic.

Professor Rudolph Tanzi
Director of the Genetics and Aging Research Unit and Professor of
Neurology, Harvard Medical School

I understand that but what I am staying is it is there in theory and it is there in structure
but is anyone doing that is the FDA actually open to people doing that?

Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

Yes, we are doing it. Certainly A4 is doing that. The API Generation trial is doing that.
Just because the drug had some issues it had to stop. Eric Reiman is on here. The DIAN
group is doing that. So it is happening at least for amyloid.

Professor Rudolph Tanzi
Director of the Genetics and Aging Research Unit and Professor of
Neurology, Harvard Medical School

A4 is looking long term at whether you are reducing the risk of cognitive decline, so it is
still not technically strictly a biomarker trial that was what I am asking about.

Professor Jonathan Schott
Professor of Neurology, Dementia Research Centre, UCL Institute of
Neurology

I agree with the comments about the need to consider trials earlier, and that the advent
of fluid biomarkers for screening is particularly exciting. Another pragmatic issue we
may need to consider is whether it is possible to influence the regulators to speed up
the approval of studies. I have been very struck with what we have learnt from covid-19,
where drugs have been developed and licenced extremely quickly – so quickly that
in some cases people offered vaccines have been suspicious that corners have been
cut. That tells me that as a world community we have got used to the drug regulatory
processes being very slow. Can we learn from the covid-19 experience not just in terms of
drug discovery and biomarkers but also to accelerate the regulatory process e.g. having
aspects moving forward in parallel rather than sequentially?

Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

That is a good point Jon and I think learning from all these experiences are going to be
really important. Eric?
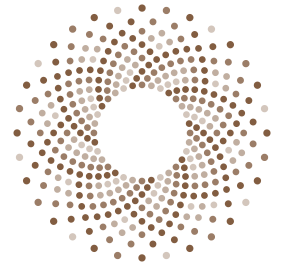
Professor Eric Reiman

Executive director, Banner Alzheimer's Institute and chief executive officer, Banner Research

Thanks Maria. I wanted to follow up in response to Rudi's questions. There are these prevention trials that are going on with a primary end point being either a composite cognitive test score or time to clinical end point. In the meantime, there is strong interest in seeing what happens with ongoing trial in both the symptomatic and pre-symptomatic states, about the relationship between a treatment's biomarker affects and clinical benefit. If for example aducanumab, donanemab and other treatments are confirmed to have a clinical benefit there will now [indistinct] be an opportunity to clarify the extent to which different biomarkers treatments with different biomarkers affects [indistinct] are associated with clinical benefit.

While we would all love to use biomarkers, say our interest in two-year prevention trials with biomarkers endpoints, there are a lot of things that could go wrong with biomarkers and trials. So, we would like to be informed by those studies, particularly those that have demonstrated to have a clinical affect. To figure out which of these biomarkers are theragnostic and might be ultimately deemed reasonably likely to be associated with clinical benefit such that they could lead to accelerated approval. I think there are opportunities for that. We look forward to seeing the results with aducanumab and donanemab. We have already seen some CSF reductions in p-tau for instance we would like to see other downstream biomarkers and in particular including NFL. With the advent of blood-based biomarkers, you can go beyond the paucity of individuals who have had for instance lumber punctures or certain imaging measures to have everyone at every time point with blood-based biomarkers to show that relationship.

If we can do that that will help to inform drug development, it will help to inform possibly the accelerated approval of treatments, so that relationship will be a very important call for us in the next couple of years.

Dr Maria Carrillo

Chief scientific officer, Alzheimer's Association

Yep absolutely. What I think that means Rudi the FDA is incredibly open they are quite forward thinking in waiting for this data to mature. To get these biomarkers embedded in trial to give us that demonstration that a biomarker alone especially very early on can give you information that later it might be representative of an improvement of a disease modifying action.
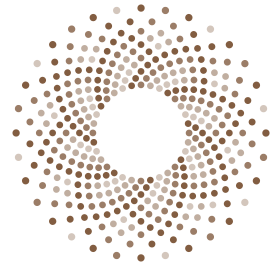
Dr Eric Siemers
Former distinguished medical fellow,
Eli Lilly and Company's Alzheimer's Disease Global Development Team

Actually, it is more of a question for this group. If you look really broadly and this is actually focussed on amyloid, we started off with gamma-secretase inhibitors and they didn't work. We then moved to BACE inhibitors, which were very disappointing because basically, they didn't work. But the monoclonal antibodies, even though they aren't all the same and some of target more plaques some of them more monomers, as a class they seem to be shifting the needle in the right direction – some of the effects are bigger than others but it is going in the right direction. So, do people agree with that?

And the second point and this gets back to the pre-clinical question is the population that we are seeing a signal are typically now MCI plus mild dementia. Which I think is important because actually you don't have to go all the way back to pre-clinical where the measuring outcome variables becomes quite difficult actually.

So, it seems to me there are two important things that have come out here. One is that monoclonals as a class are moving things in the right direction and secondly you don't have to go all the way to pre-clinical to get a signal. I just wonder if people agree with that or what they think about that?

Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

Hopefully people will start responding to that. I have a lot of people waiting for their opportunity and I think Frank was next.

Professor Frank Gunn-Moore
Professor of Molecular Neurobiology, University of St Andrews

Hello and welcome everyone to my front room in Edinburgh. I would like to say great talks guys I thought it was very interesting. We can have all the money in the world, all the best drugs in the world, but if we don't have participants willing to roll up their sleeve or swallow the pill we are not going to get anywhere. I was stuck actually with the fact Jeff that you have got 39,000 people are actually involved. I was wondering are you seeing a bit of an uptick in people wanting to get involved in light of covid-19? Because there you see people doing extraordinary things to volunteer themselves. Do you predict we will see more people get involved? That is my question.

Dr Eric Siemers
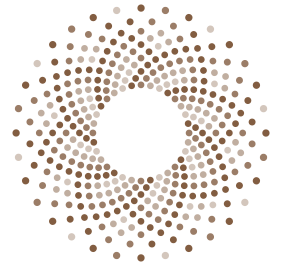Can we put our hand up in the chat?

Professor Frank Gunn-Moore
I apologise, I don't seem to have a hand to raise, so I am doing this literally...

Dr Maria Carrillo
Yes, chat works too!

Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

One of the things that will bring people out is hope. And it could be this summer if the FDA deems that aducanumab should be approved, and EMA does something similar, or gives conditional approval (who knows that that would look like), that would bring people out because of the hope. We do see that as something that moves forward the field. But if it doesn't it is incumbent on all of us, people that engage their patient and encourage, people like us non-profit patient advocacy groups, to continue to encourage patients to go despite the fact we have negative results reported. So, it is really incumbent on us. Frank what do you think?

Professor Frank Gunn-Moore
Professor of Molecular Neurobiology, University of St Andrews

I think one of the things we need to do, and a number of us are involved in various cohorts, obviously I know about the EPAD one that has a Scotland side. And it is really important that we keep those going. But the funding landscape means a lot of these cohorts are actually under financial constraints now or actually stopped. So, we do need to make sure that the regulators keep the funding going for these long-term experiments. They are not sexy in one sense. But you've literally got to keep the data flowing for the next ten, twenty years.

Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

Very important point Frank and something we will all have to work on together no doubt. Gill, Wiesje, Chris. Gill next.

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

I wanted to address the point about heterogeneity in clinical progression because even if we have great biomarkers for selection, we still have clinical outcomes as our primary readouts. And especially I wanted to address the question of clinical readouts when you are going very early. In preclinical AD, but even in prodromal AD or MCI, it is clear that selection by amyloid status alone doesn't differentiate very well people who may be years from progressing from people who may be close to progressing or are already progressing now. So maybe stratifying by tau levels will help. I am curious what people think about that? I don't know if it will fully solve the problem.

Professor Rudolph Tanzi
HAND RAISING OPTION IS UNDER "REACTIONS"

Dr Maria Carrillo
Eric S then Frank

Dr Maria Carrillo
Eric S, Frank then Gil

Dr Pierre Meulien
Maria- I would like to come in with a funders perspective when appropriate. Thanks - Pierre Meulien IMI

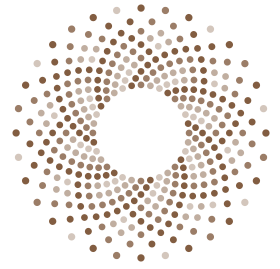**Dr Maria Carrillo**
Thanks Pierre

Dr Clifford Jack
I can make a comment on biomarker read outs in trials

Dr Mark Mintun
Maria; I can comment on the issue of doing a trial at risk while the biomarkers are validated

The second issue is the co-pathology issue which is kind of the elephant in the room. Just getting back to Mark's example of the 80-year-old and the 60-year-old who have the same amount of tau. The problem is the 80-year-old might have TDP43 that is much more actively involved in their memory loss, whereas in the 60-year-old tau may be much more directly involved in driving the memory loss. Since we don't have biomarkers for so many things that we know impact cognition – TDP43, synuclein, microinfarcts – the option we have now is just to hope that randomisation will account for that. But we have seen that there can be imbalances, even with randomisation, in rates of progression.

So, I would pose to the group the other way is to go into much more homogenous clinical populations. Autosomal dominant AD is a great example of that. But another example is patients with sporadic early onset AD, which has been a research focus for many people on this call. These individuals have fewer co-pathologies, more plaque and tangle disease driving their cognitive impairment. So, I would just highlight the importance of that population especially when we are thinking of phase 2 and platform designs which I strongly agree with. I'll stop there.

Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

I totally agree with that because as a co-principal investigator of the LEADS study I think that is a great platform but maybe I am bias about that! Great thanks Gill. Wiesje?

Professor Wiesje van der Flier
Professor and head of clinical research at Alzheimer center Amsterdam at Amsterdam UMC

Thank you very much. Great talks and great discussion so far. Great to be part of this. My comment is similar to the one that Gill also made just now. I think one of the large challenges we have in designing trials and finding treatments that work is the heterogeneity in clinical progression. So, we have just seen in the aducanumab trial for example that there was an in-balance in the rate of progression between groups.

I liked the suggestion made earlier by Mark about having a really strict biomarker selection criteria but letting go the cognitive criteria. When you look at amyloid alone however, at least you see the rate of progression is really different depending on your clinical stage. And when you add CSF-tau and p-tau it doesn't add much predictive value in the rate of progression. It is awaited what PET-tau does in that respect. So, I think that is one of the big challenges, how to better select patient groups. And I couldn't agree more that early onset sporadic AD is a great group to start with.

Professor Henrik Zetterberg
I could follow on with a comment on "pre-validation" use of biomarkers.

Dr Jose Molinuevo
I can follow on eric Siemers comment

Dr Maria Carrillo
Gil, Wieje, Chris, Cath and George and Cliff, pierre, henrick, and mark m
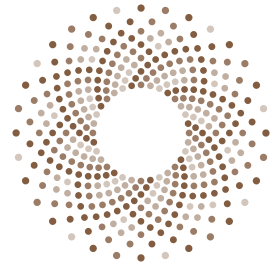
Dr Maria Carrillo
Cath, George, Cliff, Pierre, Henrik, Mark M, Jose Luis, Sandra

Dr Heather Snyder
@Jeff and Christopher - There is also a need to have trained clinicians to run these studies.

Dr Christopher Chen
Associate Professor, National University of Singapore

I would like to move away from selection into the practicalities of running trials. I was very struck by Jeff's observation on the lengthy delays in conducting trials and how tough it is to get patients onboard. And one of the suggestions he made was that we should advance regulatory engagement. So, one of the highlights of last year was listening to Peter Horby the principal investigator on the RECOVERY trail. I was struck listening to him on how he managed to get the RECOVERY trial started in less than a month. The point he made was the regulators, the IRBs, the legal departments vetting contracts, who delay trials were simply told that we had to get on with it as there was an urgent need to find treatments with well-designed randomized controlled trials and you had to take it or leave it. Now of course we are not in the same situation with AD but could Jeff comment on how we can accelerate the regulatory process because there are often long delays with ethics committee approvals and contracts and so on.

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

I wish I had a brilliant solution, Chris, but thank you for highlighting this issue. There is a lot of activity in this area. I would highlight GAP for example as one of the organizations, it is trying to focus on trial efficiency as well as a single IRB that has been useful. The Association has had some initiatives along these lines. But we are far, far from solving this. The covid example is so great because it shows it is possible, if we can get everyone to agree and prioritize this effort.

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

Thank you everyone it is lovely to see you. I wanted to come back to Jeff's talk around recruitment because there was something that was really striking about one of your points Jeff where you spoke about the different trial period when dividing groups into preclinical, MCI mild, moderate etc. You made the point about it being a fifty/fifty split between the recruitment period in the preclinical. But actually, it was far greater if you went to MCI/mild and again greater if you went to mild/moderate. So, it took five times as long to recruit relative to the treatment period for mild to moderate than it did for preclinical.

And from my experience, we always thought it going to be really hard to recruit pre-clinical, that we were going to have a 10-1 drop out rate, that it was going to be difficult to get people in through the door to understand these trials. But we see from your graph that actually it is much easier, and I just wondered if you wanted to comment on that because perhaps we can learn from it? And I know Reisa's on this call and will have huge experience as well.

Professor Clive Ballard
Biomarker ckearly important for treatment target and reducing heterogeneity, but some of the concurrent factors such as cerebrovascular disease drve the rate of decline -so we do have to be careful not to select non declining populations
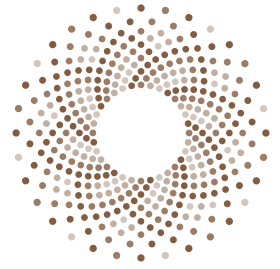
Dr Christopher Chen
Dear heather, you are absolutely right, especially given the increasing complexity of trials

Dr Maria Carrillo
Clive agree, then on the other side will our drug be generalizable, to a gen pop that has the usual many comorbidities…. but need to start somewhere to look for successes.

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

Thanks, Cath, for those comments. One of the peculiarities of course is that the clinical trials are very long so there is also a longer opportunity to recruit because the trial is going for a longer period. When you are comparing that exposure period to the recruitment period you have a much longer exposure period you are contrasting. We have done a good job as a field at using some levers to attract participants like those with a family history, for example. Also using cohorts of normal elderly; and, of course, "normal" elderly means many of them have a substantial amyloid burden in the brain. We have had had a lot of innovation in that preclinical area, and we should look for innovation in other areas as well; we can learn from those successes in preclinical disease.

George Vradenburg
Co-Chair, Davos Alzheimer's Collaborative

A couple of initiatives I would like to mention that could use the brain power that is on this particular zoom call. One is a platform study that GAP is doing that is called Bio-Hermes which is taking about twelve different biomarkers and comparing their predictive value to PET scan. This is with a view that if we can find a pre-screening biomarker that can be introduced immediately after consent then you could reduce significantly the time and cost of recruitment based on very heavy biomarker work very early in the recruitment process.

While Jeff's slide says 40,000 participants my guess is it is 150,000 volunteers. A lot of people are volunteering but because of screen fails they are not getting randomised. So, trying to find an efficient way, very early in the patient processing process, that reduces significantly the rate of screening fails I think is a way to shorten that recruitment period. Because it is not just recruitment that forms the challenge, it is the sorting and stratification of patients for trials.

The other is the Davos-Alzheimer's collaborative that some of you may be aware of, announced at the Davos meeting. It is a $725 million effort over the next six years to invest in biomarker development and upgrading research cohorts in non-European legacy populations around the world and comparing them to the UK biobank. That would permit us to identify new biomarkers and new targets in a much more heterogenous discovery research platform. Second prong is a global clinical trial structure. We will announce I believe the first transatlantic trial, partnering with EPAD, later this year. And the third is getting our health systems, Jeff made the point about our chaotic and disorganized ecosystems which this is part of, to be able to identify patients at the right time for the right drug.

So, there are initiatives here. Lenny has been involved in the Davos Alzheimer's collaborative and I thank him for doing that and thank him for organizing this call, but there are some efforts underway now to try and address what Jeff was suggesting.

Dr Heather Snyder
@Christopher - which is the COVID study you mentioned in your comment?

Dr Christopher Chen
Dear heather - the RECOVERY trial which is successfully recruiting globally to trials of various different treatments for covid-19 - it could be a model for dementia trials consortia https://www.recoverytrial.net/
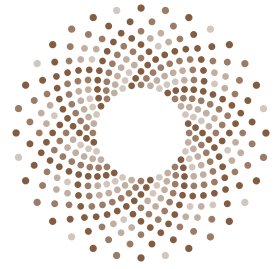
Dr Maria Carrillo
Pierre, Henrik, mark m, jose luis, Sandra, david h

Professor Clare MacKay
I was also thinking about lessons to learn from RECOVERY. Every patient a (potential) participant, and every hospital physician a (potential) trialist.

Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

Thank you, George. Cliff Jack, I know you have got a lot of thoughts about this since the 2018 framework what are your thoughts about the future?

Professor Clifford Jack
Professor of Radiology, Mayo Clinic

Well actually I was going to address a couple of points made by Rudi. One question that was asked was when are trials going to start that have biomarkers as primary outcomes and the answer is this has already started. The primary endpoint in A3, which has started recruitment, is not a clinical but a biomarker endpoint. The primary endpoint in A3 is the reduction in the rate of accumulation of amyloid on amyloid-PET. And a secondary outcome is the reduction in the rate of tau accumulation.

The second question was when will the FDA start to consider biomarkers as surrogate outcomes in phase 3 trials. My understanding of Billy Dunn's thinking on this is that the FDA is certainly open to the idea but will only consider biomarkers as primary outcomes in phase 3 trials after it has been shown that therapeutic movement of a biomarker is accompanied by clinical improvement or a reduction in the rate of clinical decline. This should be shown in more than one independent phase 3 trial. An analogy is LDL cholesterol. It was only after it had been shown that reduction in LDL cholesterol by statins produced better cardiovascular outcomes that the FDA began to accept reduction of LDL cholesterol as a primary outcome. So, the FDA is open to this but with that caveat.

Professor Henrik Zetterberg
Professor of Neurochemistry, University of Gothenburg

Yes, thank you very much for these discussions. I just wanted to make a point on the pre-validation use of fluid biomarkers, because sometimes I feel like those of us who are developing biomarkers might also slowed down things because of lack of validation and standardisation. And this is what we do in the Global Biomarker Standardisation Consortium and other consortia. It is quite heavy work to get biomarkers fully validated, standardised, and approved, and we might not have time to wait for this.

My suggestion, to speed up things, is that we already now, in collaboration with the pharma companies, use the most promising blood biomarkers according to the literature (Abeta40, Abeta42, P-tau forms, NfL, and GFAp) on samples from completed clinical trials to learn more about how the biomarkers change in response to different disease-modifying drug candidates. This would tell us a lot about the biomarkers (perhaps more than about the drug candidates), and it would help us shortlist the biomarker(s) that we

Dr Maria Carrillo
Pierre Mark m, Jose Luis, Sandra, David H.

Dr Maria Carrillo
Sorry missed Pierre.

Phyllis Ferrell
Great point by Pierre... we need to find an "in-market" solution to healthcare system readiness, because the underlying ecosystem is the fundamental problem for recruiting CTs and all of these solutions are not sustainable - is there a way that this group can connect on the public health side of the work going on in brain health/AD detection?
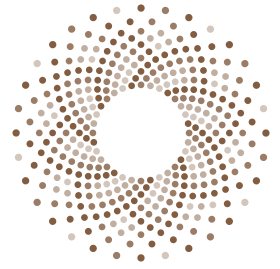
should put all our efforts on getting fully validated, standardised and approved. If we could somehow get access to samples from the trials that have been completed and done with biomarkers and collectively form some sort of consortium; I know you are working on this Maria together with many of us, so that we could do these biomarkers, we could likely find one or two biomarkers that often give interesting information, and those could be in focus for all the work needed and pave the way for the rest.

Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

Yes, and I think the field is trying to do that and we are trying to get more samples into the field and certainly I think the new IDEAs study as Gil knows we are aiming to get 6000 bloods that are diverse and those will be collected by our study and Rob Rissman, so that they can be distributed equally to the deserving biomarkers, first come first serve, so I think that is very important Henrick. Pierre sorry I missed you earlier I think you wanted to make a comment from the international funders' perspective.
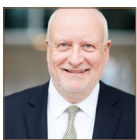
Dr Pierre Meulien
Executive Director, Innovative Medicines Initiative (IMI)

Thanks a lot Maria and thanks to Lenny for inviting me. It is a really interesting discussion. I just wanted to come back on one of the things that both Jeff and Frank were mentioning which is one of the conundrums around sustainability. And this is a real issue. Many of the funding initiatives that we start but as, as I like to think of IMI, a catalytic funder. So EPAD a fantastic project had a beginning and an end. Of course, we have a vested interest in these things being sustainable, otherwise you could say it was a waste of money, but the sustainability plans are supposed to be built within the project. Some are successful, some are not. It is very unfortunate it cannot be IMI funding that sustains these things otherwise we won't fund anything new as you can imagine. We have this collective issue, and we need to embrace different models on how we sustain these things because as Jeff said they are very important. I think what he has said about accelerating phase 2 is absolutely right and a lot of these things through collaborative research platforms can be absolutely central to accelerating things. But we need to find ways of sustaining these things through new business models or whatever. So I just wanted to mention that as a common and collective issue we all have.

Dr Mark Mintun
Vice-President of Pain and Neurodegeneration Research and Clinical Development, Avid Radiopharmaceuticals

I I want to go back to some of the comments about going earlier in the preclinical AD progression. I will make a comment then ask a question. The comment is that you may or may not be aware of the true risk that people feel like they are taking on when they take on these large preclinical Alzheimer's trials. Because the patients diverge really

Professor Clive Ballard
To step back a bit -fully endorse Jeff's view re the importance of phase 2 platforms -and we are working hard to contribute to this. Not much mention of NPS trials -I think nursing home phase 2 platforms vital part of addressing the recruitment challenge in that space

Dr Heather Snyder
@Clive - Howard Feldman and team from UCSD have been working on a drug trial - PEACE-AD - in nursing homes across the US. There have been some unique challenges that the study team has faced in this environment, even before COVID.
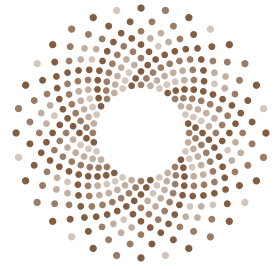
slowly the trials are not only very expensive, but they take a long time. So you have both a lengthy and expensive risk. Now someone says let's do a biomarker that may not, in the end, be pertinent, but we think we will know what it means by the time we're done. So, those risks keep mounting up.

On the other side, you can look at things that might reduce the risk. The hint that the drug works in early AD is always the biggest thing. That always changes everyone's mind so that is the big one. And then the hint that the biomarkers are making progress, some sort of trajectory as you are seeing more and more, first cross-sectional then people are doing them longitudinal, maybe not in a drugs study. So, you are absolutely right to try and get as much biomarker in cross-sectional and longitudinal studies. And these new ideas for biomarkers are so exciting, so I think it is fantastic we are doing that.

Both of those two things make a difference. The other thing though is if there is any way to make trials faster and cheaper. I want to sort of just provoke the group because now the conversation after we have watched how quickly we were able to deliver new medicines for COVID-19 is wait a second do we have to do the trial the same way? Do we have to go into sites, the typical normal Alzheimer's sites? Can you recruit virtually, can you consent virtually, can you send them for a blood test at the neighbourhood Quest? My thinking is would future trial participants would embrace that.

But now I realise we may be too rigid in the way we think about a trial. And so, I am asking does the group think it is possible that we could have highly virtual trials where people are recruited online, maybe go to a PET centre on their own? Perhaps someone gets an appointment for an infusion centre if they are getting antibodies, and we eliminate the traditional site-based thinking. Is that viable for such a group like preclinical AD?

Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

I think that is a great question. We are doing that as a pragmatic study for new IDEAS because we have to. It is a pragmatic trial. People are going to their own PET scans and making their own phlebotomy appointments through Quest. It is very much more like that. The trick is are we going to be able to tolerate that for clinical trials where we feel like we have to be much more rigid about everything because there is an asset at risk here? A lot of that question actually goes back to you Mark, it goes back to the question of what pharmaceutical companies are willing I think to tolerate because the FDA would be open but are pharmaceutical companies willing to tolerate the looseness of the type of effort? That really is a question for industry maybe?

Professor Frank Gunn-Moore
How to innovate: as a biochemist, I always wonder should we (and not just the dementia world) have a scheme, that I would liken to the human genome project, to make inhibtors to every single enzyme, irrespective if they have been linked to a disease or not. You could rational which enzymes first, and make allosteric and direct inhibitors. I am well aware that not every drug is an inhibitor!

Professor Ricardo Allegri
I agree with the proposal of Jeff to look for the acceleration of phase 2 with a global platform (like DIAN), a big cohort with the same controls and different branchs of research
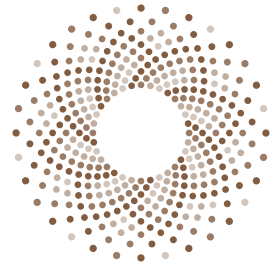
Dr Mark Mintun
Vice-President of Pain and Neurodegeneration Research and Clinical Development, Avid Radiopharmaceuticals

I think from my point of view there is a stepwise increase in the ability to think about these looser trials because of Covid. Because there were so many successes where people took steps at risk admittedly, but they did things virtually. There were far more things done virtually. I would love to know whether people think you could do the A4 like that, is that something you can do virtually, do you need to have the person come into the office to do that? Would people like that? The patient would love it I am sure! But would we all agree? It is going to be a community here, I think. But there are pharma companies that are excited by the idea of going faster and maybe being a bit more flexible but then of course you can recruit more patients too, so you win on numbers maybe?

Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

I think covid has taught us it is time to innovate right? That we have been kind of stuck. Jose, I think you were next then Sandra, David and Mike Devous.

Dr José Molinuevo
Vice President in Clinical Development Neurodegeneration, Lundbeck

Thank you, Maria. Great talks and lovely to be here. And yes, in answer to Mark I think we have to start thinking at least hybrid designs. And maybe at the beginning not risk the main outcome measure of the trial but many other things we can do remotely, that is for sure.

But my comment when I raised my hand was following up on Eric Siemers comment which is a very valid point. We are seeing with anti-amyloid antibodies, at least with aducanumab, Ban2401 and donanemab, a very early cognitive change, in a population which is quite late in the disease from a biological perspective. on top of that we are seeing other things. We are seeing that change happens quite early and there is not that much impact on downstream neurodegeneration.

So, I personally, and I share this thought hypothesis with the group, and I would love to know what they think. I think that part of that benefit is through removing the toxic soluble amyloid species from the synapse. And that clearing has an impact on cognition and that is why the effect is so fast and in fact we are seeing changes in neurogranin that are greater than the changes seen in NFL for example in some of those trials.

So that potentially brings the opportunity to think with some of these compounds in a double mechanism of action. One may be directly on neurodegeneration another can be a faster action that is not that much disease modifying but is still improving symptoms.

Professor Hilkka Soininen
I agree infrastucture is important.

Professor Linda Van Eldik
The mixed pathologies/co-morbidities issue is very important, especially in older individuals. Need coordination of optimal ways to do combination therapy trials and prioritize which combinations
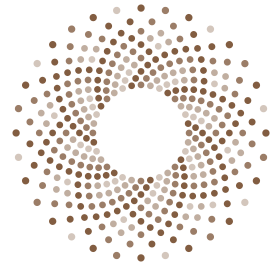
Dr Eric Siemers
ADNI4 is likely to include cognitive testing that can be done remotely. Various technologies being evaluated now.

Professor Hilkka Soininen
Great talks and discussions, thank you.

Professor Sandra Black
Professor of Medicine (Neurology) at Sunnybrook HSC, UToronto

We all yearn for precision medicine approaches to dementia, whereby we aim to identify people early, including the pre-symptomatic stage with pathological disease targets that we can beneficially modify. The idea of selectively identifying very homogenous populations that we can target has worked well in oncology with some types of cancer, but it won't be so easy in dementia because we are dealing with very complex, co-occurring pathologies especially in older age. We are pleased with technological advances enabling identification of relevant misfolded proteins in plasma as well as cerebrospinal fluid, which correlate with molecular PET imaging, which in turn has been validated in post-mortem studies. We still need to identify synuclein and TDP43 proteinopathies in plasma which can keep company with AD proteinopathies, affecting symptom presentation and clinical course, especially in those over 80. We also lack validated plasma biomarkers for cerebral small vessel disease, which is visible on T2-weighted/FLAIR MR and present to some degree in >95 % of elderly.
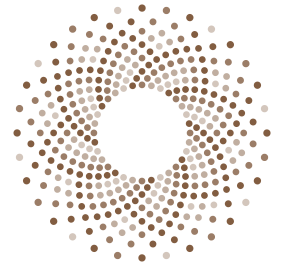
Another desideratum is not just to identify proteins in biofluids and molecular PET scanning, as well as atrophy patterns and vascular pathologies on MRI in symptomatic individuals. Rather, given latency periods of pathology accumulation, we need to detect them pre-symptomatically, the most opportune stage for rescue therapy and secondary prevention. Identifying the mix of proteinopathies at all disease stages will be important for treatment and prognostication, along with detailed individual endophenotyping, including demographics, medical, psychosocial, vascular history and lifestyle habits, current clinical, cognitive, mood, behavioral and functional status, and their genetic profile. These are indicators of overall frailty, and brain/cognitive reserve, which influences symptom onset and progression rate. The plasma protein biomarkers reflect pathologies in the brain but can also reflect degree of brain damage, inflammation, blood brain barrier leakage, etc, and we will always need standardized quantitative MRI to assess incidental pathologies, atrophy patterns, subtypes of cerebrovascular disease, some of which may require action and also determine treatment eligibility, such as siderosis and microbleed counts for anti-amyloid antibodies. Retinal imaging may also help triage. Molecular PET scanning of amyloid and tau will be necessary to map burden and topography of protein deposits. PET signatures for metabolism, neurotransmitters and inflammation may also be useful depending on symptomatology and availability. Obviously cost effectiveness will be a major concern if Disease Modifying Therapies (DMT's) do become available, though targeted delivery methods using low-field Focused Ultrasound may mitigate costs.

We also need to find biomarkers for small vessel disease to better understand cerebral microvascular health. There are candidates, such as oxylipins, potentially targetable lipid metabolites (eg soluble epoxide hydrolase) which regulate polyunsaturated fatty acid oxidation and may be associated with white matter hyperintensities. We need to recognize heterogeneity and seek plasma biomarkers of the common pathologies co-occurring especially in the elderly. Unless we account for co-morbid neuropathologies, we may fail, as people will progress differently depending on common comorbidities in brain and body, sometimes subsumed in the concept of frailty.

Dr Maria Carrillo
We will save the chat so that we can include these comments, thank you all!

Detecting neuro and microvascular pathology profiles in the blood will revolutionize our field, and give new insight and impetus for understanding temporal dynamics in multiple domains using Machine Learning techniques. We need strategically-informative, standardized MRI brain scanning to enable to quantifications of regional atrophy patterns, and of subtypes of cerebrovascular pathologies. Microstructural integrity, blood flow patterns, resting state functional connectivity, and cerebrovascular reactivity could also be included with 3T MRI availability and would provide insight into baseline structural-functional connectivity patterns that could become outcome biomarkers of therapeutic benefits. Cost-effectiveness guidelines will be needed for baseline imaging biomarkers, monitoring and as efficacy measures, in correlation with clinically meaningful outcomes at various disease stages, should DMT's become available.

This same approach can be adopted based on multimodal assessment in the pre-symptomatic, prodromal and dementia stages. We can start understanding the complexities while people are still alive at different stages of evolution of their vascular-neurodegenerative processes, and how predictive these biomarkers are as modifiers of decline rates and patterns. This will enrich our understanding of vulnerabilities and resilience.

Genetic profile will also obviously be important as we move toward Precision Personalized Medicine approaches. Advances in in-vivo understanding of natural history of decline with comorbid pathologies at different ages and stages, and their moderating factors, will likely mean new approaches including clinical trials of combination therapies, always in conjunction with optimal vascular risk factor, sleep health management and healthy lifestyle choices, including exercise, diet, social engagement. Hopefully, some day people won't be excluded because of complex mixed pathologies, but will need cocktails with appropriate expectations concerning their decline trajectories, if no treatment were offered.

Professor David Holtzman
Andrew B. and Gretchen P. Jones Professor, Hope Center for Neurological Disorders

Thanks Maria. Sandra, I agree with the comments about other biomarkers we need to still develop. But I raised my hand after Eric Siemers comment and Rudi's comment because I think Eric made a good point that there does look like there is some obvious therapeutic signal in MCI and early dementia with some of the anti-amyloid antibodies. And I think there should be a lot more effort in that stage of the disease with some of the other targets to really try to an even better effect than has been seen so far. But I do think, and this has been brought out by others, that as much effort as possible we take in developing treatments and diagnostics should focus on the fact that there is such a long preclinical stage of disease and we need to focus as much money and effort as possible in doing trials to prevent or delay the onset of the clinical manifestations of the disease. That is where we are going to have the biggest impact on public health. I know in this conversation there are many caveats to doing that in a proper way but anything we can do to do that more and more is going to lead to a much better outcome in the longrun.
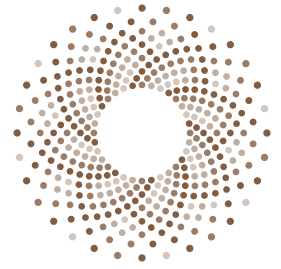
Dr Mike Devous
Vice President of Imaging Development, Avid Radiopharmaceuticals

I just want to follow up with something Mark said initially about combination therapies that might be aimed at either the disease pathology or the co-morbid pathologies that we know are present. If we were in a world with aducanumab or donanemab approved I am wondering what patient populations would be available to participate in clinical trials. It seems that we might have a one- or two-year window to figure that out. What lessons can we learn from the covid pandemic to help us address this question? How do we recruit patients that aren't already on an approved therapy? It might mean we are going to focus on earlier populations or on ethnic minorities or other groups that are not really engaged in clinical trials. We likely need that one- or two-year time period to figure out how clinical trials will move forward in the face of an anti-amyloid approved therapy.

Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

All those are really important questions and one of the things that Lenny challenged us with from the start is thinking about where do we go from here? What we have is the mature phase threes, much of them, as we saw from Jeff's talk focussed on amyloid. Certainly, the donanemab example of using a tightening of the patient selection process though a biomarker that has also matured and helped us to do that.
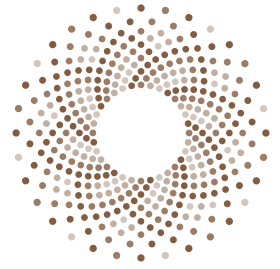
So, we have got a picture of a field starting to mould a little bit better right? It is not just all comers in this huge funnel. We are trying to frame that funnel a little bit more. We recognise we don't have the populations that need in those studies. We recognise there are early populations that we need like LEADS and DIAN that can help us with early pathology that maybe are not as messy as people who are an average age of 73. So, we have all of these things in place. So, what are we missing? We are trying to do all of it. We are trying to do it all with blood and we are trying with CSF. So, what are we missing? What should be pushed forward faster? Any ideas?
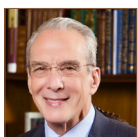
Professor Jeffrey Cummings
Founding Director, Cleveland Clinic Lou Ruvo Center for Brain Health

Maria can I comment on that? I think infrastructure. These cannot just be hit or miss, one-off initiatives. We have to have infrastructure. That is why I emphasized the platform trial. I think that would be very useful for that particular set of problems. Right now we have the ACTC for example. It will do five trials in five years. But we have 126 molecules in play! We have a pitifully small infrastructure to accomplish the goals that are needed. I really appreciated Pierre's comments that we need to think about sustainability in new ways. My own feeling is we have to concentrate at the legislative level about creating infrastructure.

Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

I think infrastructure is absolutely very critical. Anyone else what we should do more of?

Professor Sandra Black
Professor of Medicine (Neurology) at Sunnybrook HSC, UToronto

Can I just comment on that? Because I think maybe the analogy is cardiac care and cancer care where there are thousands of more people because they set up networks and they have infrastructure, government funded infrastructure. And the reasons we may have PET scanners available in Ontario in major centres for example is because of cancer and they need PET scans for their cancer treatments.

So, I think we need the same thing in dementia, but we are going to have to have a disease modifying therapy to get there. I think the pre-symptomic stage is the most promising especially if we can identify it because then the brain isn't as injured as it will come over the next ten and fifteen years. So I think it is like detecting cancer early. Detecting the proteopathies early. Because that is the way to go.
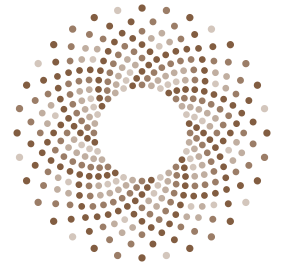
And then in our various societies, we can, as we advocate for cancer care networks, advocate for dementia care networks because early detection being really important and having a treatment!

Dr Maria Carrillo
Chief scientific officer, Alzheimer's Association

I agree with you Sandra. And I think June might bring a big hope. Many of you might not agree with the FDA if they do decide to approve aducanumab. But that approval will bring a lot of hope. And it may well galvanise lots of people to try and not only get the drug – and we will have other issues that we would have to deal with as a society certainly in the US and also in Europe afterwards depending on what EMA does. But also, in the discussions we have already started with a group of experts on how we continue to enrol people in clinical trials in an era of an approved treatment like aducanumab. We have slightly been in this space before ten, twelve years ago, when we had the other treatments the first-generation treatments in Alzheimer's. I remember these discussions then about how people would behave. And right now, we are having discussions with the national multiple sclerosis society because multiple sclerosis has already been though this.

There is lots to be learnt on this, but it will make a change. And it will be another opportunity. Just like covid provided us with an opportunity to be innovative as Mark put forward about our clinical trials in the future. It is another opportunity to innovate

and move the field not by nudges and baby steps but by leaps. And that is what we need. So with that let me thank you and hand to my co-chair and my friend Philip Scheltens to wrap some of this up but this has been a great discussion.

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

Thank you, Maria, because of covid we should reflect we can discuss this at the same time at the same moment with sixty really thoughtful leaders in the field, we wouldn't have done this before because of travel etc.

So, I think a couple of points a couple of points Jeff raised were really crucial. A thing I took away was that it is important to realise that there are more targets now than amyloid and tau. That the ecosystem is really not appropriately designed yet. We need to better on that. The infrastructure was mentioned as well. Platform trials is one way to go. I think phase 2 is where the most emphasis should be and as Jeff showed there is a lot there. I was a little bit worried about how little there was in phase 1 – and I hope the explanation is what Jeff said – because phase 1 is the pipeline that we need to optimize the future trial landscape.

But all in all, the biggest problem is recruitment. Trials take too long, and recruitment takes too long. So how can we help this? Biomarkers were mentioned. Biomarkers for pre-screening are I think very important. Trial ready cohorts were mentioned. Extremely important. The homogenous groups that were identified are familial AD patients as well as non-familial early onset AD patients. But on the other hand, another lesson of covid is that it is possible once the urgency is so high that you have all the patients going into the trial. I also look to the oncology field and the cardiovascular field where this is much more common. I envy my colleagues where they basically put everyone in the trial. And we in the field lag behind a lot. We have lots of trials, we have the drugs to be tested but we do not succeed in getting our patients into the trails. We should learn how this was done in covid. Especially using all the materials we have now, the virtual way of doing trials, virtually recruiting patients, perhaps doing the first few visits virtually before they come to clinic.

Those are all the elements we took from this discussion. I would say in that sense we can be optimistic because we have done a lot in the field already. We can see the biomarker development we talked about last time is a good example of what the field is capable of and now the next step is testing all the drugs that are in the pipeline and having as many shots on goal as possible.

So, I would conclude with the observation I take from this discussion that the future looks brighter than the past did. With that I will hand over to Lenny to close.
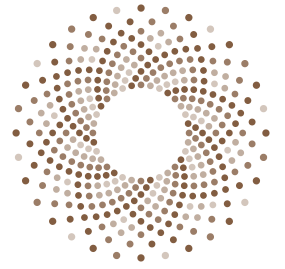
Lenny Shallcross
Executive director, World Dementia Council

And on a very optimistic note Philip! A bright future ahead of us on what is still, as I said at the top, a bright sunny day here in London! So just to say very briefly we will be following up with a transcript of the discussion. Thanks to Maria and Philip and Jeff and Mark. To remind you the previous discussion and the essays are online. With that I wish you all good morning, good afternoon, and even for those in Japan who are up late online, a good night. Thank you all very much.

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

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