World Dementia Council
Leading the Global Action Against Dementia

2024 WDC Summit

The next decade: Therapies and brain health

Transcript of the World Dementia Council Summit

26 March 2024

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World Dementia Council
Leading the Global Action Against Dementia

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

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



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We are delighted to introduce the transcripts from the 2024 World Dementia Council Summit. We are grateful to everyone who took part in the meeting.

This is an exciting moment for our field and the conversation we had in London reflects this moment. There are treatments for Alzheimer's disease. And, over the decade ahead there will be more treatments, both for Alzheimer's and for other forms of dementia. But today's patients cannot wait for those future treatments. It must be for the patient, with their family, and advised by their clinician, to make the choice of whether to access approved treatments.

As we work to deliver these first approved treatments, it's clear there are big challenges ensuring access to patients who can benefit from these treatments. No health system around the world is prepared for where we are today. And in the decade ahead along with more treatments, health systems will need to deliver new diagnostics, particularly blood-based biomarkers, and prevention initiatives. It is our responsibility to ensure these systems are ready to deliver these innovations patients. This means we must bring people into the health system earlier in the disease progression. Patient and public awareness and understanding is going to be key.

This marks a fundamental shift in the way health systems address dementia. This will be a challenge for every country's health system. And it is important that as a global community we share our thinking and learning, and alongside that collectively advocate for progress. If one question we face is how you deliver innovation — be that a treatment, a new diagnostic or a prevention programme — another is how you drive innovation faster? Our challenge, from the lab to regulation, how do we enable disruption to make progress faster.

And throughout this decade of disruption ahead, people living with dementia will still need care. It is care and support systems that need disruption. Disruption will come in part from new technology but also from new patients. As we diagnose people earlier in the disease trajectory care and support will be disrupted.

These are all themes we explored in our London meeting with global experts from around the world. There conversation will be the beginning of activities over the year as we develop with all of you a report on the global dementia challenge that we will launch at the 2025 WDC Summit on 25th March 2025 in London. We hope to see you there.

Philip Scheltens
Chair

Joanne Pike
Vice Chair

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Therapeutics and diagnostics: 10 years of transformation?

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Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

My name is Philip Scheltens for those who don't know me. I'm Professor Emeritus of Neurology and founder of the Alzheimer's Center in Amsterdam. I have moved now to private equity. I'm the head of the EQT Dementia Fund which invests in new therapies for the next 10 years or longer.

That's also the theme of today at what is really a sort of landmark moment. Last year when we met, we were still waiting the approval of Leqembi. Now it has happened. There is a sort of shared optimism in the field. If you go to ADPD or AAIC — or even CTAD, and that used to be a very sobering event because nothing happened, nothing, everything failed — you now see people smiling. Now, things are moving. So, there's optimism, but there are also challenges.

And I think, first of all, the challenge is that not everybody endorses this optimism yet. The therapies are not approved globally yet, so we're facing challenges. And if are approved, how do all these individuals get these treatments? How about getting diagnosis earlier and earlier? How to implement blood-based biomarkers, for instance?

All these things will matter for the next years. And of course, we also have to realise that we're just at the start of a whole new beginning, because these disease modifying therapies that we're now discussing are only the start of medications that we will see over the next 10 years. These will range from active vaccinations, small molecules, intrathecal therapies, gene therapies, and so on. There's a lot that is going to happen in the next 10 years.

The session is on "therapeutics and diagnostics: 10 years of transformation?" What does that mean? What are we going to do over the next decade? Will it — I think it will be — but, will it be a decade of transformation? And how does the panel see this future? You will see from the panelists that they are really coming from different backgrounds. So, they hopefully will give a perspective on the next 10 years from their different backgrounds. So having said that, I would like to introduce them:

- Fiona Ducotterd, Chief Scientific Officer at the Alzheimer's Research UK UCL Drug Discovery Institute (UDDI)the ARUK Research UK UCL Drug Discovery Institute;
- Niranjan Bose, he's Managing Director of Gates Ventures. He's on the venture side in terms of funding research;
- Art Toga provost professor of anatomy, neurology, psychiatry and behavioral science, at the University of Southern California; and
- John O'Brien professor of old age psychiatry here at the University of Cambridge.

[short inaudible section]

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

Any spontaneous reaction already from the audience? Agreement? Disagreement? I'm happy that you brought up the other dementias as well, John. I think it's always forgotten that we are talking about Alzheimer's but there are many other forms of dementia. So just a question for the panel in the next 10 years do you think there will also be adequate treatment, and there I really mean treatments, maybe perhaps even causal treatments for these other degenerative diseases, the other dementias?

John O'Brien, *Professor of Psychiatry Cambridge, UK*

There are trials ongoing, as we know, there are just not many. If you look on clinicaltrials.gov, you find that of all the dementia studies about 80% are Alzheimer's disease, 4% are Lewy body about 10% for FTD. So, these studies are ongoing but they are really going to have to be done at improved scale to produce benefits over the next 10 years. We know this. Because how long have we had the monoclonal antibodies for, at least a decade, with different studies ongoing. So we know we really need to up our game with studies on the the other dementias. And vascular might be the most challenging of all for various reasons, including challenges over defining the right targets for interventions.

Fiona Ducotterd, *CSO, ARUK UCL Drug Discovery Institute*

I was just going to add that is where the underlying research into each of the different dementias, the common and different features of each of the dementias and the trajectory of the diseases are also important. People presenting in a memory clinic are given a very similar diagnosis and by then it is late. The improvement in biomarkers, particularly early ones, you were mentioning earlier will allow us to identify what type of dementia someone has early. And then we can begin to understand the underlying biology/causes and also what changes in terms of the different biomarker trajectories overtime across dementias and what we may use to intervene. But that change, getting from how diagnosis happens now to how it will happen in the future, potentially before symptoms/damage, is not going to happen overnight and we will also need the tools for intervention being progressed alongside.

And that is something we really need to drill into defining what type of dementia someone has and what the underlying biology is so we can exploit therapeutics that target biology we already know about and also identify other new targets and translate those mechanisms into therapeutics. And that is the exciting moment we are at now where we enrol actual humans into our trial and collect data using initiatives like ADDI we can use in the future to tie which intervention to the biomarker signature at that time.

Art Toga Provost, *Professor of Ophthalmology, Neurology, Psychiatry and the Behavioral Sciences, University of Southern California*

I was just going to say I think the notion of differences in dementia are really important. Right now, one of the most exciting aspects of plasma-based biomarkers is finding people in an efficient way that's affordable. You can go to your health centre and when you get your test for cholesterol, well soon you'll be taking a blood test for how much amyloid is in your blood or how much tau.

What will be important for policymakers and funders is encouragement to fund experiments and projects that allow us to create a wider family of plasma-based biomarkers to look at other dementias that may have unique characteristics so that we can better stratify who is where.

If you live close to a high-performing academic medical centre, you have one kind of care. If you live out in the countryside and that academic medical centre is too far away, the likelihood that you have the opportunity for getting access to a brand-new blood-based biomarker or some other set of tests is much lower. So, we must find an affordable way to make these tests available to everyone so that we can collect the data from them all and make the decision about what therapy is the most appropriate.

Niranjan Bose, *Managing Director, Gates Ventures*

Just to build on what Art said about plasma proteomics, I want to give a shout out to Simon Lovestone and J&J. To highlight that we should not underestimate what can be done through the power in coming together. J&J have done plasma proteomics in 10,000 samples, including many mixed dementias and a spectrum of neurodegenerative conditions. We joined them and supported them for another 10,000. That resulted in 20,000 additional samples coming in just out of sheer goodwill of labs and researchers who had done it and had it with them. So now we're sitting on a 40,000 sample, analyzed 7,000 proteomics platform, ready for insights to be gleaned, this includes mixed dementias, we can do stratification, we can do early diagnosis. So, the potential is there.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

Do you see also a ripple effect from Alzheimer's disease? I would say the modest successes in Alzheimer's disease, does it have an effect on the attempts in other diseases also to do research. Do you see this happening? Because if it seems we are able to modify the disease course in Alzheimer's, that also, I would say, inspires people to look at other dementia as well. Do you see that happening?

Art Toga Provost, *Professor of Ophthalmology, Neurology, Psychiatry and the Behavioral Sciences, University of Southern California*

I do. The research on Alzheimer's disease in the UK, EU, United States and in other countries has had an enormous effect. It has shown how cooperation and commitment can produce a remarkable transformation in how science is done. We now share data all around the world. We were the first to do that. The Alzheimer's community was the first to not only develop the technology to facilitate it, but alter the culture so that it was expected, and people wanted to participate.

And not just the patient population, but the scientists who are by their very nature competitive wanted to share their data with their colleagues because they know that by doing so, they would get more out of it. There would be more discoveries, they would participate in more interesting projects. That has altered the landscape at the National Institutes of Health in the United States to the point where all new awards now mandate this. That was unheard of 10 years ago. You must do it. You must have a plan in your award before you get the money. And so countless other research groups focused on other diseases have said, "how did you do it? What is it that is necessary to make people behave in the way that the value of the data is great enough that everyone can learn something from it?" And so, Alzheimer's has done a great deal of good in that regard alone.

The second thing I would like to say is the value of real cooperation between the pharmaceutical industry and academics. That also has been rather unique, where there is true collaboration between pharma, universities, and funders so that it becomes a true partnership. It has already resulted in the development of new compounds based upon the results of research and working together in a seamless way. In fact, money is often commingled now in Alzheimer's disease, which historically has not been the case. And so, I think we have really led the way in terms of how to solve previously intractable problems in a way that is cooperative and forward thinking.

John O'Brien, *Professor of Psychiatry Cambridge, UK*

Your question Philip was about disease modification in AD and its impact in other areas of dementia research. So, I think there is optimism. There is a but! You'd expect a but! Over the years I have been involved in Alzheimer's disease the pendulum has swung. Everything is Alzheimer's disease, nothing is AD it is all vascular, and back again. We just need to be slightly cautious that amyloid doesn't necessarily mean Alzheimer's disease. We have learnt that from some of our treatments, some of our research. It is not called the amyloid hypothesis for nothing. It triggers lots of other processes. Tau, inflammation, other things as well. And one potential risk we need to be aware of is that people with other dementias aren't just called Alzheimer's disease with a bit of co-pathology because I think that could be a danger. And some of the new criteria for AD says amyloid is Alzheimer's. So we just need to be aware of that.

I think in regard to patient expectation, and Lenny mentioned this, I think it is really important. Because the advent of disease modification will change the perception of the disease and other diseases that cause dementia. Fundamentally. Because patients will say if you can do something for AD why can't you do it for Lewy body and FTD and so on. And that will have a major and positive impact.

And it will also help the message, which is somehting that the scientific community hasn't always agreed on, that AD is a disease, it is not a part of normal ageing. We still see that all the time, that people think that it is. And if you can tackle the disease, and ultimately stop it, that will prove a powerful rebuttal to such thinking that it is an inevitable part of ageing.

George Vradenburg, *Chairman, Davos Alzheimer's Collaborative and UsAgainstAlzheimer's*

This is very much in your spirit of a conversation not a question. So, this goes to Bose's question about sharing of data because the Bio Hermes project, which is a project of the Global Alzheimer's platform foundation, is partnering up now in Scotland for a Bio Hermes dimension Data Challenge. This would permit anyone, anywhere, to get access to samples from 1,000 deeply phenotyped participants, focusing on underrepresented communities. So, it's a highly diverse dataset, 80,000 multimodal dementia biomarker data points, blood, CSF, genomics, proteomics, cognitive tests, imaging, and digital. It is giving access to a very rich data set of diverse populations with a wide variety of data. And it is the BioHermes Dementia Data Challenge for anyone who wants to go to www.brainhealtharc.com/data-challenge. So, anyone can now apply to get access to this data set, to the notion of Bose's challenge. So not 40,000. This is a mere 1,000, but nevertheless it is symbolic of the sharing ability.

Esme Moniz-Cook, *Professor in Psychology Ageing & Dementia, University of Hull*

I just want to pick up John's point about messaging having worked all my life with hundreds of patients who have plenty to say about what we do in research and data sets. These data sets that we have can be very old. When you start searching for what is meaningful and interesting for people, not just low level quality of life measures that we tend to use, but the fact that some people want to get some little pleasure. But actually, getting some pleasure on the odd occasion, from people, family and so on. And these measures of in the moment experience as it were do not exist. And data sets don't successfully capture them. Over the next 10 years we may get better at capturing that through digital and so on, but the problem will be people not liking to use digital devises perhaps.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

Let's take on this one, because it points to the fact that we're talking about blood-based biomarkers, so we're talking about biology that you can measure in blood, but there's a whole new world with the digital markers that measure other things. So how does the panel feel about the digital biomarker field?

Niranjan Bose, *Managing Director, Gates Ventures*

I'm happy to start and say there's immense potential there, but we also have to realise there's a lot of noise and we need to figure out what the signal is in the digital exhaust. We all have so much digital exhaust from our phones to wearables to digital voice. So how do we make sense of that?

I look for ideas from everybody here. Like, how do we do this? How do we do this quickly? How do we do it in a way that is privacy preserving? But privacy preserving is if I consent, you got my data, you should be able to analyze it. How do we do it in a seamless manner with less friction? We're looking for ways, we've already started with digital voice.

And George, thank you for that data challenge. A lot of groups are doing the data challenges, and we want to open up the field in a secure manner for people to analyze the digital noise.

John O'Brien, *Professor of Psychiatry Cambridge, UK*

Just on data, just to make a plug for the Dementia Platform UK, which has a portal with two million data sets of patient level data with varying types and phenotyping, which again can be applied for and for people to access.

I think the previous response was about quality of life and data and outcome measures. There is an important point that these data sets are fantastic and are really helpful and you can interrogate and make sure things work or see that they don't work. That's incredibly powerful, but they don't answer all the questions. But they don't answer all the questions because the data is historic and collected for another purpose, in other words not always collected from the right people in the right way to answer the question you want. Maybe the validation isn't as good as you want it to be. So there is always going to be a role for other new prospective studies. Studies that are asking particular questions that have particular measures, and how these measures change over time as we develop new cognitive tests, new quality of life tests and so on.

With regard to digital, I think quite a lot is said about it. But there is — as Bose said — also a lot of noise around such data. It is going to be powerful but it is important to use it in the right way. So, at group levels people can show these markers change before diagnosis, but what does that mean for individuals, that is less clear. What is also less clear is the extent to which people are willing to engage, will there be digital overload? I can see more use for them in disease monitoring and outcomes and more useful if focussed in that way.

Fiona Ducotterd, *CSO, ARUK UCL Drug Discovery Institute*

The quality of the data you collect and how you use it are both important for any part of the discovery process or the clinical process. If you do a clinical trial everything is collected in exactly the same way with a very uniform process. And that means that what you put in is consistent, regardless of where you're running the study. And that's more difficult in the broader field, whether you're running basic cellular experiments or human experiments. And I think that's where, as a field, we can think about how to align on the ways we collect data and the types of data we collect. And I think the point raised earlier is really important, that that includes how people are responding in real life as well as what the biomarkers are telling us. It's just a general point that the quality of the capture of the data and the consistency of that means we can do more with it. So, if the field can come up with ways for doing that across the board, then I think that would help.

Susan Kohlhaas, *Director of Research, Alzheimer's Research UK*

My question is a little bit bigger picture. It's taken 30 plus years between the amyloid cascade hypothesis to treatments. Do you think can beat that? And what's your top priority for doing so?

Art Toga Provost, *Professor of Ophthalmology, Neurology, Psychiatry and the Behavioral Sciences, University of Southern California*

I want to answer the last one because it was easier. Yes, the data are noisy. But we have entered a time where technologies that can facilitate this, such as artificial intelligence. Strategies that can be used to find signal out of noise are here. We use them in clinical practice now in radiology and in other applications. So, AI may give us some capacity, in digital based but noisy systems such as real-world data, but their value might be quite great. So, I think we should attempt to do that.

And the other aspect of this is there are now ever-increasingly large repositories of this stuff. There are real world repositories, ALZ-NET is one, where we have vast amounts of data, which will continue to increase, that allows these data to be mined and find the signals out of them, so that we could prioritise which of the digital signals may be useful.

And the final thing I want to say is, putting it bluntly, privacy is highly overrated. The fact of the matter is almost everything is known by some system. And when I ask Alzheimer's patients or care givers that are involved in our study, "is it okay if we use this?' They usually answer, 'absolutely". They do not care most of the time. Some do, but most do not. And so, some education about the reality of our digital footprint, needs to be considered.

I will just give you one final example, and it has to do with imaging. I am an imaging guy. With MRI, it has been possible to reconstruct the face similar to a photograph since day one. Only in the last few years have many programs resorted to refacing the participants, altering the face so that it is no longer


recognisable. And this, after hundreds of thousands and millions of scans have been let out into the scientific community. That is nonsense. Refacing was initiated because of the liability. But the data that is already distributed, is gone and widely available. And it did not bother anybody. Now, mind you, there are now methods on the internet where you can find a face and match it to a person's identity. And in fact, when you come into the UK, you no longer show your passport, immigration just takes a picture to identify you. So, face recognition is highly advanced. But my point is, we need to use policymaking to educate people that identity is not as secret as may be suggested, and data about you as a participant has value in contributing toward scientific discovery.

John O'Brien, *Professor of Psychiatry Cambridge, UK*

So maybe a friendly disagreement. At a public meeting we had on Saturday for The PREVENT Dementia programme, funded by the Alzheimer's Association, the Alzheimer's Society and others, one of the biggest concerns of participants there was about their privacy. Participants thought we could get access to all sorts of data that clearly we can't, like internet searches and so on. Clearly there are aspects of data, people are willing to share, but privacy and particular behaviour is a really big and important issue and we need to be very cautious about that.

I did actually want to get back to Susan's question, I have two answers. One is we want to look at cross diagnostic mechanisms, and I think inflammation is emerging as an incredibly interesting and important one. We have known about it for a while, particularly around prevention, lots of good evidence around that, but we have never been able to take it forward. But now the biology is starting to emerge that should allow us to do that should allow us to do that. So that's one answer.

The other is that one of the things that have held us back over the last 30 years is the complexity of clinical trials in dementia. My goodness when you see a protocol and you explain to people it is *only* 12 visits, six MRI scans, two PET scans and two lumber punctures and each visit is a whole day and whatever it is sort of draining. You look at studies in other areas and they are very light touch. So, if you can make our studies lighter touch, involve more people, make it a routine part of clinical care, that would be a huge advance. Obviously for some new compounds we cannot, but particularly for some of the repurpose trials we can make the trials light touch. Then we will get quick answers whether positive or negative. And platform trials have been very helpful in this regard. They have been very positive in other areas, cancer we always talk about. Treatment doesn't work you stop it and move on.

Niranjan Bose, *Managing Director, Gates Ventures*

Can we do better than 30 years? Yes. And we have to. I mean, there's no two ways about it. We have to accelerate things. And trends always prove that we do better. We learn from mistakes. But in this field do we apply those learnings? It's up to us. I think we can do it.

But there are two things that I might suggest. One is that we try and put a considered effort towards address clinical trial bottlenecks. It could be platform trials, but even enrolment efficiency and enrolment rates. How do we do better than what we've done in the past two, three decades? And I think the second is implementation science. How do we introduce these blood-based biomarkers in a systematic way, the correct way? And how do we do that as soon as possible?

Fiona Ducotterd, *CSO, ARUK UCL Drug Discovery Institute*

I just think if we're not targeting the right mechanism with the right therapeutic, it's not going to work, evidently. And I think when we started with amyloid, we couldn't identify a patient with amyloid pathology before we started a trial. So, all of the investment and the progress in the field in terms of what you have mentioned about biomarkers, identifying patients, getting in early and also targeting the right mechanism are important. And the right mechanism, as we have all said, might be different for different

patients, knowing what target is going to work at what time. So that investment in early discovery, and early research for next generation mechanisms, is part of that to build the portfolio of next generation therapeutics. That is not only a plug for my work in early discovery, but it is really important that we build a toolbox to apply it at the right time for the right dementia.

Shibley Rahman, *Honorary Visiting Professor, University of Liverpool*

I spend most of my time in social care. I'm well aware you've got to bring the public with you. I'm very concerned that we won't have treatments that patients view as meaningful and we will struggle to bring patients along with us. We have to communicate with patients, and their families.

Johannes Streffer, *Senior Vice President and Head of Global Clinical Development, Lundbeck*

First on, we don't know as much on some of the other dementias, especially with regard to progression of clinical measures and biomarkers. I think there is a give and take between the big population and the smaller populations. The smaller populations currently benefit much more from gene therapy other novel therapies, which typically go into smaller, more targeted disease populations. Larger disease populations like sporadic Alzheimer's disease rarly have that. Now on the other side, the immunotherapies and a lot of the small molecules are earlier in larger populations, like sporadic Alzheimer's disease. Though I think we have to learn from both sides and bring them together, I do not think that there is a specific focus only on Alzheimer's disease. There is a lot ongoing especially novel technologies, new platforms in small dementias and smaller populations.

On the 30 years point, personally I find it always a pity that people say amyloid cascade hypothesis and think it's only amyloid. I think the amyloid cascade hypothesis came about because all familial autosomal dominant disease are amyloid genes. This is why the cascade started with amyloid. But even the initial cascade had tau and inflammation in it. When Alois Alzheimer made his drawings, it had tau inflammation and plaques. And obviously we learned a lot about tau and inflammation in these last 30 years. All the diagnostics we are now looking at are much more tau related and the staging of the diseases is stronger by tau. 100% we cannot wait 30 years for another drug, but on the other hand so much progress has been made on all the other targets on the way.

John O'Brien, *Professor of Psychiatry Cambridge, UK*

Well, firstly, I just wanted to thank Shibley for his comment because it's very important. And to say that I think the dementia charities have a huge role here. And it's fantastic to see Alzheimer's Society and ARUK, the two main UK dementia charities, sitting right next to each other here, unified as it were.

One comment I would make is I am talking about the common dementias not the rare diseases. So, there is a gap. There are the bespoke dementias, gene therapy and so on. There is Alzheimer's disease. There is also the other 35% of causes of dementia. So, Lewy body dementia, 150,000 people in the UK. These are big numbers. The point I was making is that it is important they don't get left out in the gap between the very bespoke, where you have a few hundred a few thousand people, and Alzheimer's disease. That is very important.

Niranjan Bose, *Managing Director, Gates Ventures*

I agree with Johannes.

John Harrison, *Chief Scientific Officer, Scottish Brain Sciences*

I agree entirely that people living with Alzheimer's disease deserve early detection of disease, access to new medications and personalised medicine. However, it is very hard to imagine how we will achieve this if we continue to use outdated measures such as the MMSE, the ADAS-cog and CDR-sb. We have had digital cognitive measures for 30 years, but sponsors have been very reluctant to employ them. This is despite the FDA requesting the use of sensitive neuropsychological measures in 2018 and again earlier this year. We need to get pharmaceutical companies to move away from CDR sum of boxes as a measure of disease. That is what is holding back progress. We have had superior measures now for many years. We need to use them.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

I knew this was coming, but any comments on this? I think it is a valid point.

Art Toga Provost, *Professor of Ophthalmology, Neurology, Psychiatry and the Behavioral Sciences, University of Southern California*

I agree, it is a really valid point. It reminds me of heart disease the patient has a stress test and asks, "is this reliable?" and the answer is, "yes as long as you don't have a heart attack on the way out"! So, the test is reliable in some situations but not others. It is important that any test has sensitivity, and accuracy, but also for general screening the tests need to be efficient. Cognitive measures are relatively easy to administer. But maybe there are others that could be used such as plasma-based biomarkers as well, or other physiologic measures that relate to the behavioural consequences relative to these measurements. So, we may not be able to just pick one. We may need a series of observations that will allow us to characterise the individual and the subgroup accurately, and those can be used in the decisions about what therapeutic intervention is provided.

Jane Rylett, *Scientific Director, Institute of Aging*

I was wondering about your predictions for 30 years down the road what is beyond what we have been talking about which is treating people who have clinical symptoms. And the questions that often arises is the fact that dementia or at least changes associated with the pathology that will lead to dementia start decades, perhaps, earlier. So I'm wondering what your predictions are around starting and developing treatments that are for before symptoms arise, at a point in time when it's possible to actually recover brain damage, rather than waiting till symptoms arise and there's so much brain damage that cannot really be repaired. What are your predictions around actually looking for treatments that start much earlier and what sort of time frame are you thinking about given that we were talking about 30 years down the road.

Fiona Ducotterd, *CSO, ARUK UCL Drug Discovery Institute*

I think it's a really important point that the earlier we treat the better and there's no one in the field that doesn't agree with that. But the question is how do we identify those people and how do we show the efficacy of the therapeutics in that early time frame because there is a lot of human genetic data that shows if you have certain variants you have some resilience to pathology, there is great data in the Amsterdam centenarian cohort for example that shows if you have certain genetics you have a better chance if you get pathology. We can try and mimic that with therapeutics but how we do that is an open question. It is something we are thinking about all the time in the early discovery space. What is our patient population, how would we find them, how would we measure efficacy at that early stage. All open questions for the field. But we have to go in earlier and target broad mechanisms underpinning the biology. The way to prevent is to stop the neurons dying in the first place and keep them functioning in the way they are supposed to. If we can't do that then we can slow or modify the progression or help the brain to cope with what it has got left, but that is not enough to cure the disease. It is something we think about everyday but we don't have a good answer to it yet.

Art Toga Provost, *Professor of Ophthalmology, Neurology, Psychiatry and the Behavioral Sciences, University of Southern California*

Yeah, I have a comment. I think early is better. I will just give you an anecdotal story. My daughter and son-in-law just had a baby a couple of months ago, and I watched the gestation. And during that time, my daughter had ultrasounds about, I do not know, seemingly every month. There were genetic screens, everything was done, early, early, early, to catch the possibility of various diseases so that intervention, if possible, could be applied early. It is an interesting story because it was very different when my own


daughter was born. And I am just telling you that story because that progression in a period of about 30-odd years has been dramatic. The sort of screening and assessment at every stage is overwhelming, and yet it is now done as part of standard prenatal care. Maybe the same kind of thinking can be applied in dementia disorders so that earlier in life we begin to take measurements, whatever they may be, to track risk factors beyond just genetics, but other factors that may increase the likelihood of subsequent dementing disorders.

And as the interventions become available, they can be prescribed prior to damage, prior to cognitive symptoms, prior to complaints in the clinic. And so, what we are seeing is this transformation. As biomarkers become more available, whether they blood-based, imaging, cognitive, whatever, they will provider and indicator earlier in the progression of the disease. Obviously, restoration is more difficult than prevention. We are going to see a transformation in routine, regular clinical care that will include tests that may be applicable here.

John O'Brien, *Professor of Psychiatry Cambridge, UK*

I can't think of any situation where prevention isn't better than cure. The current readouts, as you'll know on the studies of asymptomatic amyloid have not been positive. There are all sorts of reasons for that. There are other studies ongoing. I can't see its widespread use from a pharmacological point of view until we get a simple treatment for lowering amyloid. That's the thing. We are not going to get infusions given to the whole population. Until then prevention is key. We know that there are messages on prevention and dementia, what we need to know is what are the slightly different messages for dementia then from say cardiovascular disease, stroke and cancer. A lot of them are common but for public health we want to focus on dementia specific ones.

Megan Cully, *Associate, Deep Science Ventures*

One of the challenges, Art, that you proposed was to develop a system and a series of biomarkers that can predict response to therapy. And I think that this is actually really well aligned with some of the ideas that have been proposed by ARPA-H, for example, in cancer, where they have a call out for a group of individuals to come together and find the right biomarker aligned to the right treatment in various key cancers. Is the same thing happening in dementia, either in Alzheimer's or Lewy body, and perhaps, John, maybe you can fill in a little bit on Dementia Platforms UK, but is there something where we're bringing together multiple biomarker discovery entities in order to design something that predicts response to therapy? And if not, who should lead it?

Art Toga Provost, *Professor of Ophthalmology, Neurology, Psychiatry and the Behavioral Sciences, University of Southern California*

I would just say absolutely right. The creation of these data systems that several of us here represent, whether it be ADDI or GAAIN, DPUK or ALZ-NET or any of these systems, they are designed to be interoperable. We all actually work together. And the point here is there does not have to be a single solution because the digital connectivity between these systems enables us to work together, so they can be almost fluidly traversed and scientists and clinicians can poll those systems and look for relationships between biomarkers and therapeutic successes. We have democratised access to data by design. These are the kinds of adjunct developments that have direct applicability to this question.

Rianna Patterson, *Founder, Dominca Dementia Foundation*

I wanted to bring the conversation back to having cultural measures in terms of dementia research. So, there's a cultural treatment adaption framework, and that is not only for dementia interventions. But I don't know if you can use it for genetics. But if there's something similar like that, that would be quite useful. So, taking it a step, recruiting diverse populations but also using cultural appropriate measures to analyze these results and then also having more PPI involved in genetics are all important. I don't

think we talk about it enough, but having public interaction will be very useful in terms of disseminating information for public understanding based on the regions that you are representing and engaging with. It could be language, it could be, just having that conversation and co-collaboration will be quite important in genetics in a way forward of getting a collective voice on the matter.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

Thank you very much, extremely important point. Any brief reactions from the panel? Ah we all agree. And you.

Zul Merali, *Founding Director, Brain and Mind Institute, Aga Khan University*

I'm the founding director of the Brain and Mind Institute in Kenya. It is really commendable that we're all talking about bringing patients along this journey as central informant and participants. And I just wanted to bring to the table the fact that majority of people with dementia are going to be in low- and middle-income countries in the next couple of decades. In Africa, for example, is going to have 65% of the people with dementia. Yet, all the biomarkers that we're talking about, all the genetic information that we're collecting, are devoid that population. And so, I would like to hope that we can work together and make sure that we don't catch up after, but we are part of the process in developing the proper biomarkers and proper diagnostic tools so that we're capturing that information as we go forward.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

Thank you very much. We're nearing the end of this session, but I'm going to ask the panel for one final line. We have talked about 10 years. We've talked about 30 years. But I really want to make haste. So, I think what needs to happen in the next 10 years? And the answer cannot be just funding, because we know that. What does need to happen over the next 10 years to accelerate the speed with which we develop drugs for Alzheimer's outside of the monoclonal antibodies, but also the other dementias as well. What is the single thing that you can think of as that needs to happen in the next 10 years, outside of funding?

John O'Brien, *Professor of Psychiatry Cambridge, UK*

So everyone with dementia or at risk of dementia is offered an opportunity to participate in dementia research and it is our responsibility to make sure there is studies for all participants from all parts of the community.

Art Toga Provost, *Professor of Ophthalmology, Neurology, Psychiatry and the Behavioral Sciences, University of Southern California*

Commitment. It reminds me of the joke about breakfast. So, when you order a breakfast of ham and eggs, the chicken makes a contribution, but the pig makes a commitment.

Niranjan Bose, *Managing Director, Gates Ventures*

All right, it's hard to follow that. I mean, three words. Collaboration. Maybe three words in addition. Call to action. We need a call to action that we co-create. And I think the third thing is clinical trials. We gotta get it right very quickly.

Fiona Ducotterd, *CSO, ARUK UCL Drug Discovery Institute*

I agree with all of those. I think also we need to understand the healthy brain and what changes in disease brains and that involves all the things you all said, but if we don't, the brain is extremely complex and lots of noise in everyone's brains because we all respond differently to different things. We all have different things we're good at or not. And I think we need to understand more of those complexities in order to understand the exact things that are changing in disease progression.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

More basic science. Thank you very much for the panel. I know I know there are many questions still but many of the topics I actually will come back in different panels again. So don't be sort of afraid, your question will not be lost, you can do it in another session as well. Thank you very much.

Post-diagnostic experience: 10 years of steady progress?

Joanne Pike
Chair

Louise Robinson
Speaker

Laurence Geller
Speaker

Ishtar Govia
Speaker

Chris Lynch
Speaker

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

Welcome back, everyone. This session, we are going to be talking about "post-diagnostic experience, 10 years of steady progress," but with a question mark. So, we can think about that post-diagnostic experience as everything from community to residential to in-home; everything that occurs or needs to occur once a diagnosis happens.

Now, we just heard in the first session about so much progress that we are seeing within the diagnostic space, within the scientific realm, and what treatments mean moving forward. And, as dementia science is moving at an incredible speed, we also have to consider whether care science and the application of care is moving at that same speed.

The current care paradigm is based on the past. It is based on not having the innovations that we are seeing in the marketplace. And so, we have a challenge in front of us to think about *how does care need to change? How do we need to influence care delivery?* Again, in multiple forms, medical to end of life.

As we reflect on what that care needs to look like, we also have to think about the power of care. Implications within that space, because all too often, policy is what dictates how care gets delivered. The incentives within the health system dictate how care is delivered. So today, we have quite the esteemed panel to go through what does that mean in multiple different forms and in different places. We have:

- Laurence Geller, who's the founder and chairman of Loveday;
- Ishtar Govia, who is the founder and CEO of Amagi Health;
- Chris Lynch, who is the deputy CEO of Alzheimer's Disease International, which by the way, turns 40 this week. Happy birthday, ADI; and
- Louise Robinson, who is a professor of primary care and aging at Newcastle University.

So to open up our discussion, and I hope we treat this the same way we did before, we will go to the panellists for opening remarks. And then we will either turn it to you or I have a few questions in my back pocket just in case we need to go to those.

Let's turn to everyone here and Ishtar, if you don't mind starting let's just think about, what does the next 10 years need to look like? And as we think about the care model that's built today, what should it represent into the future?

Ishtar Govia, *Expert Advisor & Independent Researcher, Founder & CEO, Amagi Health Ltd*

Hello. So, what does the care model look like? First of all, it would look like not having this massive divide between cure and care. And that's something that has been affecting this area of work in Alzheimer's disease and related dementias for way too long. We know that in so many of our contexts that are different from these high resource contexts, that there isn't that clear, delineated pathway. And so we can't make this clear divide between cure and care and so we need to be focusing a lot more on care pathway development and thinking especially about differential diagnoses.

Laurence Geller, *Chairman, Loveday Care*

Well first of all I will tell you any of you that get diagnosed soon with dementia you will end up leading better lives with care than praying for a cure. I am going to have dementia; my children are likely to be an age group where they get dementia. I fund cure research, but I fund a lot more care research. I do think that care is the most primitive and inexact part of our world. Nothing has changed in many care homes since the 1980s. Well, I hope that isn't the case in my homes, but across most of the sector. Training and education is poor. There are no common standards for pre-admission, admission, in hospitalization, discharge, or post discharge care. So while you are all working on your Nobel Prize, could some of you work on care.

Louise Robinson, *Professor of Primary Care and Ageing, Newcastle University*

I think the positive thing is that many of us in the audience have been working consistently and tirelessly on care. And we know an awful lot on what good care should look like. In the UK for example NICE spent over two years reviewing all the evidence before releasing updated guidelines in 2018 about what good evidence based but person-centred care looks like. But my question is why is that not consistently and equitably implemented. Why aren't people who are diagnosed, regardless of age, geography, ethnicity or dementia subtype, why are they not getting that evidence-based care in our country. Because currently huge geographical inequalities exist and huge inequalities with other disease areas. And that is just unfair.

Chris Lynch, *Deputy CEO, Alzheimer's Disease International*

And is exacerbated in low and middle income countries but I know that is something we will come on to as part of the panel. I know Joanne when you and Lenny asked me to be part of the panel today you asked about this 10 year vision. I wanted to start with something that is positive. I had hoped in the opening session we might have heard the word revolution and diagnostics and treatment. But the reason I wanted revolution in the mix this morning is because I think we need it in care as well. I think it would be incredibly naive to say it will happen in a 10 year period, because it is slower than that. I am hoping we can jump on the coat tails of the diagnostics and treatment breakthroughs to advance care. One quick observation in 2021 and 2022 ADI did two companion reports on diagnosis and then post diagnosis support. The latter was the biggest one we have ever done. But the reality was 85% of people globally are not accessing any type of post diagnosis support. So looking at the high income countries' examples, we really need to do this jointly, to ask how we pick up that speed to get to a point within 10 years where we could look back and say we did make some decent progress. I think that's a huge ask.

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

Agree totally, and I don't know if there's already comments or thoughts from the audience, but you know Louise, you just mentioned something that I think is really important. We know what this looks like. Many of our organisations certainly think about guidelines to care or what person-centered care delivery should look like in multiple systems. But there's a gap between knowledge and reality and I would be curious to know from each of you how do we bridge that knowledge to implementation in the short term?

Louise Robinson, *Professor of Primary Care and Ageing, Newcastle University*

Well I think speaking from the UK/England perspective I think what was introduced as a positive way of improving care, local commissioning, has perhaps been disadvantageous. So what is missing with dementia is we need some kind of national evidence based pathway, so local commissioner can sign up. That is what we have with other disease areas. So anyone who has diabetes, regardless of whether they need insulin, a tablet or diet change only, gets a standard format of care. From a specialist nurse, from a dietitian, from preventative health. That is irrespective of their treatment or the type of diabetes they have. So what we need is a national standard, that can be implemented locally in slightly different ways. But at least there is a national standard that says if you are diagnosed with this condition you can expect this standard of care.

Laurence Geller, *Chairman, Loveday Care*

I couldn't agree more. There is a difference between discussing it and trying to do it. I have been involved in sport most of my life, and because I was involved in dementia, building these homes in London, I was asked to chair a rugby charity. And then I saw the implications of concussion and dementia. The government asked me to lead the effort on putting together a system where we issued the first in the world national guidelines on concussion on the field, off the field and return to play. The UK is suddenly the world leader. So now learning from that we went to the government, and they supported the establishment of the Geller Commission on post-diagnosis dementia care and many of you in this room are involved I this. And it is the object of simplification, standardization to try and make recommendations to government, it is supported by the Prime Minister, by the opposition. Whether it will fall on deaf ears I don't know. But it is an effort. But not merely on what to do but what the cost-benefit analysis is because in the end money for any of this thing comes from the Treasury. If we don't get it from the Treasury in the UK, the NHS isn't going to get it. So, it is really a whole thing. I'll talk later about what we do directly on research, what we do on a dementia care, but I couldn't agree with you more. I just for once, for once, I beg everybody to get behind the national effort for standardisation and to get the money behind it and it isn't impossible, woe is me and hope are not strategies.

Ishtar Govia, *Expert Advisor & Independent Researcher, Founder & CEO, Amagi Health Ltd*

There's this typical divide that we see between health and social care and there's been a lot of advances over the last couple years here in the UK related to the development of an integrated care system. Because we traditionally know that health and social or community care don't play well together. They're supposed to be talking to one another and they're supposed to be fuelling and directing persons. But even in the UK sometimes when somebody sees a GP, and between that time, and the time that they can access a memory care clinic, maybe as long as two years in some cases. So you have a context like the UK, where there is an established care pathway. That care pathway is ineffective in many cases. And you have people living with a neurodegenerative disease, or neurodegenerative diseases, who are progressing in that disease and they're not being linked.

There is an enormous potential here, as there is in the majority world context to use technology. And to use technology to do things like community resource mapping, to identify where are the sites that are providing resources, where are the sites that care that is based on a task shifting type of model and a task sharing type of model, where that care is located to visualise that care. And then to link persons who are passing through the health system, and especially those who may not even be in the health system. Once you can identify people, it's really then important to link them. And so important for us to focus on, particularly for relevance with the majority world context, and context even in high income countries that are resource constrained, to really build out this type of infrastructure. We are at a point now what tipping point as many people have been talking about in terms of technology and the role that technology can play and we really need to harness that.

Veronica Franklin Gould, *Founder & President, Arts4dementia*

I'm Veronica Franklin Gould president of Arts for Dementia, Arts for Brain Health. Social prescribing as soon as symptoms start to address risk factors for dementia, such as arts and physical activities, would be enabled if the national guidance 97 would be amended, as it is for mental health, to allow social prescribing as soon as symptoms arise, it can go side by side with clinical offer. But there is a difference between symptoms arising and actually diagnosis. So you can keep people well if they are engaged on a national basis. And if this was standardised by going into the national guidance for dementia this would be a real help.

Martin Rossor, *National Director of Dementia Research (NIHR)*

I wonder if I can explore the title of this session by posing a question around what is meant by diagnosis. So I am going to pretend I am 58 I am deteriorating in my cognition I am scoring a MMSE of 20 and I have a presenilin mutation, I get a diagnosis and I have access to your care pathway (whether it is good or bad). I am now going to be 78, I left school at 15. I worked as a manual labourer. My cognition is going off. I live alone. I live in a polluted area. I am socially isolated. I have diabetes. I have mild heart failure and I have a MMSE of 18. Am I going to get the same access into care and what do you mean by diagnosis in this scenario?

Louise Robinson, *Professor of Primary Care and Ageing, Newcastle University*

So was your question about diagnosis or about post diagnosis care?

Martin Rossor, *National Director of Dementia Research (NIHR)*

What is a diagnosis that allows you access to care. Easy if you have Alzheimer's and a molecular diagnosis but in my second case, with low cognition and multiple potential causes, would it get me in to the care pathway?

Louise Robinson, *Professor of Primary Care and Ageing, Newcastle University*

Well I think it gets back to my day job, I see this every day as a family physician, it gets back to we have evidence based guidelines on what happens for people to have a diagnosis but what happens in reality is a very different thing. So you have two scenarios there, a much older more complex patient with co-morbidities, and more vulnerable because of co-morbidities and living alone. But in terms of post-diagnosis support will be harder to access.

It gets back to inequities. How long will that second person take to get seen for a diagnosis? I suspect it will be longer than the first. Depending on the pathway. And then you have all the time, as Ishtar says, when they are degenerating. While at the moment, we could, if we had guidelines, something to think about it, in that increasing period between diagnosis, what can primary care do? So for example, what is his hearing like, what other medications is he on, does he have to have a diagnosis to access support for memory problems, that is something that the Alzheimer's Society has been looking at do you need a formal diagnosis or is the issue that you have had problems with your cognition and you need help to improve function of daily living.

The key point is there are inequities here and we are not getting evidence-based care routinely into practice. And you have just nicely given an example Martin of how that scenario over the next 10 years, especially if you see how money is moving and the amount of money going into the research for new treatments, probably to the detriment of dementia care and prevention, than those inequities may well increase. Because the first person will get formal diagnosis with the biomarkers and treatments and the second will get very little.

Chris Lynch, *Deputy CEO, Alzheimer's Disease International*

I would just broaden that if I can at a global level, we are looking at a diagnosis rate of less than 25% and that means in many countries a non-diagnosis rate of 90%. So, it is a forerunner to the types of questions we have here now, around post-diagnosis support. We are though entering this momentous era where we will have new diagnostic breakthroughs alongside treatments. We are going to find an awful lot of people getting diagnosed. And the lack of integration between health and social care is going to put an immense amount of pressure on the care system which is already underfunded. And if I can I will take Louise back one week, because we did a webinar last week and because we have done a lot on treatment and diagnosis over the last six months, we wanted to put that question forward. And Sube Banerjee had a super phrase in this space, he said it was an "assault on care". And he was very much thinking about the UK market. But what can we do about that? And I think that was what underpinned this session, is that we know it's coming and it's going to come at an even bigger scale, but what can we do to start to tackle it?

Ishtar Govia, *Expert Advisor & Independent Researcher, Founder & CEO, Amagi Health Ltd*

So a couple of things. When we're thinking about contexts, like majority world contexts, it's important to remember that many of these places don't even have standard of care guidelines. So, we appreciate what Louise you're saying in terms of what we see here in the UK. And there is a clear care pathway, but in contexts where there is not a clear care pathway this issue about what exactly is diagnosis and at what point diagnosis happens, and then what's supposed to happen after diagnosis is extremely problematic. And this is where we really need to focus on workforce. This to me is the key aspect here for majority world context. We have to upskill our workforce. We have to upskill primary care, and we can only do that by collaboration, even within health. Often health is very siloed, specialists are functioning in one area,

neurologists are functioning in one area, endocrinologists in one area, and then primary care, which is the first port of call for so many people in majority-world contexts. So what we really need to do is, we have to upskill our workforce, be doing is focusing on that workforce, focusing on health and making sure that there is interdisciplinary and multidisciplinary resource sharing, information sharing, educating. And then in our context, in majority world context, I would hypothesise that it really would be important for us to just let the high-income countries really fixate on this idea of disease modifying therapeutics. And we need to focus on prevention, as Louise is saying, large scale population level prevention. We're not talking about just individualised interventions here, population policy driven interventions. And we need to be focusing on the care infrastructure as I was mentioning earlier, thinking about how we can mobilise technology, how we can mobilise things like pragmatic trials, not clinical trials where the end point is extremely problematic and we're thinking about therapeutics, but thinking about interventions that can lead to improved quality of life and the types of outcomes that are really important to the people that we're interested in. The people for whom they're not clear whether they're having a maybe stroke, a stroke, whether it's hypertension, whether it's diabetes that was not diagnosed that needs to be managed. So, all of these potential morbidities need to be effectively managed before we can say that we have a clear diagnosis and before we get fixated on diagnosis we really need to just create a care pathway.

Laurence Geller, *Chairman, Loveday Care*

Let me try and reverse the hope strategies and the why not strategy and answer the 10-year question. We have care homes, we have invested £350 million here in London. We have also invested millions in research through a number of universities. One of the studies we are doing now is to mitigate, we are working with Imperial and Hammersmith and Fulham. The gentleman who is 78 lives in on his own. He's not alone. There are a lot of people in that situation living on their own. Carer comes in 20 minutes in the morning maybe, 20 minutes in the afternoon if you're lucky. Person falls, carer's gone, lying on the floor until the carer comes the next day. So what we've been looking at is how can we wire people's homes in an economic manner so there is a central hub so you know when the biometrics change, if there is a call for help, there is two way communication and so on. The trial has been going on for two years and showing tremendous results. The results go to government because it goes partly to mitigate loneliness and so on. My mother-in-law had an accident in my son's house. Six hours it took for the ambulance to come. But they notified them. But if you had been lying on the floor all night what damage will be done? And technology, on a small scale, can be rolled out to a big scale if it works. And so, if we're looking for something in 10 years, there's good practices, best practices, we can do that, there's education systems, but technology, artificial intelligence is just part of this game.

Shibley Rahman, *Honorary Visiting Professor, University of Liverpool*

I'm going to back to Martin's example of a 78 year old man, I would bring up loneliness. Family carers are very lonely, people they look after are very lonely. Falls are a very obvious example. Louise rightly talks about primary care but home visits were a thing once, part of a community. But that has gone. And then there are things like how do you manage delirium?

Louise Robinson, *Professor of Primary Care and Ageing, Newcastle University*

I think the key thing there is looking at the workforce and the training of them. You rightly say continuity of care is really important. The more GP continuity you have the safer the prescribing is. That is waning post covid. NICE say someone with dementia should have a named GP. I don't see that happening anywhere really. But that continuity should go from post-diagnosis to end of life. We know the majority of support groups are focussed in the first few years post diagnosis. So I think we do have answers, we certainly know research funded by the Alzheimer's Society which I was involved in, shows that if you provide expertise in dementia care it benefits not only the person with dementia and their families but the health infrastructure around, because they are not experts in this. They need a rapid phone call to secondary care or they need

people with higher expertise around them such as dementia advisers as first port of call, but the Admiral Nurses who can see that care through all the way to the end of life. We know that the Netherlands has a similar model and these are potentially cost effective but it is having systems in place that are pro-active and not reactive.

Howard Fillit, *Founder and Chief Scientist, ADDF*

I'm the co-founder and chief science officer of the Alzheimer's Drug Discovery Foundation but I've also been a geriatrician for over 40 years and taking care of people with Alzheimer's disease for over 40 years. And you know I totally endorse everything that people are saying here in terms of the way we should be practicing both from a physician point of view as a geriatrician, which by the way is kind of a dying field in the United States unfortunately, and maybe even in the UK. But I think a lot of what's been said is very UK oriented. And of course it is the World Dementia Council, so I'd like to introduce briefly a US point of view. And basically, the bottom line is, that Medicare in the United States. States, which covers 97% or so of elderly people, doesn't pay for long-term care. And I think as a policy issue, you know, we've been struggling as a nation to try to get over this, but there's just not enough money. The average annual cost of caring for someone is about $100,000, $120,000 per year. And so, you can imagine that eliminates most people from getting care. And so you know if a person with dementia is lucky enough to have a spouse or a relative nearby then they might be able to get unprofessional care if you will, maybe that's the wrong word, but otherwise if there if there's no spouse that person will be living alone with dementia until something catastrophic happens they fall break a hip go to a hospital and then they go to a nursing home where again Medicaid pays a good portion of that. But to get Medicaid people have to become impoverished and they have to give up all their assets and play games financial games to transferring assets to other family members. I don't know what policy initiatives we can have in the US, but all of these wonderful guidelines and so on which I practice by, most physicians don't have the time for it, they don't have the interest for it, they don't know the name or the telephone number of a social worker who might be able to help them. And there is no time. So I think I'd love to see a policy initiative here where we could change things in the United States.

Laurence Geller, *Chairman, Loveday Care*

Can I comment, as an American as well, I lived 40 years in the States. What brought me to dementia, and there's a point here for you, what brought me to dementia is I had to deal with both my parents dying six years apart, fully riddled with dementia. I then got tried to get involved in dementia, both in the States and in the UK. I'd go back and forth. forward. I found it was impossible for me to work the American system to get any national trial, even state trials. In the UK, there is a chance of, as it was with concussion and sport, of taking a leadership role. That's why I think it's relevant to be UK centric, because there is a chance in this smaller community of influencing the national dialogue. And that's what we must all be committed to doing.

Chris Lynch, *Deputy CEO, Alzheimer's Disease International*

If I could broaden it further. The WHO are here. Action area four of the WHO Action Plan on Dementia is a bundle of guidelines on diagnosis, treatment, care and support. The care and support bit is the bit that tends to be forgotten. In our engagement with ministries, the first question is usually "how much will that cost" if you are talking about a national dementia plan including care. And obviously it is an impossible question to answer. But thinking ahead for 10 years, with increased prevalence, and the ability to diagnose more efficiently, less costly, less invasively those numbers are going to increase and increase. And I think that is what troubled when thinking about the invitation to this panel. At a policy level what does that mean for care provision at a global level. Informal care is 50% of the true cost of dementia. But even professional care is too low a skill level. It is forcing at a global level is a migration of care and care workers from one country to another, which brings its own raft of really difficult scenarios as well, you know, where you are losing a skilled trade workforce from one country to another. And I can only see that accelerating again in the next 10 years as well.

Elisabetta Vaudano, *Principal Scientific Manager, Innovative Health Initiative (IHI)*

Hi everybody, thank you. And my name is Elisabetta Vaudano and I work at the Innovative Health Initiative, a European public private partnership funding collaborative research between industry active in the health care system and all the other actors. We fund collaborative projects that are really trying to get the end user engaged from the beginning with those that create the solutions in order to get something meaningful and openly implementable. Now talking about this and in particular focussing on integrative solutions that can

be implemented along the health care pathway my question is this, considering the fact that the health care pathway, health care approaches that could improve the situation would be only as good and strong as the weakest link, which could be the weakest link that could be addressed? Maybe not only delivering new solutions but really just improving this link would allow to better deliver at the end? And how can this be achieved ensuring that can be reproducible and applicable aacross many different identities such those that we have for example in Europe where regions are very different? Also how can we ensure that the end-users are on board on this journey in order to really get a result that will be effective?

Laurence Geller, *Chairman, Loveday Care*

One man's view, only mine, and I'm the most illiterate amongst you here. Once you know that, you can take it or leave it. It's education and awareness in general, and education in specificity. for all levels of dementia carers, whether they're from the doctors downwards, and it is a sad indictment that geriatricians is a losing profession. I don't know why, because it's a growing issue, but it is education and awareness at every level. Public awareness, public education and specific education of the implementers. That can be, can translated, especially with these multinational universities. Every university, major university in this country is all over the world. That can be implemented on a global basis if there is a will.

Mahadev Ramjee, *Medical Director, Panthera Biopartners*

Hi, I'm Dr. Ramanji Panthera Biopartners, I'm the medical director, and we conduct clinical trials on behalf of Pharma and Biotech companies. My background is in stroke and geriatrics, and it's a shame that geriatricians are a dying breed. One of the things I wanted to highlight around care, I think we have left the NHS now about seven years ago, but when I look at the progression, and yes, we always have these beautifully written guidelines, but the problem is at the ground level. And I think one of the ladies highlighted earlier around workforce, it's not just workforce, it's number of bodies on the ground, but also skills. And on top of that is the funding to actually supplement all of that.

I will share a bit of an anecdote which I encountered seven years ago, during my medical registrar time, I was on call and walking around the wards and I was called to see this 80 years old lady who was admitted with delirium on the ward. And once I was walking towards and I saw the lady scratch one of the health care assistants and the health care assistant picked up the pillar and hit her with it. And I was shocked. And it took me a while to process that, and being a registrar at that time, there's a number of stuff you had to do, and one of the things that the next day I had to do is write a reflection on this, and to kind of, okay, what did I learn from this experience? And it was, I found it quite challenging writing this, because everybody was taking sides. She had delirium and she scratched the person she doesn't know anything about it but then on the other side was this 18 years old health care assistant who was only a month in the job and we told her okay why did you hit her and so on and I'm well what training did that person receive to deal with this kind of of patients. And that's still relevant now. And we change guidelines after every two, three years, saying this is not working, we change a lot of things, while actually the two points of failure that keeps happening over and over again is bodies on the ground and skilled workforce. And until we tackle this, the care is still going to be a problem.

And I think that gentleman over there highlighted it around the diagnosis thing. In the stroke field, you have a stroke, and you get discharged literally within a week now and there's a parade of facilities, speech therapists, physiotherapists, occupational health people that goes out to the home of these people and nurture them pretty much back to a certain function. However, if you have a different diagnosis, you don't get that. And it comes down to function in the end.

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

Thank you. I appreciate that. And I think you highlight two very important policy needs, training, and the number of workforce that we have of health care workers. So we have someone in the back, and then we we're back up front. And then I might ask the panel one more question too, but we got about 10 minutes before we break for lunch.

Tim Ferris, *Consultant, Morningside*

Okay, very quickly. I'm Tim Ferris. I'm the former national director of transformation at the NHS. And I had the good fortune of speaking here in my first month in the job three years ago. I wanted to come back because I had a lot of work to do. because I spent a lot of time representing the delivery system in both the US and the UK with people in Treasury and in the department. And I'm gonna challenge this group because the conversations that I have with the people who control the purse strings don't last very long! And they

don't last very long because every proposal that comes the guidelines are completely unaffordable. And just to be clear, the numbers are massive. If you were to actually calculate what it would take to deliver guideline-based care in this country or any country, those numbers simply are not rational for anyone. in government.

And so I would challenge this group to think about not what ideal care is, because that is typically what we think about when we develop guidelines, but actually what is the MVP? What is the minimum viable product that will enhance the care, improve population health and provide care in a way that is actually affordable. Because I mean, I'm saying it for the third time, but the conversations in government in both the US and the UK that I participate in don't last very long. What can we do to advance care with numbers that governments say we can have that conversation.

Katrin Seeher, *Mental Health Specialist and Technical Lead at World Health Organization (WHO)*

I totally agree with the comment being made that recommendations and requests to implement recommendations need to be sensible and that financing those requests is a big issue. I just want us to also consider that just because someone has not been diagnosed, doesn't mean that they're not costing the health care system. There might still be crisis points, they might still need help, they might not be registered as dementia in the system, but it will still cost. So I think in that whole conversation, it's also important to factor in what we potentially could be saving in additional costs by applying better, more streamlined care.

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

There is a cost of unmanaged comorbidities because of a lack of diagnosis, but I think there's also something that we have to also grapple with, which is that value should be self-defined in a lot of ways, right? Now I heard some response on that one.

Laurence Geller, *Chairman, Loveday Care*

Tim, I agree with you 100%. having beaten my head in both nations. I learned something I learned that a marathon is one it starts with one step, and I've done too many of them, but so in this case, let me give you an example from concussion I talked to you about the first thing I then went with the proposal to the government for a network of national sports concussion clinics well, I didn't have a long conversation. So we convened a group from the industry under the guise of one of the ministries. Convened a group, came up with a method of doing a prototype, a single clinic, arranged third party funding through charities and individuals and sponsors. It's being built, and with that, we will have the chance of a rollout. Not of a hundred of them to solve the whole process, but in a small part. In the same way as we funded the trial in Hammersmith and Fulham, one step towards the finishing of a marathon. No other way. We can have glorious plans and global strategies, be very pious. One step at a time will get it done.

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

I think one of the things as we think about the bridge between our last session and where we are right now and looking at the future of care models, we also have to think about the building and the knowledge that we are gaining around diagnostics and when diagnostics come into the marketplace and in primary care. You heard the previous panel talk about prevention and the potential for diagnosis before clinical symptoms. And as we think about the next 10 years, maybe we can end on the note of, in 10 years we may have a population that is diagnosed before clinical symptoms. How does the care model need to change to adjust to this new normal?

Ishtar Govia, *Expert Advisor & Independent Researcher, Founder & CEO, Amagi Health Ltd*

And I just say that's not going to happen in low- and middle-income countries. So let's be realistic here. I appreciate it Joanne that we're talking about a select group of countries so in the meantime while everybody focuses on these DMTs as I was saying earlier let us figure out what infrastructure needs to be built, we do need brick and and mortar facilities to do some of these these in-person studies, these observational studies, these clinical work that needs to happen in terms of monitoring people for brain-related, as the Lancet's recent paper was showing, there's a high prevalence of neurological disorders in many low and middle-income countries that is not detected because there isn't the appropriate infrastructure. So, I think while we do that, it's important to think outside of health. and social care as well and what are the other sectors, what are the other ministries that can provide some type of infrastructure building, whether that is employment, workplace policies that would support informal carers, whether that is building out things like conditional cash transfers because we are constantly concerned even with MVPs who is the buyer here. And in low- and middle-income countries the government has to be the buyer for the vast majority of the population So how can those be funded? It's things like conditional cash transfers that can really facilitate respite care that can encourage health care utilization That can provide some of these other resources, and I think that's what we really need to be thinking about in our context.

Chris Lynch, *Deputy CEO, Alzheimer's Disease International*

Very quick response. A thought at a global level would be if we took a national dementia plan, that adhered to the global dementia plan, and had treatment, care and support at the very heart. But at the heart of that was the person living with dementia and their carer, and then at a country level assign a navigator that can help with the incredible complex interactions that come with diagnosis, especially as we diagnose earlier. And also, a role that doesn't get terminated after one year.

Louise Robinson, *Professor of Primary Care and Ageing, Newcastle University*

For me it is about using the noise that has been created about the potentially new biomarkers and treatments, that excitement and enthusiasm, as a vehicle for improving the minimal standard of care whether they qualify for the drugs or not. And that is true in LMICs and high income countries. Many of the core issues, like access to diagnosis, and support and so on are the same. It is just the level of infrastructure is different to provide that support. We need to press for things that are going to bring wide benefit like getting the routine medicines on the WHO medicine list.

Laurence Geller, *Chairman, Loveday Care*

Education, awareness, collaboration and please remember my residents, your families, your loved ones are not a statistic, not a global problem. They are an individual that you can change the world by changing their world. Please focus on changing the world, but in the meantime, could you focus on the individuals one at a time? They deserve it. Thank you.

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

With that, we will close for lunch. I do want to quickly thank the panellists for a lively discussion and certainly all of you for making it a lively discussion as well. Thank you all.

Population Behaviour: The Barrier to Timely Diagnosis


Joanne Pike
Chair


Jean Georges
Speaker


Brian Lawlor
Speaker


Katrin Seeher
Speaker


Kate Lee
Speaker

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

Okay everyone, we are about at that time where we're going to pull back together for our afternoon. We're going to talk about population behaviour, the barrier to timely diagnosis. So really focusing in on some of those barriers we are actively seeing in order to get a timely diagnosis. Get ready for the dialogue and start thinking about things that you want to bring up, whether it's comments or questions for our panelists. Our first panel today is inclusive of those in Europe, those in the UK, and certainly broadly globally as well. We have:

- Jean Georges, the Executive Director of Alzheimer's Europe;
- Brian Lawlor, Site Director of the Global Brain Health Institute, Trinity College, Dublin
- Kate Lee, the CEO of Alzheimer's Society; and
- Katrin Seeher, Mental Health Specialist and technical lead for dementia at the World Health Organization.

Timely diagnosis is one of those topics that we certainly deal with today. But as we know, the challenge is not just to think about today and what needs doing but think about tomorrow and 10 years' time. What does the market place need to look like, what does health care need to look like what do the barriers look like? Certainly, at the Alzheimer's Association we have been looking at the barriers to timely diagnosis and it starts even in the home with stigma and goes all the way through to the fact that we don't have enough specialists in America. I imagine many of you throughout the world have the same issue from the standpoint of primary care gerontology and specialist care as well.

But in between those two things, the stigma at the home and timely diagnosis and the delivery of quality care within the health care system. There are a whole host of barriers we need to address and be able to talk about as a society in order to be able to ensure that timely diagnosis happens, because timely diagnosis is ultimately the key to better care and to accessing what the innovations that are going to be coming out of the treatment pipeline will deliver in the next decade.

So with this, and our esteemed panel, why don't we just start with a quick introduction for each of you. What do you see in terms of opening thoughts that you would want to bring to the table around timely diagnosis and what we need to do?

Jean Georges, *Executive Director, Alzheimer Europe*

I think Lenny will kill me because instead of looking 10 years in the future, I'm going to look 10 years back. I was looking at public perceptions around Alzheimer's disease and tried to get an understanding of what we already know about this. I came across a piece of work that Alzheimer Europe did together with the US Alzheimer's Association, which was a public opinion survey of the general public and their perceptions around Alzheimer's disease. What was really quite striking was that in all countries that we studied, Alzheimer's disease was the second most feared disease after cancer. The fear of the disease grew as people grew older, as that potential became closer. Also, people were very concerned about themselves or somebody in their family catching a diagnosis of Alzheimer's disease.

Despite all of that, 94% was the minimum in all European countries and the US would want to get a diagnosis if they presented symptoms and would go to see a doctor so there's a willingness to engage with the disease and we also had a question 10 years ago if there was a test that would tell you that you are likely to develop Alzheimer's disease in the future would you want to get such a test and again majorities in all five countries (but not 94%) were interested in such a test.

We also wanted to get an understanding how people that were most afraid of the disease differed in their attitudes towards dementia diagnosis? Are they less likely to want to get a diagnosis or to get a test telling them that they're likely to develop Alzheimer's in the future ? That was however not the case. We also asked the question, do you believe that there are currently treatments available or will there be treatments available in the next five years? And even then, between people that were optimistic about treatment and those that were more pessimistic about treatment, there were no significant differences between their willingness to engage and getting a diagnosis. I thought this was interesting data for today's discussions and I was particularly happy that the "value of knowing" survey had been done together with the US Alzheimer's Association.

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

I think it's always good to know where you've been so you know where you need to go, right? Even if Lenny wanted us to focus on 10 years from now.

Kate Lee, *Chief Executive, Alzheimer's Society UK*

I think I'll follow on a similar theme. I think some of the barriers that we know are about stopping the population coming forward for a diagnosis. There is a huge need to bust some myths about dementia in the UK. So we have about 900,000 people living with dementia in the UK at the moment. Depends on how you measure it — but that is as good as you get for now. And there are about 1.8 million unpaid care givers in the UK. And when we look at diagnosis and diagnosis rates coming forward, people coming forward, I think firstly there is a barrier around the fact that in the UK governments recommended target rate for diagnosis is 67%. So that says it's good enough for only two thirds of people to actually get a diagnosis. And I think that's a problem because I think we lack ambition in setting up our health care system and our public health messaging around the importance of a diagnosis.

And I think coming down through our understanding of dementia across the UK that presents huge barriers. So we know 1 in 4 people in the UK know nothing about dementia. We know 3 in 4 people across the UK really misunderstand it: inevitable part of ageing, lasts about six months and so on. That real understanding of the complexity of the disease is lacking, and even if there were treatments the perception is does it really matter. So there is very little political will in the UK in driving better diagnosis. One politicians said to me he gets more letters about bees and bee health than social care reform and that is why it is not on the agenda.

Good news, 94% of people who got a diagnosis found it was a positive experience and they wish they'd done it previously. And that included 50% who said it helped them plan for the future in a way they wish they had done before. So I think we are talking a lot about diagnosis at the moment, including among the pre-symptomatic, because we are thinking about the onset of treatments. At the moment only 2% of people are diagnosed in a way that needs to change, but I think even for those people that may not be able to access those treatments, we know there's a real positive benefit from getting that diagnosis and we've got to think about those barriers, those myths that exist for individuals but also for the people that are going to potentially end up being as caregivers that are stopping people from coming forward.

Brian Lawlor, *Deputy Director, Global Brain Health Institute*

What's the main barrier to timely diagnosis worldwide from my perspective: it's stigma and fear. Dementia is still perceived as a condition that lacks hope. And I believe that one of the important solutions to this is to rethink dementia from the perspective of brain health. This means thinking and talking about all the things that we can do to protect the brain, reduce risk to the brain, and increase cognitive reserve, because you can still have brain health, even if you have dementia. It's about seeing dementia in a more positive light. That's part of the solution to this perceived lack of hope around dementia.

Stigma related to dementia is a worldwide issue. Stigma and fear can occur in different ways depending on the country and context. So, in sub–Saharan Africa, dementia is considered to be due to witchcraft, whereas in this part of the world the stigma and the misconception of dementia is that it's seen to be part of normal ageing.

We will have to use creative ways to tackle stigma. So, we still have a lot of work to do.

Reflecting on what Jean said about diagnosis disclosure, the situation has improved over the last 20-30 years that I've been working in the field of dementia and seeing patients. Back in the 1990s family members didn't want you to tell the patient the diagnosis. That has changed now: people know that you must tell the person the diagnosis and want you to do that. So, I think some aspects of stigma around diagnosing dementia have improved, and that is just one example. But in the majority world, reducing stigma will be crucial if we are going to improve early diagnosis and access to care.

Katrin Seeher, *Mental Health Specialist and Technical Lead at World Health Organization (WHO)*

So Jean stole my idea about going backwards. I joined WHO eight years ago. And just reflecting on what we had back then at a global level and what we have now, I must say we have achieved a lot, but we're not there yet. Eight years ago, we didn't have a global action plan. We didn't have a global monitoring framework that could hold countries accountable to what they're doing, what their national response is to dementia. We didn't have many of the technical tools that we now have. We didn't have a brain health unit at WHO. So, a lot is happening in that field.

But we're struggling, and I'm honest, we're struggling with implementation, and we've heard this throughout the day. It's not enough having ideas and having action plans. It's really making them happen. And one thing that I've learned over the eight years with WHO, yes we do see a big divide between the problems and the perceptions in high income countries and low- and middle- income countries, and both positions are absolutely valid. They're big problems and issues to tackle. But we're also seeing big discrepancies or inequities within country, so it's not just a matter of whether your country is a high- or low- income country. The issue is that not everyone lives close to a university hospital or, as you mentioned it, even high-income countries don't have enough specialists. And high-income countries have 70 times the rate of specialists per population. So, there are still a lot of inequities to tackle, but I think we're making progress.

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

So, we've already got two themes arising. One is the workforce challenges that you just mentioned. But the other huge one is stigma. And stigma is one of those areas that feels a little nebulous to define. And also, how do you tackle it, and where do you tackle it? But I think there are ways that we have seen stigma change in disease over the years. In other disease areas as there have been novel diagnostics and novel therapeutics that come out into the marketplace. A great example of that is the stigma associated with being diagnosed or going through the testing process with HIV/AIDS, right? That changed significantly as there were more advances from a treatment standpoint. You know, we are certainly starting to see some of this within the US where the hope that is coming from having a treatment in the marketplace is driving some more conversation than we historically have seen. Is there anything outside of stigma that you see: one, as a barrier, and two, things that we should be thinking about to change that from a progress standpoint?

Brian Lawlor, *Deputy Director, Global Brain Health Institute*

I think in addition to the stigma, obviously, is the area of training and education and raising awareness. I think a lot of fear and stigma comes from the lack of understanding and lack of awareness. Again this is a huge challenge for the global majority countries where there are needs in terms of training and education of primary care physicians.

In terms of stigma, I think we have to really think very creatively about that and just think about it. In terms of the Global Brain Health Institute and some of the fellows work you see really innovative ways to that, for example, working with film makers or making a movie to talk about witchcraft as people believe witchcraft is a cause of treachery and trying to change the narrative that way. I think social media also gives you tools that you can get the message out, and they're kind of creative solutions to try and drive change. And I think that has to happen to be able to develop the training education and the early diagnosis and access to care.

One of the deficits is having the workforce but within that also the leaders in this area who can drive change. And that's what we are trying to address at GBHI. To train leaders to see the whole brain as if it were. To break down a lot of these professional silos of people.

Jean Georges, *Executive Director, Alzheimer Europe*

I do not want to drown you in statistics, but I wanted to highlight another survey that Alzheimer Europe did in five European countries, and this one was not a general population one, but one of carers. We asked carers how long it took from noticing something was not quite right with the person you ended up caring for to getting a diagnosis. The average in Europe was around two years.

We wanted to understand what the barriers were and asked carers to could name a number of obstacles that prevented them from getting a timely diagnosis and they could name more than one reason. 40% mentioned reluctance from the person about to be diagnosed, so issues to do with stigma and fear. The person did not want to get a diagnosis, so that the dialogue of getting the patient to see a doctor was sometimes quite difficult.

40% of carers said that they themselves did not realise that the symptoms were significant enough for them to actively encourage that discussion to go an see a doctor. So, a lot of awareness and education is simply not there. But then when t the carer and the person were finally on board to go and see a doctor, the first professionals they normally went to see were very hesitant of referring them to specialists. "Don't worry, come back in six months' time". "This is all normal ageing". So, medical training of general practitioners was the issue. And for the lucky ones that finally got to the point of being referred, 25% said there were issues around delays in getting a second opinion or being referred or that they were just on a waiting list for them to be able to get access.

I promise that this will be the very last statistic I'm going to quote, but we also asked, does the person you're caring for know that they have Alzheimer's disease or another type of dementia? And in four of the five European countries that we looked at, the Netherlands, Scotland, Finland and the Czech Republic, over 80% said, of course, the person knows that they have dementia or Alzheimer's disease. In Italy, less than 50% of people had ever been informed about the diagnosis. So, the family wanted to protect the patient, the medical professionals wanted to protect the patient. And this wasn't 20 years ago, this was a survey that was done four years ago. So, one of the key things that we need to get as well is if you want to involve people with dementia in their future and planning about activities, we need to start by informing them about their diagnosis and involve them in future decisions. Thank you.

Katrin Seeher, *Mental Health Specialist and Technical Lead at World Health Organization*

Can I add one point on barriers? What was missing aside from training more workforce so that clinicians have the knowledge and skills to clinically diagnose someone with dementia is, they also need to have the necessary tools to diagnose and identify people who experience cognitive decline. And the lack of validated scales or culturally fair scales is a huge barrier to the make a diagnosis in low- and middle-income countries. This is an area where having easier testing using biomarkers might get us a long way in increasing the diagnostic rates. But it then again comes with the requirement of making sure our clinicians administering those biomarker tests have the appropriate training to interpret the results and they can do it in a safe and responsible manner. This is one area that we're focusing on a lot at WHO at the moment with the development of preferred product characteristics of blood-based biomarker diagnostics. Once we have them, they will be great. But at the same time, we need to basically start the upscaling of the workforce already.

Myrra Vernooij-Dassen, *Professor Emeritus, Radboud University Medical Centre*

My point is about stigma. I think this is an important barrier in the way dementia is perceived. Especially the connection with the last phase of dementia frightens people with dementia and the population. Instead, what we better can do is to provide a more realistic picture of people with dementia not being fully incompetent nor fully incompetent and to help them in dealing with their problems. For instance, in the Netherlands we have case managers who are very capable of educating the patient and family. The sad thing is that stigma attached to dementia contributes to not living well with dementia

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

Thinking about an awareness campaign to reduce stigma in order to access diagnosis. I just want to draw that full line. Because I think we can focus on stigma, without getting to the point where we are inclusive of that full process to diagnosis, which is ultimately where we want to be able to think about what the next 10 years looks like. I have a couple of people over here. Howard, I know your hand was up as well.

Howard Bergman, *Professor of Family Medicine, Geriatric Medicine and Oncology, McGill University*

I co-founded and co-led, one of the McGill University memory clinics. It was the best in the world. The best in the world. Except it took one to two years to get in, and after that time my daughter who was in marketing could make a diagnosis. So that experience is the basis of the foundation of the fact that in Canada dementia is anchored in primary care in family medicine. And because in fact 80% of dementia are typical. And we said to use the diabetes model or the cancer model? But 80 to 85% of people with diabetes are managed primary care without screening endocrinology. They see endocrinology for the more complex cases and complication. We're trying to develop that model in different ways in different parts of Canada in order to increase access. And so with training, family physicians, nurses, et cetera, interdisciplinary practices. And I think that's one way to go forward, because there will never be enough specialists trained and interested in dementia.

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

It's a very valid point. I think getting to specialist care takes time and long-term that's not always going to be feasible. And so how do we skill up, as Ishtar said in the last section session, around our primary care staff as well?

Participant

I just wanted to add that knowledge and understanding is, of course, really important, but then comes communication and communication researcher. And I think there's lots of communication barriers as well between the care partner and the person who experiences cognitive complaints, especially also in contact with the health care professional. Even in memory clinics, we see that in half of the consultations, or even less, the reason for people actually seeking care is discussed. So often the perspective of the patient and the caregiver has not been addressed, so I think we should do better in stimulating health care professionals and patients and care partners to express their needs, their preferences and also their fears, to stimulate control and making sure that people will actually stay empowered and feeling controlled. Control of their own decisions.

Shibley Rahman, *Honorary Visiting Professor, University of Liverpool*

I'll be very, very quick. Alzheimer's Society did a great report looking at regional disparities and race. People in the UK have different ethnic groups and significantly different experiences of care. But also health inequalities. Very difference across the UK. And that influences diagnosis.

Kate Lee, *Chief Executive, Alzheimer's Society UK*

Yeah I think the point made, which is really important, is the link between inequality not just health inequality but general societal inequalities and the likelihood of getting a diagnosis. And so, for example, one of the things that was in the report just referred to, is that we've got people in the UK in rural communities that are under the misapprehension that they will get their driving licence removed the day they are diagnosed. And in some coastal communities, more rural, it was a huge barrier to diagnosis as people felt they would lose their independence. So it is about those inequalities, economic, race, geography and so on. People need to know there will be culturally appropriate care and support available post diagnosis. There are issues around the combination of mental health, disability and dementia. Issues in the black community around people having higher rates of mental health problems and for longer and that tipping into diagnosis.

The other point that I want to make, there was a really good point about keeping people in control. And we've seen a huge uptake of the symptoms checker that we produced at Alzheimer's Society. It has been incredibly popular. It has been approved by the Royal College of GP in the UK. We have a partnership called Sports United against Dementia Partnership where we have been promoting it at different sports events, football, cricket and so on. What we ask people to do is keep a record of their symptoms before going to that first primary care appointment so they can talk about what is actually going on with them. Because in that moment it is quite hard for people to capture what it is about them that they feel is difficult. And we know that our evidence shows that primary care are also seeing that symptoms checker flowing through into GP appointments. So, what we know is really popular about that is it helps people remain in control, which is part of that really positive communications piece as well.

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

And it's a great example of using technology to increase the inflow into primary care or to a doctor.

Brian Lawlor, *Deputy Director, Global Brain Health Institute*

In terms of more positive messaging around dementia, we should think more about arts and creativity how arts can be used to tell stories about how people living in dementia can be included and how they can still contribute. So, arts and creativity are a valuable tool in this regard.

In terms of improving diagnosis at the primary care level, we must go back to nursing and medical school training and make sure that doctors and nurses get more extensive and deeper exposure to dementia and what a lived experience of dementia means. And health care professionals should be taught how to communicate to people living with dementia. There isn't enough time and attention paid to communication skills with patients and families during medical student training.

Jean Georges, *Executive Director, Alzheimer Europe*

Again, from these kind of comparisons that we do in Europe, where we see that certain countries are faster at doing a diagnosis than others, those that are slightly faster are very often the countries where GPs have a much more active role in the whole detection and diagnosis process, rather than solely referring to specialists. And in certain countries, the reason why it was given to specialists was very much a reason for containing budgets and limiting access to cholinesterase inhibitors at the time when they reached the market because it was one way of saying well these drugs should only be prescribed by a specialist and so we need to have specialists to diagnose we need to have a specialist to initiate treatment to monitor treatment and to continue treatment. And the more barriers you introduce and the fewer people you allow to diagnose and initiate treatment, the longer that whole process takes.

And there's a whole range of European countries that have changed that system, where GPs really take a very active role in diagnosing, and they only refer those cases where patients present with atypical symptoms, where they are much younger than the majority group, and also those patients that have very significant behavioural issues that need much more specialised care than others. And those countries, especially Nordic countries, are more successful and faster in diagnosing than those countries that limit all of this to specialists.

Zul Merali, *Founding Director, Brain and Mind Institute, Aga Khan University*

From the perspective of developing countries, I think the issues that are prevalent here about barriers to access, to care, are really very valid. Stigma is huge. Normally stigma of diagnosis, but even before diagnosis, the symptoms of the illness itself, it is huge. Very scary in those kind of rural areas. We've

already talked about maybe etiology misconceptions about being due to witchcraft and things like that or being possessed. And the consequences are very severe. Sometimes they get ostracised in the community. Sometimes they even get killed. This is the reality on the ground. And so coming to the diagnosis part, the tools that we have access to are all developed in North America or Europe and are not necessarily very accurate or appropriate in those geographies. For example, a clock face, many individuals in the rural areas have not even seen a block face or if they see a clock face, it's a digital clock face. And so neither have they had experiences of paper and pencil, for example. Those are the realities. And so we need to have tests that are more appropriate for them, easily administered. And there's something where there's more work that is ongoing and needed.

Kate Lee, *Chief Executive, Alzheimer's Society UK*

I've just got one thought, I think it's not only a global issue, it's also an issue within each of our own countries because if I look at the diversity and the complexity and the internationality of the UK population that comes up time and time again about the inappropriateness of some of the tests, the lack of understanding of some of the tests, the language that's used. Certain communities, no language for dementia, no translating word for dementia. So, I think the more we operate as a global community, the better, because we're bringing in that best practice from countries that have practiced this, the witchcraft issue is most definitely an issue here in certain communities within the UK. So, understanding how that has been tackled, overcome, what methods, what communications in those countries where it is a significant issue, I think has global value to all of us.

Brian Lawlor, *Deputy Director, Global Brain Health Institute*

Just to add to that, there's a great opportunity here to work together, to collaborate and to learn from one another. Literacy is another issue in the use of cognitive tests. The learning can be bi-directional: what we learn from the majority world we could bring back.

Participant

With the increased availability of new diagnostic methods, what are your thoughts on routinely screening as a method to increase diagnosis rates, particularly maybe using blood-based biomarkers or something else? Particularly as we know that early diagnosis pre-symptoms is probably going to be the best way for new treatments to work.

Brian Lawlor, *Deputy Director, Global Brain Health Institute*

I'll make a start on this topic. I don't believe that blood-based biomarkers can be used on their own to make a diagnosis; when they become available, they should be used as part of a standard assessment. The field needs to move together on this. Plasma biomarkers look very promising, but there are risks and dangers in making a diagnosis based simply on a blood test. For example, a person's cognitive complaints may not be due to a positive biomarker but related to something else that's treatable or reversible. Plasma biomarkers are going to be helpful and important in supporting a diagnosis, but we will still need to carry out a comprehensive assessment as part of making a dementia diagnosis.

Katrin Seeher, *Mental Health Specialist and Technical Lead at World Health Organization*

Yeah, maybe to add, this is exactly the kind of context in which we're framing the preferred product characteristics that WHO is putting out for public consultation. The intent is absolutely not that everyone can go and get over-the-counter fingerprick tests and then have a result. That will not be reliable. But you can perform these tests as part of a diagnostic workup. But again, even then, the tests need to be tailored to

the level of training and experience that the clinician has on the ground, and I think the point that during our discussions came up again and again is that the level of experience and the context in which the blood-based biomarkers are being developed may be very different from where we ultimately want to use them and we do need to be careful and take this into consideration and make sure that once we have them, we can use them reliably and responsibly.

Kate Lee, *Chief Executive, Alzheimer's Society UK*

I think the thing for me, and of course long-term, would be to get to a population screening point which would give you a risk indicator and you know exactly what to do to reduce that risk. Well that is in the future. The thing that is fixating me at the moment is that if you can get these biomarkers what then? What happens afterward? If I think about Alzheimer's Society now we have 5.2 million interactions with people a year post diagnosis. What is the support need of those people who find out that they have amyloid, not suitable for treatment, they have dementia but it is not Alzheimer's. But we need to work alongside each other to provide systems and support in the future.

Jean Georges, *Executive Director, Alzheimer Europe*

I just wanted to add an angle to that because you also asked about routine screening. And routine screening is not just blood biomarkers, but routine screening can also be if you have a patient of a certain age that comes to your practice and whether you should you be asking a number of cognitive questions. I would say yes to that type of screening. But when it comes to blood biomarkers to be routinely used just to see whether people are amyloid positive, I don't think that would be the way forward at this stage. Making sure that GPs that see a certain elderly population start including cognitive questions and tests s would be a good way forward at this stage.

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

And I know we have four minutes left in this panel, and I recognise that we're not going to get to all the questions or comments in the room, but just as a quick closing to what barriers do we need to address in order to move forward. I would love to turn to each of the panellists for closing comment. If there is one investment you would make to improve diagnosis, where would you make it and what would you do?

Katrin Seeher, *Mental Health Specialist and Technical Lead at World Health Organization*

Training and capacity building.

Brian Lawlor, *Deputy Director, Global Brain Health Institute*

As I said at the outset, we need to reframe dementia from the perspective of brain health. This will help change the narrative around dementia and reduce stigma. There are things we can do if you have dementia. There are positive reasons to get a diagnosis. We can help people with dementia. We can improve brain health even if you have dementia.

Kate Lee, *Chief Executive, Alzheimer's Society UK*

Mine would be thinking about those inequalities that prevent people coming forward for a diagnosis so that we really properly research and understand what prevents different communities different intersectionality coming forward and getting a diagnosis at the same speed and pace, the same access and then the same post diagnosis support. Because I think unless we really crack that soon, we risk developing a system built on improving diagnosis that's still only benefiting a certain part of this population.

Jean Georges, *Executive Director, Alzheimer Europe*

For me, every person that gets a diagnosis should be informed about the diagnosis and proper post-diagnostic support should be made available to every person being diagnosed. So my focus would be on what happens after diagnosis rather than what happens before.

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

I love the connection to our first session this morning around post-diagnostic care, so thank you for that. And I appreciate the panel. Thank you for your time today and appreciate all the questions and comments. My apologies that we couldn't get to everyone in the room. Feel free, when we finish here or after our next 45-minute session, to connect with anyone that you might want to ask additional questions to. Thank you.

Case finding or population detection: How should health systems diagnose in the future?


Philip Scheltens
Chair


Chris Fox
Speaker


Howard Fillit
Speaker


Siddharthan Chandran
Speaker


Hilary Evans
Speaker

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

Thank you for being here. Congratulations on navigating your way over here with the room change that was a perfectly well carried out task. We're here for a panel which is called "case finding or population detection; how should health systems diagnose in the future?"

And we know sort of diagnosing is the start of everything there is no treatment modality ever if you don't have a proper diagnosis. I think that is made clear very often now, and it sort of all boils down to making a correct diagnosis. But how do we see this evolving over the next five to 10 years? There are countries where there is an enormous portion of patients who are under-diagnosed, takes a year on a waiting list to get a diagnosis, for instance, that sort of thing. But so how do we challenge the system and how do we change it also in the future?

I have a panel here with me consisting of people that will sort of discuss this from their specific angles. First of all, I would like to invite them to the stage.

- Hillary Evans, is the CEO of Alzheimer's Research UK;
- Chris Fox, Professor of Clinical Psychiatry at the University of Exeter;
- Siddharthan Chandran, he's the Director of the Dementia Research Institute; and
- Howard Fillit, co-founder and Chief Science Officer for the Alzheimer's Drug Discovery Foundation.

Well as we do with all the panels we asked the panelists first to give a brief inspirational sort of view on how they see this topic and what their view is on the topic for the next 10 years so let me just start with you Hilary.

Hilary Evans, *Chief Executive, Alzheimer's Research UK*

From my perspective I have been Chief Executive of Alzheimer's Research UK for 10 years, so for me this is why we exist as an organisation, this is why I do what I am doing. Previous to that I worked in an older people's charity here in the UK so for me it is really exciting when we start talking about the practicalities of how we find our patient populations, how we diagnose, how we get treatments to patients. I am also co-chair of the UK government's new dementia mission. This is a mission that is trying to unite industry, our patient voice, our regulators, are NHS, our health care systems, our scientific community. And bring all of that together to think about how we can accelerate access to new medicines as they come through but do that in an aligned way. It is a really exiting time, it is a conversation we weren't having 10 years ago and it has shifted even in the last 12 months.

Chris Fox, *Professor of Clinical Psychiatry, University of Exeter*

I am a front-line clinician in the NHS in memory services but I also work in Exeter as a researcher. And I am one of 14 national medical directors of the NIHR HRC and I co-lead the one in Exeter and we are the lead for industry and partnerships and I am a champion of dementia. In my view you have got to have technology, I see technology as increasingly important in the early diagnosis of dementia and am quite excited by the exposure we get. Practically on the ground, we have an 8-14 month waiting list in my clinic and we don't see technology coming into our memory clinic. Our service leads often ask me have we any technology to help filter faster patients so there is a clear need. We have one of the largest backlogs in the country. In another service I know wait times for MRI's are two years. We need to do something and we need to do it quickly. It is frustrating as an academic seeing all these new products and reading about all these great trials and I am sat there in my room in Norwich thinking what is it all about. So it is an exciting time and a depressing time. And it is great to hear what Hilary said about all the strategies.

Siddharthan Chandran, *Director, Dementia Research Institute*

So I am a neurologist I lead the Dementia Research Institute having succeeded Bart de Strooper. I'm sure we'll come on to it, but there will be three areas that I'd flag, none of, neither of which will surprise you, they're separate but linked. One is disease heterogeneity. This is a big problem. We need simple, scalable, multi-modal, clinical instruments at the point of first contact of the person with the health system. We don't have those. The second which is linked is this is a global problem, there is a risk we see this through the lens of European biology. But if we really want to get at this disease which is global, we need to diversify our datasets. So genetic heterogeneity is a key area for us to better understand. And that directs you towards long term solutions: we need to think about things that are scalable and are relevant to low resource countries as well.

Howard Fillit, *Founder and Chief Scientist, ADDF*

Hi, Howard Phillips. I'm a co-founder and Chief Science Officer for the Alzheimer's Drug Discovery Foundation, been a neuroscientist for about 50 years, and geriatrician. And I come to this based on my experience in the late '90s as a corporate medical director for a very large managed care organisation in the United States. I went from sort of having a small academic practice at Mount Sinai in New York, a couple hundred people, to being responsible for 150,000 people in seven regional markets around the United States in terms of what's called the now called the Medicare Advantage Program, but it's the Medicare Managed Care Program. The thing about it is that the health system in the United States is very fragmented, primary care doctors are often part now of health systems but there's no sort of overhead in terms of coordinating care. What we were able to do in the managed care organisation was bring administrative resources to the care of people in these regional markets.

So I ran a screening program for 150,000 people and had some experience with that. And part of what I did also was monthly care management calls with our nurses that we had in the various health plans in the various regions. And they would present to me a case, I remember very vividly, of an elderly man who kept getting hospitalised for his diabetes and he was on insulin, because part of our job was to try to keep people out of the hospital. So he would go in they'd ramp up his insulin, they teach him how to administer it, and what his regimen would be, and send him home. And I asked if they had ever done any cognitive assessment of the guy and they said no we wouldn't know how to do that on the telephone. So I said well listen I want you to go out there, he was about 50 miles outside of Houston, and go to his house and see what's going on there. And he lived alone. They went out there and it was a mess, of course, and he was very cognitively impaired. So what happened was, every time he came into the hospital to get his insulin regimen fixed, as soon as he walked out the door, he forgot everything that they said, and of course he kept coming in this revolving door, which was very expensive and disruptive.

From that, I worked with Richard Mohs, who was really the psychologist who invented the ADAS COG, which many of you know is a really primary type of cognitive assessment for patients in clinical trials these days. And we developed a very short telephonic screen that the nurses could use on what's called the welcome call as they introduced new members into the managed care organisation. And it was a very brief 3 or 4 question telephonic instrument that had very good validity in terms of picking up cognitive impairment on the phone that they could incorporate into their initial telephonic assessment of patients. I also ran a screening program for 150,000 people on their health risk assessment and I could talk more about how that was done but it incorporated a lot of data from our pharmacy benefit manager.

And the last thing I'll say is fast forward into the modern era, we're working with Gates Ventures and our other partners to develop a speech consortium where speech data would be validated as a method of assessing cognitive impairment. You can do it on your phone or whatever. And I think this would help tremendously in addressing the issue from a practical point of view of whether case finding can be done from an administrative health system perspective and/or whether this kind of technology can be used in an individual doctor's office to pick up cognitive impairment. Let's say a nurse is going to confirm an appointment for next week with the patient. They have a telephone conversation. They use our algorithms from the speech consortium, and they can detect cognitive impairment with high sensitivity and specificity.

I'll stop there, happy to drill down on the details of how we did all that, but it was a pretty interesting experience.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

Thank you. Thank you for sharing this. Any first comments from the audience, questions, things that you want to have clarified or reacting on each other? I mean, we have heard different perspectives from a research organisation to a clinician in Norwich with issues with the Dementia Research Institute and the US perspective. So how do you react to all these perspectives yourself? I mean, what do you get from this?

Howard Fillit, *Founder and Chief Scientist, ADDF*

The backlog is terrible. I mean, we're starting to see that in the US. It's hard to get appointments. But I think what it points to is we need these other technologies to be able to assess people, if we're specifically talking about cognition. At least in the US, video conferences have become quite popular. We use Zoom to talk to patients. And I think it's very hard. I've tried in my practice to do cognitive assessments on Zoom and it's quite hard. I mean, there are some instruments like the ticks which you could use for the thing, but some of it you really need reading and writing and it's very hard. I think these new technologies would help a great deal to pick up cognitive impairment.

Chris Fox, *Professor of Clinical Psychiatry, University of Exeter*

Technology would help in my practice for sure. But I don't just want to talk about that. My question to the audience is many of us have smart phones and smart watches and some of us have may one day have chips in our brain from Elon Musk apparently. There is a trial at the moment. So, the question is should we have industry involved in this? Before you think about it my experience on the NIHR Health Technology Research Centres I have come across some really unusual technologies around inbuilt chips to monitor diabetes that are in your body, and sounds like it is science fiction but it is here. But is that something we should think about. Some of the products we are working on are looking at young people. We have a bid in now to the European funding agency to phenotyping cognitive risks in young children for a dementia pathway. Industry has problems, sometimes ethical issues, sometimes not. But I put it out there that maybe this is a solution to some of the enormous costs we have heard about this morning.

Ruth McKernan, *Venture Partner, SV Ventures*

I work at SV Investors but for the purposes of this conversation I am the chair of the scientific advisory board of the UK governments Dementia Mission. The point I would like to make is we are not short of tests. DIAN the international organisation that follows tests for dementia says there are 99. The challenge is implementation not research and invention. And actually, to run a straightforward cognitive test, a digit substitution test, that looks at cognitive function on an annual basis in the UK should be pretty well straightforward actually and we have lots of ways of doing that I just think there's an opportunity to get on and do it that would be my comment thank you.

Howard Fillit, *Founder and Chief Scientist, ADDF*

I agree with you there's lots of tests and some of them will be better than others or whatever, but it is implementation. I think the issue is what makes a cost-effective screening program if that's what we're talking about. And way back when I remember we published the paper you want to look at yield and the cost of the test, right? That makes a prevention screening program cost effective. If you screen at age 65, maybe you'll get one in 10 people that have some cognitive impairment. If you screen at 75, you might get one in, I don't know, one in four, maybe something like that. The yield as you go up, maybe there should be an age variable in the screening. It makes it more cost effective.

And the other thing is that in the US there's an organisation called the United States US Preventive Services Task Force. And they make recommendations about what screening procedures are worthwhile. They do big analyses and they decide. And for years they've given screening for cognitive impairment a C recommendation, which means that there's no evidence that if you screen there's any benefit to the patient down the road. And basically they do that on the basis of whether or not there's an effective treatment. They don't really care about care management. But they make recommendations on payment for screening to Medicare, which then has the power to decide what kind of screening instruments. Now it may be that with the advent of these monoclonal antibodies, they would up their recommendation to a B or an A rating to give the payers the ability to pay for screening — which is the other thing that has so the thing has to be cheap as well.

I think there's a process here of implementation that's kind of in a broad description of how it can happen but it's going to take a while and you know who gets screened, when should they get screened, how often should they get screened, what's the value of screening, how much is it going to cost what are the instruments we are going to all agree on, I think these are the questions that need addressing over time. Whether I think screening should be done in people over 70, over 75, I do because otherwise it won't get done.

Ruth McKernan, *Venture Partner, SV Ventures*

Quick response. Can I very quickly? So it is like having an eye test. Is your cognitive ability getting worse relative to decline at that age for a normal person. The cost of the test isn't the true cost. The actually cost is what happens in the memory clinic if you have a lot of people who don't really have a problem that are clogging the system up and the cost of health care for the larger population. So I think the health economics for doing routine cognitive tests to remove people who really haven't got a problem is worth looking at.

Chris Fox, *Professor of Clinical Psychiatry, University of Exeter*

Can I just talk about the primary care bit. Just to come back slightly with my personal experience of the over 50s or over 55s health check. The three questions if you remember. So I went to see my GP and they weighed me and they said right "you're too thin". And I said: "what are you talking about". And it was basically a technician who had been told to look at them and if you weren't scoring normal there was something wrong with you. And I thought this is a mockery. And they said next year they are adding a cognitive test. So, it is all implementation, which is key. We are involved in ECLIPSE across 27 million patients, about 4,000 practices, and they struggle to get their practices on board because they are all completely overloaded. Primary care in the UK at least is under huge pressure. It is not obvious what the answer is.

Clive Cookson, *Science Editor, Financial Times*

I am Clive Cookson and I am a science writer with the Financial Times. Unlike most people in this room I am not a professional. I have a great interest and follow it closely. I want to draw attention to a source of confusion among the public which is what is diagnosis. Because people have been reading about new molecular diagnosis, precise test of amyloid, tau and other proteins which might show what sort

of dementia you have. Or does it mean going to a memory clinic, which is far far more prevalent at the moment, which will show you have some form of cognitive impairment, memory loss, compared to normal at your age. But will tell you very little, at least on first visit, about what form of dementia you have. I don't know whether there is a way of clarifying the terms but when I talked to people about coming here and about diagnosis half of them thought it was about general diagnosis and half thought it was about the new wave of molecular diagnosis.

Hilary Evans, *Chief Executive, Alzheimer's Research UK*

From a big picture perspective, I think what this shows is where we are societally, and not just in the UK, about an understanding of the diseases we are talking about. People don't get a good diagnosis. In the UK about 2% of people get a gold standard diagnosis. And when we talk about a diagnosis of the underlying disease and what the future treatment options might be we are such a long way from getting to that space. People are still confused about Alzheimer's disease and the terminology and the majority of our public don't understand that we are talking about a condition that is caused by disease to start with. There is a big gap on public understanding that is a lot of the work that the charities have been doing.

I think there is also a piece on our health systems being prepared and ready to do this. I think the advent of the first treatments coming through are focusing health systems leaders' mind. That is one of the things that the Mission is doing. We want to ensure everyone is around the table so that when we are talking about the future of diagnostic tests or the future of biomarkers and which ones are going to be clinical valuable we are doing it at a time when we have regulators at the table, we have NHS England and we can think about what that pathway needs to look like for patients rather than trying to do each bit of this incrementally and I think that is the only way we are going to see that sort of change.

But we also need to see that patient power. We already see that with headline in the paper. We get a big upsurge in people phoning our research help line asking how do I get these treatments, how do I get into clinical trials. And the trust is very few people get on clinical trials in dementia in this country, or many others.

And the gap we have to close, when we are talking about new innovative ways to do diagnosis, is big. But we have to be ambitious because if we carry on doing what we are doing now the pathways aren't there, they are not going to deliver for patients, we are not going to get the right people through memory clinics. They are not going to be the right patients for some of the new treatments if they are waiting so long to get seen at a memory clinic and then get a diagnosis. So, we have to fundamentally rethink this. As Ruth said the tests are there. We have rich data pools, we have the science here. We have to work out how to get them into the system and we have been looking at how we make that a reality.

Siddharthan Chandran, *Director, Dementia Research Institute*

It is a good question. The truth is, and I am speaking here as a neurologist, we are comparatively in the dark ages compared to other areas of medicine. You wouldn't be asking me that question if we were at a cancer conference. No one talks about lung cancer or breast cancer. They talk about precise molecular diagnoses which are based on the genetics, which is derived from the biopsy, and then there's targeted molecular interventions. We simply don't have that. And so, I think it's about managing expectations. So today — and even if you just step away from the NHS and globally — our ability to make a precise diagnosis beyond cognitive problem or dementia remains crude. Much of the pathology is also mixed pathology. It's on a turning point, as others have indicated, because of the availability and emergence of now scalable, if we start with simple blood-based markers that begin to shed some light on the disease underlying biology, which will be linked to the diagnosis. But the key point I'd make is we've still got a very long way to go. And if you move out of the elite diagnostic research centres, in this country and elsewhere, and talk about diagnosis we really are in the dark ages.

Chris Fox, *Professor of Clinical Psychiatry, University of Exeter*

Can I just talk about under-served groups. Some of my research groups we work with the Chinese community and the South Asian community. And it is sad to hear they say that they're very scared, they don't know what to say to family members, how to come forward. And also, the cultural aspects, and certainly in the Chinese community, they try and keep things within the family, so they don't come forward. And there's an even higher load of under-diagnosis in that group. And just to reach out beyond Norwich again, lower middle-income countries, I think we've got an opportunity in some countries, Africa with its larger mobile phone impact in peoples lives, if we could deploy things there and work with those sort of countries, there's re-purposing technology, which could allow them to do some very simple screening, whereas in the NHS, we're mired with multiple systems, aren't we? So maybe I'm calling it out there internationally beyond the NHS, personally. I think that we need to think about that.

Howard Fillit, *Founder and Chief Scientist, ADDF*

Well, I'd just like to distinguish between screening for symptoms and diagnosis. They are two very different processes. The screening in the early detection of mild symptoms should lead to a diagnostic algorithm. And I do think, at least in the US now, we have blood tests on the market in 49 states out of 50 where doctors can simply order a blood test. Somebody comes into a clinic with a memory problem, and the primary care person, as they become aware of this, they can just order the blood test and with 90%, 95% accuracy, predict whether someone has amyloid in their brain and so that can be done quite clearly on. So, there's a diagnostic algorithm.

Siddharthan Chandran, *Director, Dementia Research Institute*

So you mean pTau 217? Just to push on this, because this is the World Dementia Council, the vast majority of people don't have access to that. The other point to make is the validity of pTau 217 is high in people of European ancestry. It's relevant to be stress tested in the global population. Population is an area we also need to address. Many people in this country, the US, are not of European ancestry. I make that point not provocatively, but just to highlight this is a global problem. Disease heterogeneity is a massive issue. We're now getting the beginnings of the tools to address this through data-driven collaborative research.

Mahadev Ramji, *Medical Director, Panthera*

Hi, I'm Dr Ramji, I work for Panthera Biopartners Medical Director and we conduct clinical trials including Alzheimer's and Dr. Fox probably touched on this earlier around the role of industry in this whole thing. One of our key challenges that we've been experiencing at ground level, conducting trials for the big pharma and biotech, has been innovation in the clinical trial design itself. When you look at the moment, how we run our clinical trials and have been doing it the past 10 years, it's not changed much. We're not short of tests, absolutely right, but they are usually workforce dependent. Like, we're doing feasibility for one of the studies recently and we have to we've said okay we can contribute 64 patients to our trial across six sites in the UK. Now to find those 64 patients we will have to pre-screen and screen over 100,000 patients now you do the maths on how many clinical hours goes and that's in a clinical trial setting we're not thinking about primary care where you know where innovations need to trickle down. I think the gentleman mentioned ADAS-COG and before somebody mentioned CDR rating and so on. These are all run in clinical trials, but in actual fact, in actual clinical setting, people don't use it. I have three principal investigators retiring this year and they've been national coordinators and so on, but yeah, there's nobody to replace them as pharma companies say that people lack experience.

Hilary Evans, *Chief Executive, Alzheimer's Research UK*

So on that point one of the things the Mission is doing is bring industry to the table. So we are looking at setting up a public private partnership. We have £50 million of public money and we are looking for industry partners. And the ultimate aim there is to ensure we have industry at the table, we have got regulators and NHS there as well. We are looking at how we run trials better. How do we do that from a biomarker perspective but how do we bring that through a whole pathway. And we have industry all together so it is not just one company. So we have been talking to a number of companies over the last year or to, about what is it that would be a really game changer for them and how that would accelerate are ability to do trials based on new biomarkers that are coming through that would then be validated clinically as well.

Chris Fox, *Professor of Clinical Psychiatry, University of Exeter*

And we have the dementia translational research centres in the UK which is trying to expand that. I would say I feel your pain on that. I went through some years ago the process it took about six months and I got through. But by the time I did the things had moved on and the site was doing other trials, so I was

essentially a PI with no trial. So thinking how we can give people a trial. I am working with a company at the moment who came to me and said we want people in your network and we will train them and work with them. That is flexibility and it gets them up to standard. We need a new generation of researchers coming through.

John Gallacher, *Director Dementias Platform UK; Professor of Cognitive health, University of Oxford*

So, if you want an example of patient power go to the MND community. They have lobbied heavily and successfully for the deployment of resource. Going on to cognitive testing I think there is a difference between systematic diagnosis versus early detection and they involve different tests. The value of early detection for stratification of trials and reducing screening failure is self-evident. But that does involve detecting change not status. That gives you a direction in terms of the sorts of test you want to do. They are not just scalable but repeatable. And I think that is a really important issue surrounding the technology of testing. And I think if the trials community worked together with regulators and academics to assess a small number of well validate tests then that would make the whole process of conducting the trail, getting regulator approval, being very simply about the question, stratifying your patients and so on. It is not rocket science to get together in a room to do that.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

But that means people have to agree on a number of tests and so on?

John Gallacher, *Director Dementias Platform UK; Professor of Cognitive health, University of Oxford*

And I think that is where you would like to clarify the question. There will not be one test for all. But nonetheless one response time test can measure very similar things to another. So it is just a matter of getting in a room deciding what tests you want done, doing the validation and then sticking to those tests.

Siddharthan Chandran, *Director, Dementia Research Institute*

Just on that and a previous point on trials and a wider point which was made earlier in another session. A goal for any of us is getting to the point where everyone with a diagnosis has the opportunity to participate in a clinical trial. So we are not short of people with a diagnosis. But we are short of people participating in research, cohort studies, biomarker studies, trials. Then that links to re-imagining trials, much more disruptive, community hybrid type designs, also platform designs, which are more inclusive. There are a few lessons to be learned from COVID in terms of how you run trials at scale and the hybrid model. So these areas need to move, but the challenge is, whilst that may well happen, the point, the other person made earlier, is workforce. If it's too predicated on classic workforce, which are doctors, you're finished. We need to be thinking about the workforce and building capacity in terms of not just the discovery scientists, but the delivery professionals who will help run these trials. And they need not be doctors, really important point.

Howard Fillit, *Founder and Chief Scientist, ADDF*

I think the trials, especially with the monoclonals, are burdensome to patients, the infusions. And even in Alzheimer's disease, I mean, these are elderly people often frail with frail spouses. So, to reduce the burden, right now, patients need to be validated for the trials with often an amyloid scan, which costs $8,000 and is somewhat invasive or a spinal test. But now we do have blood tests, as I mentioned earlier, that I think greatly reduces the cost and burden of screening and can also be used as an entry criteria. And then the other burden of trials is often the psychometrics that have to be done, which take time, they're expensive, and they're done maybe once every couple of months or every three months, and so you're just getting a point in time on patients. So there's not a lot of reliability, and there's a lot of variability, inter-individual variability across time and also among all the patients on the neuropsych. Whereas with digital technologies where we can do cognitive assessments on phones or other tech on the computer, we can get data points almost every day in a clinical trial that are just as valid as what the neuropsychologist can do once every three months. And that also reduces the cost of the trials and decreases the variability in a very variable and key assessment, which is the cognitive testing. So I think that's going to change trials and make trials more attractive to patients because they won't have to come into the office as frequently and we'll get better data because we'll have more frequent data. So I think those are advances.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

I mean, we all agree with that. I think that's, but I find the sort of the pharma companies, the ones who do the clinical trials very sort of almost risk averse or averse against changes because it has always been using the ADAS cog. So why don't we again use the ADAS cog? While everybody agrees that's not the perfect test! It's very difficult to get the field moving into adapting to new tests, because they always say, "Yeah, but the regulators won't accept it". I don't think that's true, so we have to, this is something we really have to advocate. And we have to start doing it actually, and you and I, we are funding companies that do trials, but you can also say, "well, I only do this if you have the proper design". And I saw, Johannes is already sort of, sort of, not agreeing with me, but I think this is really an issue. Johannes?

Johannes Streffer, *Senior Vice President and Head of Global Clinical Development, Lundbeck*

No, agreeing and not agreeing. So, I guess we all agree that some neurocognitive tests are old and well used because they're old, besides regulators ask for them in part as well? And then, as a company, you really have to do what you are asked for. If there is another measure that is new, people will want to compare with the existing. So they want to compare these results with earlier results. So then, if you add a new test, that normally means you have to carry on the old test. And then some people come and say, your trials are much too complex. You do too many things in your trial.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

So that's a catch 22, so how do we get out of it?

Johannes Streffer, *Senior Vice President and Head of Global Clinical Development, Lundbeck*

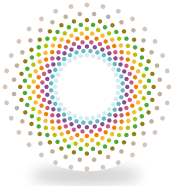
I don't know, but the thing is, you know me, we try to take better tests, newer tests, and the appropriate tests, but it's not so easy. You cannot jump from one to the other.

Howard Fillit, *Founder and Chief Scientist, ADDF*

Well, I agree, but we can incorporate digital tools into subsets of patients in the trials and show how they correlate with the old fashioned neuropsych, and the same thing with using the blood test as entry criteria, for example, a screening criteria. We've already proven that pTau correlates very highly with the pet amyloid scans, and I think the regulators would probably accept that at this point.

Siddharthan Chandran, *Director, Dementia Research Institute*

I mean, just the simple point, when the science moves the design has to move. So some of these measures that we're talking about and still using, digital wasn't even around, pTau wasn't around, other emergent technology, they're no longer emergent, they're established. What the sort really means is a partnership, not just with industry, but with regulators, who need to be in on the ground floor with the new designs.



Participant

Yes, I probably was gonna say, like, you know, it's always difficult to kind of state where to start. And I think how about this? Like, why don't we start with the patients? What's best for the patient? You know, at the moment, we conduct a clinical research in Alzheimer's before we can, first time we see them, before we can even get them to a stage where they can get some form of treatment, be it a placebo or the actual drug. It takes about 90 to 120 days. And that doesn't even count the trial setup time and approvals and so on. And then when they do come, that amount of time they spent at site level, it's not just infusion time which is 60 minutes, there's all the scores that they need to go through and all these things. We are not short of volunteers but the whole process disengages them. We need to start with what is good for patients.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

So what needs to change. To follow up Siddharthan you mentioned it is a long and winding road. So how do we shorten that. Everyone agrees here we can't just let this go on because we'll end up never changing it. We have to change something. It will not work.

Siddharthan Chandran, *Director, Dementia Research Institute*

So I think there's ground for optimism. Now in neurology you'll know that there's not a lot of progress in neurology thus far. However just think about MS. So, 25 years ago MS we were at Beta interferons which we could argue was the equivalent of the immune amyloid. What it showed was at the level of the individual the benefit was real but wasn't huge. But the key benefit was it showed the problem was tractable. That you had quantifiable objective markers that was pathologically relevant and then that triggered a flood of investment. And what you have today is fourteen multi-billion dollar franchises and the outlook for a newly diagnosed person today is light years away from what it was for a newly diagnosed person twenty five years ago. I think the dementias and Alzheimer's is at that point. I would frame it that way otherwise this sounds endlessly bleak. I don't think it is bleak. I think we can be cautiously very, very positive. To me, the key is, as has been touched on by everybody, is much better engagement with people living with the condition and rethink moving away from a paternalistic hospital dominated model, get into the mindset of every person with the diagnosis needs to be given an opportunity to participate in research. And the other element is data driven collaborative. You need to use the data to bind everyone together.

Howard Fillit, *Founder and Chief Scientist, ADDF*

I just wanted to add that I agree with what you said. And biomarkers play a critical role. And right now, basically, in primary care, patients are getting a clinical diagnosis of Alzheimer's disease, which is highly inaccurate very often. And nobody's doing the PET scans, although Medicare has agreed to start paying for it in some cases. But the blood tests, I think, are really going to change the world because primary care will likely adopt them. And then what will happen is the number of patients with a real diagnosis of Alzheimer's disease based on a blood test will increase the cohort of people living in the community who might be eligible for going into clinical trials.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

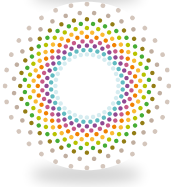
And I think Howard, it's important to note that the pTau test that you refer to only distinguishes Alzheimer's versus non-Alzheimer's, but if it's non-Alzheimer's, there's still a lot of work to do. What is it then?

Howard Fillit, *Founder and Chief Scientist, ADDF*

Yeah, I wanted to mention that. So we're also involved in developing alpha-synuclein tests, TDP-43 tests. We have to deal with the co-morbidity that you mentioned, which will be the next part of the world, will be precision medicine. I totally agree with that.

Siddharthan Chandran, *Director, Dementia Research Institute*

Just on this. I think everybody is agreed on this. The emergency of pin prick blood test that can be scaled and mailed will change everything.



Participant

I love the pTau assay, but I work also work a lot trying to do research on the relevance of pTau 217 in primary care and something that I get back from all academic primary care centres is well, okay, you have got a great test, but now over to negative and positive predictive value. And they are of course right. The prevalence of dementia in the primary care practice is much different and much smaller than it is in a memory clinic. And that means that negative predictive value will remain high, but positive predictive value will plummet. And that means that negative predictive value will plummet. That means you have a screening test that it will be difficult to say, okay, based on this test, you actually have Alzheimer's disease to a primary care patient, and that's a difficult issue I think with pTau 217 in primary care.

Howard Fillit, *Founder and Chief Scientist, ADDF*

Of course, any test has to be done in a clinical setting, and one would assume that perhaps the primary care doctor did some cognitive assessment and then went to the next step to determine what the cause was, and I think that changes it a little bit. But also in primary care, in a memory clinic, the predominance of patients is so much higher with memory problems, whereas a primary care doctor might see a few a week, and it's not really on their radar in terms of being a big problem in the practice.

Chris Fox, *Professor of Clinical Psychiatry, University of Exeter*

Can I take it away from diagnostic into non-drugs? So, lets assume we have a patient who doesn't respond to an infusion that is going to be licenced soon. What do we do? I come at it from an industry perspective where we say lets do a trial then we get investigators that say AI "what's that" and get scared. So it goes back to training and developing. We need more expertise. There will always be some groups that don't respond to an infusion in dementia, and we need to be developing markers for that and develop potential non-pharmacological alternatives.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

I am going to wrap up this session by asking the panel how do we prevent another decade of mis-diagnosis in patients. Just in a sentence please.

Hilary Evans, *Chief Executive, Alzheimer's Research UK*

The opportunity over the next decade, to repeat what Bose said earlier, is that it is all about collaboration, has to be about co-production and his third was clinical trials. Which plays a big part here. There is a lot we need to understand about the condition we are working on. We need to pull that science through. We need more of those shots on target. We can't keep talking about what is just round the corner. In five to 10 years time we should be in a vastly different spare.

If that's possible. Howard, last one. Yeah, I would say we're moving to a world of precision medicine and combination

Chris Fox, *Professor of Clinical Psychiatry, University of Exeter*

Workforce support training and innovation and working with our patients.

Siddharthan Chandran, *Director, Dementia Research Institute*

This is where the UK can do something useful is integrating health care with health research anchored around the NHS and embracing the science which including digital technologies and the biomarkers.

Howard Fillit, *Founder and Chief Scientist, ADDF*

Yeah, I would say we're moving to a world of precision medicine and combination therapy, and that's where I see it.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

OK, good. Thank you. Give them a round of applause for this. Thank you very much for being there on stage and sharing your opinion. And we'll quickly move on to the next panel. We'll stay here in the room, or you can, of course, go to the other room. But I would advise you to stay in this room.

Can we stop treatments increasing inequity?

Joanne Pike
Chair

Ryoji Noritake
Speaker

Suvarna Alladi
Speaker

George Vradenburg
Speaker

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

In this session we are going to tackle inequity and whether it is inevitable to under to think about the fact that treatments drive inequity or can we plan appropriately to ensure access at this time and at this point.

Okay, so our panellists today represent certainly a broad group of individuals, geographies, and specialties.

- Ryoji Noritake, CEO and Board Member of the Health and Global Policy Institute;
- Suvarna Alladi, a cognitive neurologist with National Institute of Mental Health and Neuroscience, NIMHANS, Bengaluru, India; and
- George Vradenburg, the chairman of the Davos Alzheimer's Collaborative and also UsAgainstAlzheimer's.

So thank you very much for all three of you joining to talk about this.

I think we have both unique opportunities to talk about countries that are already seeing treatment in place, the things that we are seeing from a blockade standpoint, what are driving potentially some of the inequities? And certainly, there's also opportunity to think about other diseases and as they have introduced treatment, what inequities have we seen develop? Because I think it is a point in time that we haven't seen in public health in quite some time where there has been a disease that has a new treatment introduced and an opportunity to be thoughtful, deliberate, and planful toward models of care that help drive equity instead of models of care that drive inequity. So these are pressing issues on us, in the US today, in Japan, I imagine, also. But as we think about globally what this does in the years to come, certainly we have a lot to think about and plan toward. So, with that, I would love just for our panellists to make any opening comments on this topic or experience what you are seeing and thinking about and planning towards as well. George, would you like to start over at the end?

George Vradenburg, *Chairman, Davos Alzheimer's Collaborative and UsAgainstAlzheimer's*

The Davos-Alzheimer's Collaborative was set up as a global mechanism precisely to link and scale efforts that occur in low- and middle-income countries with those that are going on in high-resourced countries. As a number of people have pointed out, there are low resource settings even in high-resourced countries, but there are also high-resourced settings in low-income countries. So this is not just a country-by-country differentiation, it is how do we get treatments into all resource settings. And so, what we're finding is we work around the world in research cohorts, collecting blood samples from all over the world. We need to get the understanding of the genetic diversity around this disease globally. Africa is the most genetically diverse continent on the planet. The United States or Western Europe may be genetically much more homogeneous. So how can we learn from the genetic diversity of parts of the world to import or export that knowledge into other countries? We are trying through global work in many countries around the world to bring the learnings from low resource settings into high resource settings and high resource learnings into low resource settings and to do that at scale so that, in fact, we deal with this problem wherever those with dementia are. So that's our mission, that's what we're doing. And so I'm here to learn from all of you about how best to implement that.

Suvarna Alladi, *Cognitive Neurologist with National Institute of Mental Health & Neuroscience*

I'm a neurologist from Bangalore, South India. Since Joanne asked us to predict how treatments would affect inequity, I thought I'd go back to the last three decades to address this. In the 1990s, surprisingly, a study from Kashmir found "no person with dementia" in a house-to-house survey. Even now, only 1 in 10 get diagnosed. So diagnosis was a concern. But there have been some great innovations in the last few decades. Just like we stand at the brink of a new treatment today, and new forms of diagnosis based on biomarkers, there have been moments in the last three decades just like these. So I would like to discuss what those moments of advances in the past taught us about iniquity? Have those innovations driven us further apart or have they brought us together?

The first form of diagnosis for dementia was a simple cognitive test. To diagnose dementia in India, we had to move from a culture where memory loss and dementia were considered to be part of normal aging. We then had to adapt these new cognitive tests to improve diagnosis of dementia in our patients. We just heard in the previous panel that the cognitive tests were not culturally appropriate, as they were developed for a western educated population India is a land of hundreds of languages, and variable levels of literacies, and we spent 10 years developing tests in one language, then two language, three language, nine now and counting. And we also harmonised diagnosis across linguistic diversity. But where are we now? Nearly 25% of Indians are illiterate, and we do not have appropriate ways of testing cognition in them. Some of the illiterates can perform some really complex skills like crafts, weaving and pottery. Our adapted tests do not pick up cognitive functioning nor deficits in these diverse populations fairly. So, if we had addressed this issue of developing tests for a diverse population at the beginning itself we might actually have reduced inequities. But we have now in fact exacerbated inequity, by focusing on literate people, leaving the illiterates out of our diagnostic efforts. This effort remains for us.

The second breakthrough for dementia, was maybe in the 2000s and this was in the area of treatment. I was working with a professor of English literature who was struggling with non-fluent aphasia. She had stopped speaking for six months after which we tried speech therapy for her,, with the help of her daughter Those were the times when there was no evidence for speech therapy for progressive aphasias. But I remember her completing my sentence while reciting the story of the hare and tortoise. When I said "slow and steady", she completed the sentence "wins the race!" A previous speaker was talking about enjoying while we work in the field of dementia in the first panel. So for us, that was an enjoyable moment of treatment, when our patient with non-fluent aphasia started speaking with speech therapy. So we discovered that multidisciplinary care, environmental modification and non-pharmacological treatment did work. This was exciting stuff and it changed the course of disease. But then again, this form of treatment was not made accessible to all. While rehabilitation was a effective form of treatment, this treatment has not reached everybody even in two decades.

The third innovation was in the area of prevention of dementia. We know from the Lancet commission that dementia risk can be reduced, by addressing modifiable risk factors. But these factors — such as education, vascular risk factors, social isolation, obesity, are iniquitably distributed in society, So the third lesson we learnt was that unless we address iniquities in general, we are not going to be able to reduce the risk of dementia in our society.

And finally, coming to today, when we are discovering biomarkers for dementia diagnosis, with the thoughtful planning that is going on into their use, we have an opportunity to address inequities. Learning from the past, as we develop these biomarkers, as we develop these treatments, from the very point of inception, we must think about the global implications of these discoveries. At that point of discovery is when we have to think of diversity. At that initial point is when we have to think of addressing inequity, otherwise it will again be a similar situation 10 years down the line, similar to what we are now facing with disparities in cognitive testing, non-pharmacological treatments and preventive strategies.

I do think, the concept of brain health is a fantastic way of addressing this inequity as the policymakers are actually listening now. In collaboration with NIMHANS, the government of our state Karnataka announced

the pilot project of the Karnataka Brain Health Initiative in three districts, and following its success, the Brain Health Initiative has now been advanced it to all the districts of Karnataka. The state has also announced the first Dementia Action plan. The aim is to promote brain health, facilitate early diagnosis and treatment for dementia and other neurological disorders, across all levels of care. So, I think the time to address inequity is now, with regard to biomarkers and new treatments through advocacy, and policy, and we should really do this now. Thank you very much.

Ryoji Noritake, *CEO & Board Member, Health & Global Policy Institute*

Thank you. Japan is one of the few countries where we reimbursed Leqembi. The question is whether this accelerates the chasm of social inequity. I try to give an answer: no. It's just a revealer of social inequity. Generally speaking, new innovations, new technology, will in ways reduce inequality. New printing technology, several centuries ago, brought new books, people can read more, it helped drive literacy. Smart phone help with everything from banking to telemedicine. Shall we prohibit smart phone from society because this is creating social chasm? The answer is perhaps not.

The second point I would like to emphasise is there's always the first penguin dilemma. The first penguin, through jumping into the ocean, had a risk and a benefit. It is the same for the treatment. You know, people say that the first penguin is brave, but it is a risk that it took. You get the treatment, you get the new medicine, but we know there's unknown side effects, unknown risks, and the drug is expensive. The first penguin is brave but carries the burden of risk.

Fundamentally inequality in society will not be eliminated. It is an inevitable, sad reality of human being. But we can be aware of that. Inequity actually decides your health in a way, which family you are born, which district you are born, which country you are born, that actually affects your personal health and that's social determinants of health. We can't get out of this frame as long as being the creatures of this world. So, let's face it. We can have the moral will and the political will to at least reduce it. But with certain sensitivity not to be paternalistic not to be too medicalised perspective not to prioritise medicalization too much or over human touch care.

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

Thank you. Ryoji, while you have the mic, let's stick with your experience so far, because Japan is unique in a lot of ways, and certainly as a super aging society, but geographically. And one of the things that I know we did at the Alzheimer's Association when we knew the treatments were coming was to think about where will they be located and where are the population centres within the US and what is going to create disparities and access first. There's access and then there's the ability for someone or the trust of someone to go to the system to access it. But distance was one of those first barriers. Japan, like the US, has a huge distance from one end to the other. It's the same as New York to LA right so what are you experiencing from the standpoint of access barriers?

Ryoji Noritake, *CEO & Board Member, Health & Global Policy Institute*

That's a very good point, although Japan is long the southern part is long so mainly it is just ocean. But when it comes to access, I think there's an inevitable situation, access to the provincial centre which provides PET screening is actually a requirement for Leqembi to be provided. So there's access issues, but it's not health care as such, it's more transportation, telemedicine, technology all combined.

But more importantly in terms of access is access to information, not the geographical access, but the information how the government, how the medical institutions, how society can provide people friendly information. Because we know there's a new treatment. It's been reimbursed in Japan. But if you live in a countryside with limited education you have to get information by yourself. And you have to communicate with your doctor with background knowledge. Knowledge, that's already a cultural capital. But how we can provide them with people friendly messaging, especially from patient advocacy organisations and charity organisations together, all together. So, I think that's the real access issue in Japan and the United States.

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

Thank you. And Suvarna, you mentioned the last 30 years. Thinking about the next decade and the disparities that you have in India from wealth gap to education gap, what do you feel like is one of the — I'm not even sure there's one — but an area that needs to have some policy intervention in order to benefit as innovation comes out of the pipeline.

Suvarna Alladi, *Cognitive Neurologist with National Institute of Mental Health & Neuroscience*

I think decentralization of knowledge from few pockets of power: social, medical, or it could be economic powers, to the people on the ground, is a major way to reduce inequities. How will we do that? I think by working from the level of families and local communities and by basing work on a lot of qualitative research to understand local needs. A model of care has to be developed that is locally relevant. We have many states in India with diverse socioeconomic and cultural backgrounds. Some of our states have 100% literacy, Kerala for example has 100% literacy, while some states have very low levels of literacy. So, developing a model, taking into account local health care needs, health practices, languages, levels of awareness, funds available and state level policies is crucial. I think a model that takes into account community needs, that includes primary secondary and tertiary levels of health care systems, and includes prevention, treatment and rehabilitation, that's the model of brain health that needs to be developed.

We do really want to conduct clinical trials for our patients, to make sure therapies are accessible to all. But as we develop infrastructure for clinical trials, a serious understanding of our patients' perspective is needed How does the person living with dementia and family feel about diagnosis and treatment? How do they feel about the infusions and side effects? What does clinical meaningfulness mean for them? So, I think having integrated qualitative research is essential,is needed. That's where most efforts have to be focussed. That would be the way forward, in my opinion.

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

Thank you. George, as a fellow American, is there anything that you have experienced or seen so far in your role within the US health care system that needs additional attention in the short term in order to make gains in the long term?

George Vradenburg, *Chairman, Davos Alzheimer's Collaborative and UsAgainstAlzheimer's*

I'm going to answer that question and then come back to the prior question that you asked about the next 10 years.

Well, clearly right now the rate of take up of Leqembi, which is now approved in the United States and reimbursed, is very, very, very slow. Because notwithstanding the policy of the United States government that we reimbursed for the medicine, the Medicare system is very slow paced, it is taken case by case, and as a consequence most of the people on this drug, it's only a couple thousand people on this drug, are private pay. So what we are seeing already is the take-up rate is slower than it should be, simply because of the United States government has not executed efficiently the payment mechanisms that it has promised to do.

Clearly, in the median term, I'm thinking next couple of years, we need to bring down the cost of detection and diagnosis, and that means blood base markers. We are working systematically to identify those blood-based markers, that are equivalent to PET. So they can be substituted for PET scans as a mechanism for diagnosis.

Third, we have to get this out of the neurologist community exclusively and paired with primary care physicians. And so we are meeting fellows in American health care systems that will work with the business side of the health systems to say how do we offload some of this work in terms of detection and diagnosis on to primary care physicians?"

So, in the next two or three years, there's a lot of unblocking and tackling simply to get through the American health care system.

The other question, the next 10 years. I have now been to a number of global health summits. Everyone talks about vaccines. And guess what? American and European and other nations are investing heavily in

global mechanisms on vaccine surveillance of infectious diseases and vaccine development for what may be detected in the future. Enormous amounts of money. The United States government puts in tens of billions of dollars a year. Why aren't they doing that with Alzheimer's? Alzheimer's is now a global health issue larger than infectious disease. More people around the world dying of Alzheimer's than COVID. Even during the COVID pandemic. And polling on the United States shows people are more afraid of dementia than they were during the COVID epidemic. So we need to really work on governments to think about the global health challenge.

And we need to think about vaccines. That is key for the next 10 years. What's coming through the pipeline it's not that robust, folks. People talk about 150 trials of products in the Alzheimer's pipeline. We need products that can significantly and transformively reduce the cost and increase the access of Alzheimer's treatments around the world. There is not that much that is going to other than a vaccine. Eight companies now have vaccines in clinical trials. We're working in combination with regulators from around the world about what the regulators need by way of evidence from those clinical trials in order to approve them. We will shortly start a collaboration with peers around the world to say what's the cost-effectiveness model that you will use to assess whether to reimburse for the assessment of whether someone is appropriate for a vaccine. So, this collaboration with governments on policy and with the industry and with the researchers is essential to get to a vaccine in 10 years. But I believe, and so the sponsors, and there are a number of them large pharma, a number of large, well-funded biotechs are on track with major phase 2 trials which are either reading out this year, or starting this year and will read it out in 2025.

So, we are going to be on the path to a vaccine that is going to increase access that's going to deal with inequity to some extent because we know that there's vaccine hesitancy around the world and there's not necessarily an adherence to vaccines even if available year after year after year particularly if you're healthy. So we have problems that are not only through the policy system and the scientific system, but we also have efforts that will have to be made in order to get vaccine adoption and vaccine adherence. But that will transform the inequities of current high-price, difficult to diagnose, difficult to get on drugs. Thank you.

Participant

We talked a lot about stigma, and brain health. But there's also this unspoken thing for why do we keep on seeing these inequities? Why do we keep seeing 98% white people of European backgrounds in research? And I think because of that, there's a big stigma in brain health research. So, one of the projects I looked at is why do people participate in brain health research and why are they worried about brain health research. And there's this massive fear just about getting involved in this type of research, which I think needs to be tackled, of course, with vaccine health use as well.

Shibley Rahman, *Honorary Visiting Professor, University of Liverpool*

I was having trouble following the structure to your answers but I think it would be helpful to me if you produce a full frame of looking at it. One I suggest, for example, is looking at health disparity, however so defined, amongst the people with dementia and the caregivers. Now, my position as chair is in the sociology, so I'm going to take you to an area you really don't want to go to which is discrimination. I would say the biggest cause of inequity is the market.

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

Thank you. I think that's a very valuable insight to bring up discrimination. And just a quick comment on that, we know that discrimination occurs in the health system. And we also know that people do not trust the health system because of their experience of discrimination. I think it's important to acknowledge that inequity is built on, is based on, a history of discrimination and experience of discrimination. And I know that's something that we have looked at within the Association from a reporting standpoint, but I don't think we can drive towards a health system that is fair and equitable without acknowledging it. So very valuable.

Mahadev Ramji, *Medical Director, Panthera Biopartners*

I wanted to expand a bit more on the question of why most of the trial participants are doing what Caucasian males. One of the questions I get asked is how you increase diversity across trials. It is a very good question. One reason is even though these trials and work are being run across the world, there's no functionality in a country level to change the language in that particular country unless there are technology companies involved and that comes with a cost. Which means that right from the get go, we are excluding valuable data set out of that particular general development phase. It is not just in Alzheimer's, it is across the board.

George Vradenburg, *Chairman, Davos Alzheimer's Collaborative and UsAgainstAlzheimer's*

One of our affiliated enterprises called the Global Alzheimer's Platform Foundation and we've insisted, as we do these studies for industry, that they set an inclusion criteria. It is of X percent. Right now it's 20%. It will be higher. Before they stop recruiting for a clinical trial they have to get a minimum level of diversity. Our own clinical trials in that system are getting to 25% and 30%. The staff of that particular part of our operation is now 40% diverse, simply because we have to have people in the system that understand precisely what you talked about.

The value of diversity is important, not just for the diverse populations, but for white populations. Because we'll find that in fact different people react differently. We're finding already that biomarkers, that the blood-based biomarkers do not work the same way with the same cut-offs, in black African American populations as white populations. Because it turns out that the same level of cognitive impairment in an African American in the United States, they have lower levels of amyloid. So when the blood biomarker sets its cut-off point, it sets at a higher rate, fixed because of what has been the standard for white Caucasians, when, in fact, we need to begin to think about how it is that these cut-off points are different for blacks. Why are they different? Because it may be that blacks in the United States have more vascular dementia than Alzheimer's. Maybe. We're learning through this process, but the importance of the point that you made is to think about this upfront and to force change in the system. We're not gonna be able to conduct clinical trials solely in white populations or solely in black ones or Latinos or in the trans community. We can't do the clinical trials that way. It will be impossible, but we need to have inclusion and we need to have the ability to get sub-population to see if there's any signals that in fact these drugs in clinical trials work differently in the different sub-populations. So I agree with you. I think it's important.

But right now, clinical trials by industry are done largely in major markets where they can sell drugs. That's Europe, UK, United States, and Japan. And now the industry is beginning to look to China because it's a market. And in fact, the other markets of the world will open up, you're going to start getting more clinical trial sites in other parts of the world that reflect the commercial opportunities of these drugs. But until you do, we're going to be struggling to force industry to begin to open clinical trials in India or in Indonesia, or in Brazil, or in Nigeria, because that's not where their products are being sold. That's not where they have to persuade regulators. That's not where they have to sell treatments. So, we've got work to do.

Academic trials in the United States, which is funded by the government, are worse. That allows it, because academic centres in the United States aren't close to the populations that we intend to serve. If you head to the private side, it reflects where you are located. A private site in South Texas where 95% of the population is Mexican-American, and there is a 50% dementia rate, we can locate a private site there. Academics don't follow. They don't go to the population centres. So, we have a problem here, and we're actually ready to focus on this.

Ryoji Noritake, *CEO & Board Member, Health & Global Policy Institute*

Thank you. For the ethnic diversity and inclusion in clinical setting I think we need again behavioural change proactive participation from those ethnic minorities. We can't force them force us to come to us. So how we can change behaviour. It's proactive. Which means that they have to digest the information. They have to understand the meaning and importance.

And from that perspective, I think COVID-19 was actually a great analogy. In COVID-19, even in this mature civil society in Europe, people were demonstrating against the national state, big brother, controlling your personal health, saying that the vaccine is a conspiracy. People said they wanted to have an ownership of their health. But actually, if you do a study on this group, they actually do not have that much information. They are dependent on certain, narrow, source of information. So, they actually do not own their personal health either. So how to give them, again, people friendly information to help them understand is the fundamental solution. I think information is a driver of behavioural change.

We can't tell them to change behaviour, however, we can give them friendly information.

Suvarna Alladi, *Cognitive Neurologist with National Institute of Mental Health & Neuroscience*

We did conduct clinical trials in 2000s in India. I was a part of several clinical trials in Alzheimer's disease, but even then, there was a lot of exclusion. People with low levels of literacy, with co-morbidities could not be included. But we have learnt a lot from those efforts. I think the effort to widen implementation of clinical trials has to be from both the global community, as much as from within the local community. So, within our countries we have to know whether there is enough momentum among people and decision makers, to really implement proper evidence-based therapies, not just pharmacological, but non-pharmacological therapies as well. And the global community has to get together to make sure that it includes diverse populations.

When the drug comes into India, the rich people are going to benefit. The neurologists will prescribe the drugs, but because of the high cost, again only people that can afford will get the drug, and the poor and under-served will not. So, we have to push back on that from happening and bring in the new diagnostic sand therapies in an equitable manner. I think bringing biomarkers and drugs into an economy like ours should be done in an equitable, and thoughtful way and that is where they need support of global communities. The Alzheimer's Association does a great job of educating international researchers through initiatives like ISTAART for example, So, I think awareness, education, health care infrastructure, community, local efforts and national efforts are all equally important when you're bringing in new diagnostic modalities and therapies into our country.

Sarah Lock, *Senior Vice President for Policy & Brain Health, AARP*

Ryoji, this is really the question for you. The point you made earlier about innovation not creating the inequities they already exist. Because Japan has been grappling improvement care and trying all kinds of creative ways over the last 10 years or 20 years to address this before many of the rest of the world, with regard to inequities relating to care and socioeconomic diversity what has worked, if anything, in Japan that we can take lessons from?

Ryoji Noritake, *CEO & Board Member, Health & Global Policy Institute*

Thank you. I would say Japan's Integrated Community Care Model is a lesson. Which means not only health care or medical society but also social welfare, mental health experts, working together. Not having someone bossy to decide everything, but having a sort of consensus building model of what kind of care should be provided in a local, age community. I think that model has been introduced, I think it's 20 years ago now, and at the beginning it was a little bit chaotic because it's tough to find a leader in a consensus building model. But after having this program for 20 years, there are more tailor-made, personal, community-oriented, bottom-up approach. I think it's been built. So, I think I would say that is the answer to you. But back to your comments, I don't think Japan produced that much of innovation, though, in terms of care. So we can learn from others as well.

Zul Merali, *Founding Director, Brain and Mind Institute, Aga Khan University*

I just wanted to say that I think I love this dialogue and discussion in terms of us putting the real issues on the table and talking about it. And I also wanted to give a shout out to Davos Alzheimer's because they're putting money where their mouth is in the sense of dealing with inequities and capacity building regions that would otherwise take a long time to get on the ground. So, I think that through these types of partnerships and global initiatives, I feel very confident that we are beginning to address the issues where they begin, like right from the start. And I think that's really because the communities are much more engaged, really wanting to see change in a positive manner.

Howard Bergman, *Professor of Family Medicine, Geriatric Medicine and Oncology, McGill University*

We've talked about community-based activity and this links with the previous discussion, and now how come up again here in the context of rethinking how we do clinical trials. Instead of putting people into either university or industry trials, it's to have more community-based clinical trials and going where the patients are and, consequentially, where the diversity is. And by the way, we speak of diversity it's not just ethnical diversity, it's also socioeconomic, educational, status and so on. But this came up when we did the Quebec Alzheimer's Plan, we anchored in primary care because there you're really going to get our patients for clinical trials.

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

I think that is an excellent point. From our standpoint, community is where we see solutions. And there's a there's a famous quote in the US from one of our previous surgeons general that the problems are in the community and so are the solutions. And I think that's a powerful way for us to end, Howard. But before we do so let's turn to our panel for final thoughts in terms of anything you might want to add and if you want to tackle the idea of technology and being able to address inequity as well. It's multiple choice. You can pick which one you want.

Suvarna Alladi, *Cognitive Neurologist with National Institute of Mental Health & Neuroscience*

Translating technology to diverse populations also requires work from the very beginning, i.e. at the stage of development of the technology. It is not simply a case of lifting a technology and inserting it into a new population. New technologies like memory aids and fall detectors, artificial intelligence, precision medicine, as they migrate it to a different environment require not just translation, just as in the case of cognitive testing. I think the word innovation needs to be really understood better. An idea is only innovative if it is relevant to more people than not, an idea that is truly something that will work for all people in need. Massive amounts of work therefore needs to be put into developing technologies for global societies. I think that's where we need to go in our future efforts.

George Vradenburg, *Chairman, Davos Alzheimer's Collaborative and UsAgainstAlzheimer's*

Well, I'm going to take a slightly different tack. I think something has to be mentioned, and that is the relationship of prevention in the lifestyle context to treatments. We now know from the lot of basic research that there is a deep connection between diabetes, obesity, and hypertension and dementia. And so I can see in the next 10 years in addition to a vaccine, programs of brain health programs in nations which link widespread use of GLPs to attack myocardial metabolic conditions, attached to and linked to, the collection of blood for genetic and biomarkers of aging and biomarkers of Alzheimer's, to track the reduction in the prevalence of dementia over time. So, I do think that there are new approaches that we can link on the prevention side in the sense of prevention through cardio metabolic and risk reduction techniques with therapeutic interventions. But I am extraordinarily optimistic in the next 10 years that we will have jumped way beyond where we are today both in terms of vaccines and prevention of brain health plans around the world.

Ryoji Noritake, *CEO & Board Member, Health & Global Policy Institute*

I think it is important, we spoke in the last session about stigma, but there is cultural sensitivity as well. Often it is a coping mechanism. We shouldn't blame people. Yes, we have to fix Alzheimer's disease, but we have to understand people's perspectives and their way of life. We can't just reduce this to a question of science. We need science, hardcore science, that will deliver treatments but as well we need the good will of the population. We need to bring people on this journey.

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

Thank you to the three of you. Thank you to all of you for your comments and thoughts.

Clinical Meaningfulness: do we know what we are aiming for?


Philip Scheltens
Chair


David Llewellyn
Speaker


Argonde Van Harten
Speaker


Johannes Streffer
Speaker

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

An important topic, a very difficult topic. We also discussed this last year at the WDC meeting in the Crick in a different setting a little bit, but it's about clinical meaningfulness, and we all think that we know what it means. We all have our own ideas of what it means. The patients have their ideas, the doctor have their ideas, the carers have their ideas, but do we know what we are aiming for, especially if we're talking about developing therapy it is really important that we understand what is actually the clinical meaningfulness of what we are doing. So I would invite three panelists:

- David Llewellyn, Professor of Clinical Epidemiology and Digital Health at the University of Exeter;
- Argonde Van Harten, the Amsterdam University Medical Center, Alzheimer's Center; and
- Johannes Streffer, Senior Vice President Head of Global Clinical Development Lundbeck.

What does clinically meaningful mean for you?

David Llewellyn, *Professor of Clinical Epidemiology and Digital Health, University of Exeter*

That is not a simple question. There are different elements to it obviously. For something to be clinically meaningful in this context you have to have change that is large enough, whatever that means, and I don't think that is a trivial question in itself. We have trials showing statistically significant changes on old school cognitive assessments or a change in amyloid load on scans. Is that clinically meaningful? There are separate studies showing that the changes we are seeing in these trials wouldn't be clinically meaningful. So is it a big enough change to be clinically meaningful that is doubtful. But second of all does the benefit, however big or small it is offset the risk and costs. So we are seeing treatments coming through with not trivial side effects — so maybe 20% with bleeds, swellings and the odd one dying. Does a small difference off-set that risk. I am not sure. And lastly when we do trials we do group level differences and clinical meaningfulness is whatever clinically meaningful to patient and family. To me we are looking at trials with small effect sizes, worrying side effects and we are bundling everyone together. If you were one of the people who died that probably wasn't a good trial. But if you went down three points while everyone else went down six then it probably was. So not an easy question.

Argonde Van Harten, *Neurologist and senior researcher, University of Amsterdam*

Fully agreed. Just to make it a little bit more tangible, some things have face value in terms of clinical meaningfulness. For an example, just last week I saw someone on a small molecule and he started out with an MMSI of 24, and now for two years he's been having an MMSE of 30. So I don't particularly like the MMSE I just know that he's doing well and so doing well that's easy. But the unfortunate thing is that we are talking about what's the bare minimum of clinical relevance and does it offset all those other risks and that's a think the important part and the difficult part.

Johannes Streffer, *Senior Vice President and Head of Global Clinical Development, Lundbeck*

So you already said earlier that clinical meaningfulness is a very difficult concept so I would much rather not like to talk about clinical meaningfulness. I would like to offer three other ways how we can potentially break down a very difficult topic into a little bit more palatable parts. That would be benefit risk, cost effectiveness, and patient preference. So I think benefit risk is something we have been used to talk about for the longest time, right? So that has to take into account how serious is the disease, what is the problem the patients are facing, what is the potential benefit, and what is the risk with the medicine. I think this is something that we talk a lot and I think regulators, physicians, are very comfortable talking about.

Cost-effectiveness is super-difficult because obviously that comes with a very loaded discussion how much value do you assign to health and maybe just as an anecdote, my aunt was in public health in Germany and I think already in the 90s she participated a few years in round-tables discussing health goals so defining what a health system should aim for and they did that for a few years and dissolved it because they couldn't agree on what not to do because it ended up with huge wish list that everybody wanted to have their poster child first.

And the last concept that I really like, and I think it's critically important, is patient preference. So we have to ask the patients what do they like, and patients can say that. Now, patient preference obviously comes with an effort. We have to make an effort and inform patients. So we have to inform patients about what is the risk you're facing, so potentially if we will give this drug to 100 people, there is a risk that three of them can have side effect A. But let's say, don't belittle it, but explain it in a way that everybody walking out of the room understands what this means. But it as well means that we take an effort to explain to them what the benefit would be, and that has to be in a similar way. We have to describe it in a way that patients can take a decision. And I think Lenny made the point at the beginning of the summit, people can take a lot of decisions. And I think as patients can take informed decisions, societies can take informed decisions on what we're willing to invest.

And I think if we break it down in these concepts, it's much easier to discuss, because as my colleague said, clinical meaningfulness is such a big concept that it's very difficult to break down.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

I agree completely. But still, the reality is, so, for instance, we have now a therapy that's been approved on the basis of slowing decline as compared to placebo with a certain percentage, and we think, yes, this is huge, this is enormous, this is because you remove amyloid. And then the question comes, yeah, but how do I translate that into clinical meaningfulness? Does that mean that we are using the wrong endpoint? Should we put in sort of the discussion on the clinical meaningfulness earlier into the design of our trials? And if yes, how do we do that?

Argonde Van Harten, *Neurologist and senior researcher, University of Amsterdam*

So I like quality of life for the entire system in terms of the, of course, the issue with quality of life is that for a patient living with dementia it's really difficult measure also but then there's the quality of the system and it captures a lot of things that we don't capture in a cognitive test we know from clinical practice that it's really difficult to capture someone's life in any test.

Johannes Streffer, *Senior Vice President and Head of Global Clinical Development, Lundbeck*

I think that is a great way to go. And in truth, it's as well a way for us physicians to get out of the ivory tower, right? I've headed a memory clinic for seven and a half years and neuropsychologists always will tell you, "I can measure that the most precise way". And in clinical trials, we always want to have a psychometrically precise test and that is the best thing to do. Now, then we got surprised in the trial where there was a PRO, a patient reported outcome. You ask the patient, you ask them, how they feel. People feel that will be imprecise, and the patients change their mind from day to day. And in the end of the trial, the PRO was better than the highly specialised, rated test instrument where everybody had said, "that will be precise". Now, patients can be very precise if you have the right tool.

David Llewellyn, *Professor of Clinical Epidemiology and Digital Health, University of Exeter*

I think one of the problems here is that we don't gear up to do trials in this kind of way. We'd follow them for a few months and look for disease modification. We don't look over the lifespan at, you know, long-term quality of life outcomes or whatever which is actually what we are trying to achieve but it is a much more ambitious goal. But coming back to what the previous panellist were discussing about innovation why don't we think more serious about nested trials where people are being followed anyway often through online cognitive assessments or similar. That is scalable and interesting. We could be following our patients as part of larger trials. Over 12 months or 24 months we are not going to know the long term results, even the effect on mortality. Even if we give a disease modifying treatment we slow the accumulation of the underlying pathology but if we live longer what does it mean for quality of life? You could make it better over a two year period but worse over an eight-year period. So we need to be careful about what we are really asking.

Russ Paulsen, *Chief Operating Officer, UsAgainstAlzheimer's*

So it's not a question, Philip, it's actually sort of a comment, but we would agree with Johannes that this is a really complicated question to unpack clinical meaningfulness. We've been on a five-year journey to do that —and Lundbeck actually helped us start five years ago — to try to unpack this. We've now talked to 375-380 people living with dementia and their carers, in the US. It's a diverse sample so far, with 35% black, Latino, or Asian. So it's US-specific but it's diverse for the US. And what we found when you first start talking to them and doing a long interview is what they really want is more time. That either get my time back, so reverse the disease course, stop the disease, or slow the disease progression. So at one level that's what's clinically meaningful to patients and their carers. And we discovered, we talked to people across the entire disease spectrum, that's the same for everybody, earliest to latest stage of the disease. But then you have to sort of say, "So what does that mean?" That's why it's complicated, right? So time to what? What is the "event" that matters in a time-to-event analysis? So we start asking, "What are the things you have in mind?" And that gets complicated. We end up with 42 items of interest to people living with the disease, and they all rate highly. We put them on a five-point scale, and we really found the ceiling effect, because they're all four to five, but there's 42 things that matter. We're now grouping those, there's six domains. One of the important things we discovered in the early research is that Alzheimer's is not just a disease of forgetting. The neuropsychiatric symptoms are huge, all of those things are huge. So lots of different domains. And by the end of this year, we'll be at about 1,000 people we've talked to and we'll be able to actually rank those concepts to understand: for people living with the disease and for the people who care for them, what does clinically meaningful look like? And I want to make one last thing. We need to distinguish clinical meaningfulness from minimal clinically important difference because the concept of MCID was quoted earlier already today and we need to distinguish that from clinical meaningfulness. Any estimate today of MCID in Alzheimer's is wrong because the MCID papers that are out there only asked clinicians what they thought about their patient's progress. And the people who invented MCID will tell you MCID was invented to figure out what matters to patients and what's the minimal important change to them, not the minimal change to the clinician. So we need to be careful about making those distinctions and rooting everything on what some doctors have thought historically.

Argonde Van Harten, *Neurologist and senior researcher, University of Amsterdam*

So fully agreed. It's about the patient and what they feel is meaningful. That's the most important part and also fully agreed on the MCID data that's mostly based on clinicians and then you get really, for example for the CDR sum of the boxes, you get really high scores. I saw a recent paper from the NAC database, which is also really interesting, which looked at the clinical meaningfulness for patient, study partner, or support, and the clinician, which was really, really interesting. And then a CDR sum of boxes of anywhere between 0.2 and 1.8 was determined to reach those criteria. And that just says that it doesn't capture everything that's important, I think. And mainly, it doesn't capture everything that's important to the patient. So that's a very important comment.

John Gallacher, *Director Dementias Platform UK; Professor of Cognitive health, University of Oxford*

Just to go back to the new science requires new designs, and to pick up on David's point, to have a large cohort, within which you can do stratified nested studies in the longer term is more informative and more cost effective than a whole raft of short term studies. You get the short term benefit if there is any, you get the indications of any long term benefits, you get the opportunities to test interventions, all in highly characterised stratified populations. This might require an investment in the beginning but even that isn't that expensive with new digital technologies. But that is the transformational design technology in terms of early detection and disease progression and ultimately comparing the treatments.

David Llewellyn, *Professor of Clinical Epidemiology and Digital Health, University of Exeter*

I agree. It is a variant on the platform trial design idea essentially. But you have additional information like the trajectory of those individuals before they are recruited to the active arm in a nested trial. It is a very odd mentality that we keep recruiting placebo groups for separate trials. Then we set the trials up. If Chris Fox is quick enough he gets to be one of the sites. If not he is left behind. And then we move on to the next trial. It is like building a football stadium someone said for each game. It is ridiculous. We have to be trialling things out in different ways but it has to be adaptable and at scale as well. Because we are always frustrated looking for tiny effects with crude measures in moderate sample sizes. We think 1,000 or 2,000 people is a big trial. I don't know why we accept that. We need to upscale our ambition.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

Which will be another challenge for recruitment. Which isn't a problem in cardiology. They have 10,000 people in a trial. They never rest these cardiologists. They just put everybody in a clinical trial. But in our field, it's almost un-discussable with the patient. No, no, I want to care. It's all MRI, lumbar punctures, what's said this morning as well. I mean, this has to change. But it changes with us. It has to change with us as well, to be honest.

Johannes Streffer, *Senior Vice President and Head of Global Clinical Development, Lundbeck*

I feel, we all agree on everything. Maybe I have to disagree a little bit. We are not looking for tiny effects, right? I mean, I think the overall agreement for all disease modifying treatments is you have to be somewhere between 20 and 30% slowing of progression. That is actually what we're talking about as well for the current treatments. That's not tiny, right? And if you go to a patient and say, "you progress 20% less this next year," that's not tiny. They want that. And we have to ask ourselves the benefit-risk question is very important. And maybe, and now I don't want to sound too arrogant but sometimes we have to protect people and if Lenny's mother wants to go to the Kilimanjaro we should tell her that there are risks in that and I think we have to have in a way duty to explain to people what the risk is. When we did preference studies the amount of risk people would be willing to take for that 20 to 30% slowing of progression was enormous. They accept significant amount of stroke. So that was actually a non-ARIA drug. But we asked for stroke, all sorts of things including dying from a hypothetical adverse events. Patients are willing to accept quite some risk. Now, would we accept it, is a different question. So I think physicians have to come in a little bit in that discussion about risk. But it's not tiny and patients want new therapies.

David Llewellyn, *Professor of Clinical Epidemiology and Digital Health, University of Exeter*

Yeah, I think we need to be very careful when talking about relative differences in risk. We're not part of an advertising campaign for these drugs. A relative difference of 20, 30% can be a tiny difference in the absolute levels of decline. If you shift the dial, a couple of extra points by a scale that has more than 100 points you are talking about small differences. That doesn't mean they are not important, it doesn't mean that they are clinically meaningful, I am not arguing either way, but to take small absolute differences and then say well that is a 20% or a 30% reduction, I think is part of the problem with the communication. The risk benefit balance to patient if we are not very careful in the way we present this evidence. It is easy to pull the wool over people eyes. It might be a difference response if we said you would generate a couple of words extra on a cognitive assessment but the risks are this. It is so much down to the way we present it. And I think there are small effects personally. I have no conflict of interest here, just to be clear.

Johannes Streffer, *Senior Vice President and Head of Global Clinical Development, Lundbeck*

I have no conflict of interest in the meaning of this discussion. I would very, very strongly suggest that we go away in our current discussion from anything that is out there right now, as it is very loaded. When I say

20 or 30% that is what I had heard in discussions earlier, independent of all the results we're seeing right now. When we before there were any results and when people said what are we shooting for, then people said 20-30% of slowing of progression. So you can read these papers, it's out, published, patient preference, and then you explain that to people and say this would mean if you're in an MCI stage for five years You could be in an MCI stage, and MCI obviously as a concept has to be described, you will potentially be five to seven years. You're 100% right. We have to explain that to patients in a very down-to-earth understandable way but let's move away what it means on a given test, right? It cannot be one test alone. It has to be a functional test. It has to be a cognitive test. It has to be a slope measurement. And then maybe let's discuss what other tests we would be accepting to be meaningful in the progression of the disease.

If it's the wrong test, then it's the wrong test, right? But we have to be — just we have to agree that we can measure a change in slope and that is for all of us.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

I think if we translate that slope into time I think Ross will be happy because that's what people actually ask for isn't it and it's time it's what oncology patients also asked let me at least survive until I see my grandchild being born so I think time is of the essence to translate it to meaningful outcomes for patients time is one of them if I listen to you correctly. So, yes, go ahead.

Leonie Visser, *Senior Researcher Medical Communication, Amsterdam University Medical Center*

My name is Leonie Visser, I'm from the Netherlands, and we actually did a similar study, I think, like you did Russ. In Europe, we asked people what they thought is most important to know about the disease trajectory and on what outcomes or end points medication should have an effect. We also came to a list of 59 outcomes. But when we then fed back the items that people ranked as important and asked them to give them a top three to just shorten the list, a lot of these things came down to cognition. Well, that's nice because it's one of the outcomes of the trials, but the other category is that what's most important to them is function and independency, and it's then not an outcome on a test. They just want to know how long can I live with my partner together at home. So I think those are the outcomes that are meaningful to people and that we should take into consideration when designing trials or even when following up people in registries that we take these outcomes into account as well.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

Exactly and have the proper sort of measures to measure exactly that type of outcome in a trial as an adjunct to other ones as well.

Johannes Streffer, *Senior Vice President and Head of Global Clinical Development, Lundbeck*

100% agree, and I think that this is a task for everybody here in the room, and everybody presenting here in the room, right? There has to be an agreement on that, and it has to be based on what can be measured, what do patients want, what is accepted by the community. The worst thing we now have is that we have these enormous trials, and in the end, we discussed the outcomes, when the outcomes were known for a fact all along, So let's make sure before the next trials read out, we all agree it will be acceptable and we don't, as a community, fight about what does this now mean while everybody knew this will be coming.

Susan Kohlhass, *Director of Research, Alzheimer's Research UK*

I just want to go back to the innovative trial design and delivery. What is stopping us from doing that now.

David Llewellyn, *Professor of Clinical Epidemiology and Digital Health, University of Exeter*

Some people are trying to do it. There is something called the trial readiness platform in DPUK. There are studies like protect following people online with cognitive testing and doing nested design within them. But there is no obvious funding mechanism for much of this infrastructure. In the UK at least. You would have a conversation with NIHR for trial funding, with MRC for cohort funding but it doesn't do trials. And then you get into a tangle. Is it politics, or a lack of imagination, or funder preference? I don't know. This has not been the direction of travel so this would be a change. So couldn't we take some of the best ideas from epidemiology, AI and pharma. It involves thinking creatively in a different way.

John Gallacher, *Director Dementias Platform UK; Professor of Cognitive health, University of Oxford*

Well as director of DPUK let me respond to that. We have found that contacting is very difficult. The academic are slow and the different NHS centres are different and all the lawyers refuse to compromise. We have also found that establishing a standard set of procedures for biomarkers, cognitive tests and so on is extremely difficult because of staffing issues within memory clinics. We have found the will of investigators is high, they want to do this. But finding ways to do it that are contractually a way forward, so standard contract, standard costing, standard assessments, everybody would like to do it, but there seems to be a bureaucratic gap in the ability to do it.

Johannes Streffer, *Senior Vice President and Head of Global Clinical Development, Lundbeck*

And there are nested trials, right? So if you look whatever is happening within DIAN, it's perfectly nested within a cohort. I think the Healy study for ALS is more or less very much nested in a cohort. It is happening. It depends on what you have to demonstrate in which trial. I think for sporadic Alzheimer's disease, you will be in a specifically tough spot because the ask for these trials is potentially higher in a very unfair way because it will be a huge population treated with it in the end, right? And that is something we as a community potentially as well have to bring forward as a discussion point. Are Alzheimer's patients treated different because there are so many?

Harry Johns, *Board Member, ALZPath*

Just a few quick things on the meaningfulness. Harry Johns, former CEO of the Alzheimer's Association. Number one, no one has said in the discussion Alzheimer's is degenerative, progressive and fatal. The people who have it know that. They are rightly risk embracing as a result of knowing that. We should not deprive them of opportunities that are comparable to people who have cancer. Where added time in a minimum has been embraced as rightful for their access. And ultimately, as a prior panelists said in a different panel, in MS, for example, when we see the earliest treatment, when we see the path that is created to better treatments. If we go back even as far as early hypertension treatment, the earliest treatments were not very good not very well tolerated. So it has virtually always been the case that the first are not the best, that is reasonable to expect, and that those that are not the best lead to the better and ultimately what will be the best.

Johannes Streffer, *Senior Vice President and Head of Global Clinical Development, Lundbeck*

I hope I was not misunderstood. I definitely think patients should take an informed decision, but we have to make a real, real good effort to explain to them benefit and risk. And I think if you take benefit and risk and patient preference, you certainly come to something where patients very well tend to tell you. Unfortunately, there is the cost-effectiveness thing where we are all a little bit stuck.

Harry Johns, *Board Member, ALZPath*

Yeah, and then let me follow up too, if I can. I want to be very clear. Where every patient, of course, should be perfectly informed about what those very real risks and what those benefits are. My net point would be, we should not impose upon them choices made by the system that are not equal for them for what we provide to other patients in other diseases.

Argonde Van Harten, *Neurologist and senior researcher, University of Amsterdam*

Fully agreed. Yeah, but really. Oh, you want to challenge it first?

David Llewellyn, *Professor of Clinical Epidemiology and Digital Health, University of Exeter*

Yeah, I'll challenge that. So the amount of research funding going in to dementia is not in any way equivalent to the conditions you're talking about. So the options they have to recruit people to trial is not the same, it is not equivalent. And I just worry that our enthusiasm to discover disease modifying treatments we might make bad decisions about when things are ready for human trials, we might push things through prematurely, and, as we have seen to great controversy in recent years, we may rush to approve things without necessarily adequate evidence for clinical meaningfulness. There are lots of things in the pipeline. We have a duty to those patients not to give them things that are not ready and not appropriate. And there is a risk benefit to recruiting people to more trials. We all want to see more research. And more trials. Of course we do. We are all agreed on that but it has to be appropriate and responsible. And I don't think the other disease areas, which are decades ahead of us, in terms of publications and research and disease modifying treatments. We can't just pretend to bypass all of the work that they've done to get there.

Harry Johns, *Board Member, ALZPath*

If I can disagree back some. I mean, fundamentally I agree with everything you said in terms of protection of the patients, of course. The patient always has to be first in this. There's no question. But on the funding side, the Alzheimer's Association over the past several years has gotten the US federal government to go from $450 million to what is now more than $3.7 billion annually. Now that's still behind cancer, but there is a parallel in terms of the process to achieve what are the outcomes for patients. Those things that must be done to get the research and the outcomes of that research that will ultimately provide those answers, cancer was at about $6 billion when that process was initiated. Higher now, and the Alzheimer's Association, I'm no longer there, they still deserve credit for another $100 million just added in the last few days. So of course that has to go on, but I'm not sure there's a full recognition of the parallel of approvals in the cancer world in terms of the nature of the discussion for what is the amount of added time in the context of full information being provided to those patients to make their choices about what is available. With the proper things, of course, being the things approved.

Argonde Van Harten, *Neurologist and senior researcher, University of Amsterdam*

I agree, as I already mentioned in terms of effect sizes. We are looking at similar effect sizes that we are in the cancer field and maybe even in terms of to stay in the neurology field in terms of intravenous trauma lysis, which we all do even without asking patients informed consent sometimes to save time. So, I think effect sizes and numbers needed to treat are in a similar, in a ballpark figure, of those diseases, so that's really important. And the next important thing is the individual choice, and so I am not a health economist, but I'm wondering, will the cost be so very high if we select patients rightly? So, for example, in the Alzheimer's Center Amsterdam, only 7% of newcomers in 2022 were eligible for the current disease modifying treatment. That's a very small subset, actually. And then you can present those accurate data and the best information, to that 7% and in our experience, if we're trying it out a little bit, about 50% will say yes, that's worth it for me. And the other 50% says, well, okay, no, I won't go get an infusion every two weeks, for example. So individual choice when it's about these types of effect sizes is really important.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

So what I'm missing also, I mean, disease modification, as we measure it now with slowing of disease progression, patient themselves won't notice it. So what we actually need is of course symptomatic treatments basically that actually make patients feel better and actually improve We don't have them So why is that not happening?

Johannes Streffer, *Senior Vice President and Head of Global Clinical Development, Lundbeck*

It is happening, and I cannot comment directly as I might have a conflict of interest. There was a lot of effort. I think it's as well a question on how do we move compounds from non-clinical into clinical. Obviously, let's say, with the hypothesis around the amyloid cascade hypothesis and tau and inflammation, we have very good handle on the mechanism. What we currently think are mechanisms to go into the disease modification.

We do not understand the brain overall that well that we can have one pharmacologic intervention that would treat a deficit, like we see in Alzheimer's disease. There are a lot of different neurotransmitters, so I think there was huge efforts and you've been part of that and I've been part of it as an investigator to have cognitive enhancers and they are still ongoing. It's not that people don't try, but it's not so easy to have in a brain that is progressively losing function; to have the magic bullet that by a sudden brings you back to spring.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

True. But there may be other effects that you may sort of like sleep or other things that may improve the quality of life outside of cognition.

Johannes Streffer, *Senior Vice President and Head of Global Clinical Development, Lundbeck*

That is ongoing.

Participant

Because that made me think like if we think about symptom control or maybe just empowering people to better manage or live with their symptoms or maybe in their environment that people know better how to live with people who have cognitive symptoms could also have large effects if you look at outcomes that people find important, right? So staying at home for longer or having meaningful conversations with people that they love, and then it might not be medicines, but more cognitive behavioural therapies or helping counselling and I think we don't do enough in that regard as well.

Jayne Goodrick-Roberts, *Caregiver*

One thing I haven't heard until almost just now when you have talked about the size of the effect is that you get the double effect for those living with someone with dementia. What matters to me what my meaningful outcome, is to live with Chris as he is now for as long as possible to delay and slow down the progression. We'd be willing to take the risk on side effects. As his wife and supporter any benefit the clinical benefit the patient you have the double effect for me. There must be a cost effective benefit there.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

If you look in the Lecanemab study the caregiver burden and the quality of life, they're all in favor of the treatment, actually. And those measures we never actually look at, but you said quality of life is important. Well, it's there. Quality of life for the patient and rated by the caregiver as well. So there must be something there. So John, the last questions for you?

John Hardy, *Professor, University College London*

Two quick things. We haven't mentioned Down syndrome at all during the day. And people with Down syndrome who live to the age of about 35 well 95% of them die of Alzheimer's disease. So for them it is a fatal disease. We know when it starts to be fatal. I hope by this time next year the argument will have moved on. Because there is now real world use of these drugs. I have been listening to people from the Mayo and there experience was very positive, they have been very conservative with their use. I think in a year's time this argument will have moved on in some ways.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

I think given that I thank the panel a lot for their active participation.

Maintaining Brain Health: 10 years of incremental progress?


Joanne Pike
Chair


Sarah Lock
Speaker


Melissa Chan
Speaker


Franca Gatto
Speaker

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

Thank you very much. Let me introduce first the panel for this session:

- Sarah Lock is Senior Vice President for Policy and Brain Health in AARP's Policy, Research and International Affairs (PRI) Department;
- Melissa Chan from the University of Luxembourg is leading the co-development of a brain health workplace programme; and
- Franca Gatto is the Director of the Division of Aging, Seniors and Dementia at the Public Health Agency of Canada.

Now, one of the things that we certainly have seen more and more in the headlines is the promise and the opportunity that we have for brain health and prevention. From The Lancet report to the work in clinical trials, whether through a FINGER study or through another mechanism of looking at interventions and how we can change the trajectory. But one of the things that we have to be able to bridge is the research-to-reality chasm. And to think about what does that mean from a public health perspective, from different places within the world, from different cultural attitudes around nutrition and physical activity, and different thinking around what is available and how can we make that more available from the knowledge, the awareness, and the education about brain health?

So with that, each of our panelists comes to this with different experience, exposure, and certainly opinions. So we're going to open it up just with each of them from the standpoint of what are they thinking? What are they seeing? And what are they doing to tackle and think about brain health in the next 10 years? We'll then have a couple of questions for the full group, and then we'll open it up for comments and questions from the audience. Now, I will give the caveat up front, just like I did in the last session, that we have 45 minutes and now we're already down to 40. Once we go to group comment, we're going to try and keep them succinct and brief to make sure everybody has an opportunity to either comment or have a question. And we will do our best to make sure that we get through everyone. But I go ahead and apologise up front if I need to cut your comment short, or we don't get to your question or comment within the audience.

So with that, Sarah, I'm going to turn to you first for opening remarks.

Sarah Lock, *Senior Vice President for Policy & Brain Health, AARP*

Thank you. I just want to say that it's fantastic to be here at the World Dementia Council and have this interdisciplinary group of people come together. And I really appreciate, Joanne, your background in public health to have this conversation because I think we need to have bigger, broader conversations across the world about public health and brain health. It's terrific. And also that we're an all female panel. Congratulations to that. So I have lots of opinions, right? I have lots of opinions. And I'm going to share a few about them, about the next 10 years. Now Lenny made a mistake and he said you know throw it out there, so Lenny this is for you buddy.

In 10 years, I really hope that we stop talking about how difficult behaviour changes is. Everybody says it, everybody thinks it, but there are lots of hacks out there and ways of evolving behaviour change and some of the researchers that I work with in behaviour change are making real differences and showing that it's possible. And so I brought a little prop, it has something to bring health believe it or not! There is this newspaper iNews, I don't know what you all think about this paper I've never seen it before. But I was looking at it last night in my hotel and there's a well-being blurb. And it says, a free smart phone app can help drinkers substantially cut their alcohol consumption. This is a UCL app developed that got these people of all ages to cut their alcohol consumption by 50%. Now, if you can get a group of students to cut their alcohol consumption by 50%, I don't think behaviour change is that hard. We just aren't working on it enough.

So I hope in 10 years, that's one of the things that will change, that we stop saying behaviour change is hard and get into implementation. I know Melissa is going to talk a great deal about implementation, but I hope that everybody has implementation science as part of their tool chest trying to address the problems that we are trying to fix.

And that we are not just talking to ourselves. Employers architects, designers, musicians, everybody is talking about brain health. Because if we're going to change this big problem that we have to take it out of academia and research and have everybody talking about it. Because cognitive decline is not inevitable as you age, but people think it is. And as AARP has researched, 60% of Americans think that cognitive decline is inevitable. And the younger you are, the more likely you are to think so. So, we have to bridge these conversations amongst younger people and really start talking about brain health across the lifespan and activate people to understand there are things you can do.

And the final one is maybe we're having human rights lawyers talk about brain health at the World Dementia Council, and maybe law and medicine and academia and public policy are all sitting down at the table to think about these solutions.

So there's a few opinions for you.

Melissa Chan, *University of Luxemburg Senior Atlantic Fellow, Global Brain Health Institute*

I think a lot of the points I'll be mentioning will probably overlap with what Sarah has covered. To set a quick context, my background is in service design, development and delivery, mainly working with start-ups, corporates, and health care institutions to implement knowledge transfer projects. I look at knowledge transfer from the point of service, product, or program development. How we translate this layer of information down to the lay audience in the most effective, scalable, and engaging way using concepts like design thinking methodologies and user-centred approaches.

We're launching a Get Brain Healthy platform in June this year with Professor Anja Leist at the University of Luxembourg. Get Brain Healthy focuses on workplace employees, with the goal of guiding them towards a brain-healthy lifestyle specific to an individual's user journey or persona type. We cut across seven different domains that cover both work and life. Domains include focus, memory, skills, work environment, social connectedness, body, and emotional well-being.

The idea is to provide something that's extremely bite-size and actionable. Employees in the workplace are time and attention-constrained. They can't afford to read six paragraphs of text. How do we condense that down into two lines but still provide the science if the user wanted to dig deeper into the evidence around the recommended action?

There is a considerable amount of research on modifiable risk factors for dementia. I think many experts in this room can speak to that area of work. However, awareness of these risk factors is low. In one of the studies by the Global Council on Brain Health, more than 50% of the respondents couldn't even list a modifiable risk factor for dementia. This points to how there is a huge knowledge-implementation gap and how there is a need for us to create more accessible and contextualised interventions and programs. When we scope the market in developing the platform, most of the services are catered to the 65 plus —

those who are at higher risk of cognitive decline. There is an opportunity for us to move upstream to early and mid-life individuals, to guide them towards a brain-healthy lifestyle, as Sarah just shared in the news article. But also, to empower by setting a layer of growth mindset so that individuals know that change can happen with the goal of reducing the risk of dementia in the longer term.

Just to close with two points, and I will probably expand on them further in our discussions. In order to bridge the knowledge-implementation gap, I believe we need to tailor the communication and engagement strategies, as there is no one-size-fits-all approach. Adopting intersectoral and interdisciplinary strategies is also essential. Thank you.

Franca Gatto, *Director, Division of Aging, Seniors & Dementia, Government of Canada*

Canada is seeing a similar lack of awareness of dementia risk factors among Canadians. At the Public Health Agency of Canada, we are actively gathering, monitoring and reporting on key data points, and collecting new information to address gaps in data, including through public opinion research.

While we've been asked to look at the next 10 years, we need to go backwards a little. Over the last five years we've been concentrating our efforts to raise awareness of dementia risk factors, and our research is showing that there has been a 12% increase in people taking intentional steps to reduce their risk of dementia. We will want to continue to focus our efforts in this area in order to sustain that momentum. In taking a closer look at the data we've collected, our public opinion research indicates that people between the ages of 45 and 54 are the largest age segment to say they have intentionally taken steps to reduce the risk of dementia, followed by those aged 35-44. The only age group where the number of people taking intentional steps to reduce their risk of dementia drops notably, is those under 35. So it gives us a sense of where to further concentrate our efforts.

Prevention is one of the three objectives in Canada's national dementia strategy. The strategy is implemented across sectors, and across federal, provincial and territorial governments. The federal government provides financial support for health and social services, while it is the responsibility of provinces and territories to decide how best to administer and deliver health care and social support services within their respective jurisdictions and communities. Part of what we offer at the federal level are national level approaches to risk reduction and awareness raising, and over the last five years, we have implemented a national public education campaign on dementia, which has included a focus on risk reduction. A recent national advertising campaign helped raise awareness of modifiable risk factors generally, including 15 and 30 second commercials and print ads that focused on hypertension and physical inactivity specifically. In an effort to reach as many people as possible, messages were designed to ensure they were easy to understand and accessible for Canadians.

As I said earlier, we are seeing some success, as our research is showing an increase in people intentionally taking steps to reduce the risk of dementia, and an increase in people seeking out dementia information. During the campaign period, we saw visits to the Government of Canada's dementia website increase 15-fold to an average of over 50,000 visits each month, demonstrating an appetite for information specific to dementia. We're seeing this as a big win and are looking at ways to sustain those messages. We're continuously improving our website information and we work with experts in risk reduction in Canada to ensure that the information we share is evidence-based. In addition to the public education campaign, we also fund partners in communities across the country to raise awareness of dementia and its risk factors. Similar to the app mentioned by Sarah, we've recently funded a BrainFit app through the Women's Brain Health Initiative. It is showing some great results in terms of motivating change and sustaining that change.

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

Sarah called me out for being a public health professional. And so, my next question is really going to be couched in that idea of we know as individuals what we need to be doing. We've looked at the research studies and the behaviour change. Many of you may have either led, participated in, or may actively be using some of those interventions right now in order to in the long term improve your brain health or maintain your brain health.

That's at the individual level, but let's think about the population level and the change that we need to see from the public health community and in total across population. So, what are some of the things that we can do in public health or through policy to really impact population level change as well? And I know, Franca, you are just talking about a little bit of that, but what would you add in also for the future?

Franca Gatto, *Director, Division of Aging, Seniors & Dementia, Government of Canada*

Great question. I know, Sarah, you said, we want the answers to behavioural change, so maybe we could look at what has motivated people at a population level in the past. For example, what was the tipping point for tobacco and smoking? What happened, in Canada for example, for the population to shift its attitude from an activity that was socially acceptable in homes, restaurants and workplaces, to the complete opposite? Identifying what the tipping point would be for more people to take risk reduction action on brain health is key to motivating and sustaining these lifestyle changes.

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

Tobacco is an interesting case study overall, from the standpoint of you saw a population level change and it was multiple inputs that created that change from individual encouragement through some of the campaigns that really looked at the negative effects of tobacco to the environment in which the taxation, the inability to smoke indoors created behaviour change because it was entirely hard to do. And so, it's great. I love it — you see the public health excitement come out in me — I love it because it is a great example of using every public health lever to change population level indicators.

Melissa Chan, *University of Luxemburg Senior Atlantic Fellow, Global Brain Health Institute*

I think we need to redefine the narrative surrounding brain health. Whether it's how young people, employers, or employees perceive it, there's a need for a shift. When discussing brain health with employers, the immediate reaction often leans towards disease focus, fearing it may alarm employees. While there is progress around neurodiversity, there is still ambiguity about what brain health entails. What does brain health mean? Have we aligned on how we're going to present brain health to different demographics? It's back to the messaging again, back to the narrative, and back to the belief that change is possible.

Sarah Lock, *Senior Vice President for Policy & Brain Health, AARP*

Totally agree that the role of public health is obviously powerful in spreading awareness that action will change the result and that you can do it across a whole variety of settings. But if you don't have this kind of public health organisation of it, a lot of times it can fall on deaf ears. And so finding the appropriate levers and making sure that the public in public health is really not only brought along, but the public governments and institutions and facilities are part of those conversations from the beginning to really push the messages out.

And it's not an easy lift right. We already know that people think it's inevitable we already know that it's a huge fear. So you're going up against an enormous stereotype. It's not just that dementia is a terrible disease, but it's inextricably linked with aging and your increased risk as you age. So having public health talk about it in terms of understanding what risk is and what benefits you can achieve, even if you should have the disease, is important. I was talking to the Alzheimer's Society about these kind of conflicting messages from a public health perspective yes, there are things you can do but you don't want people to take away that for some reason they did something wrong and that there is guilt to be had.

So, I think it's really important in the public health conversation to have the dual message that these things are good for you because they reduce your risk, but they're also good for you even if you should get the disease because they're good for you. The same interventions improve quality of life. And having that dual messaging is really important along with this is good for you for your heart and it's good for you for diabetes. The idea that we would slap on yet another thing I think public health can say put it in this broader context, and so we're putting a lot on public health, but the idea is finding the simple ways that it's part of existing public health and amplifying and adding to it rather than trying to reinvent the wheel.

Kaarin Anstey, *Director, UNSW Ageing Futures Institute and Professor of Psychology, University of New South Wales*

I think we should actually be even more ambitious if we want to see real change in the next 10 years. I think we really have to look at some of the more social determinants of health. Yes, we have to continue risk assessment, we have to continue risk reduction, but the really big challenges for us, are things like obesity, air pollution and social isolation which are public health challenges affecting the whole of society, and which are also dementia risk factors. We have some really big sort of ticket risk factors are affecting millions of people. And the way we need to address that is through public policy, through government, through industry all working together.

In Australia we have a saying of having health in all policy. What we need is cognitive health or brain health in all policy. In the World Health Organization's definition of health, it has social health and mental

health and physical health, but cognitive health isn't in there yet. So if we made it a goal to get cognitive health recognised as a core part of health and then health in all policies, so childhood education, publicly funded preschool to increase brain health, we need to be attacking this at all levels and enabling people to have a brain healthy lifestyle, without having to make that individual choice, because they are living in a walkable community, they can access healthy food and so on. It doesn't have to be just something that's accessible to people who are highly educated, who have money to do that. So I think we could be a lot more ambitious here.

I also think that we still need research. It's great we have more evidence, about risk reduction. But in fact there's still a huge amount we don't know. We don't know the extent to which addressing a lot of the risk factors, will actually reverse cognitive decline. We still need a lot of clinical trials. We're really at the beginning. I know we have a lot of good evidence coming out of FINGER and related trials, but that's the beginning. We need a lot more evidence on the cohorts that are coming through. The evidence we have is on very old cohorts. So there's still a big role for research here.

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

And I want to turn to the panel because I think you hit some really incredible themes. One, social determinants of health and thinking about how do we intervene on social determinants of health or include that within the brain health conversation? But then also the need and call to action for continued research and I would say even just the implementation side, right, not just the trial itself. Any thoughts or response from anyone here on that front, on either one of those?

Sarah Lock, *Senior Vice President for Policy & Brain Health, AARP*

I violently agree with Karen. She is the new vice chair for the Global Council on Brain Health. So I would just say ditto and ambition is the name of the game.

Franca Gatto, *Director, Division of Aging, Seniors & Dementia, Government of Canada*

A lot has been said over the day in terms of influencing policy where we all have a role to play. Policy comes from a wide range of sources and inputs, and those of you in this room have an important role in making sure policymakers hear from you, and benefit from your research, your knowledge, and your experiences. In my work, I engage with Canadian researchers and civil society on a regular basis. And forums such as this one today promotes that information exchange. Having an ongoing dialogue between researchers, civil society, and policymakers, and making sure there's evidence that backs policy is extremely important to influencing the changes we'd like to make when it comes to the social determinants of health.

Melissa Chan, *University of Luxemburg Senior Atlantic Fellow, Global Brain Health Institute*

The research has to continue. We just don't know enough. However, there's a vast amount of knowledge that is not reaching the general public. We need to share what we do know better. Bridging this gap necessitates effective communication strategies tailored to diverse audiences. While research must advance, implementation is equally critical. We need to implement it in a way that actually provides value to the person that's consuming that layer of information to drive action. It's not just another public health messaging that will go in and out, especially with the amount and layers of mixed messaging on digital media right now.

Leonie Visserm *Senior Researcher Medical Communication, Amsterdam University Medical Center*

I just totally agree with what you just said in terms of that we really have to do a lot of more research into how our message is perceived and how we should bring communication or education or risk communication to the public and especially taking into account different people. I think how we perceive risk communication is totally different from someone who's from a different cultural perspective or who doesn't have the prior knowledge that we have. I think there's a lot of research to be done in how to effectively and adequately and equally and inclusively communicate with different populations.

Iain Simpson, *Director Pharma Segment, Phillips-Medisize*

Just to pick up on the behavioural side of things. I mean behavioural change is difficult. But I think what you said Joanne about smoking cessation is a really good example of where we've made progress through multiple factors. I come into this topic from the perspective of medical adherence, in fact I spoke at the World Dementia Council on that topic. In the same way we have seen progress in dementia, we have seen massive progress in understanding the world of behaviour change and how we link that to the determinants of health and adherence, whatever the driver is for that. Just to mention, the team at UCL have done a brilliant job at looking at behavioural change techniques and how you can link them to determinants of health. So I think there is a lot we can build on. One of the challenges is that at one extreme we have digital therapeutics and all the regulatory burdens that come with that. We have seen a lot fail in areas at mental health. At the other extreme we have all these apps that are poorly qualified, they risk confusing the public, in terms of whether they add value. So we need some form of standards in terms of the quality of what we offer, without necessarily expecting everything to go through the regulatory approval process. But that will limit the flow of this into the market in terms of, you know, brain training, brain health, those sorts of things if we don't find some sensible compromise in the middle to do that.

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

I think that it's an interesting perspective to think about — the perfect being the enemy of the good when it comes to what can we achieve with brain health. And I imagine there might be a little bit of response on this from the panel too. Do you have anything that you want to think about?

Sarah Lock, *Senior Vice President for Policy & Brain Health, AARP*

I used to hate that phrase, "Don't let the perfect be the enemy, the good". From an idealistic perspective, right? But I absolutely think it's the case here. We have to move. Like, our burden to change the narrative is enormous. We can't wait for perfect evidence. We need perfect evidence. We should continue to build for it. But we really have to get out there because the hurdles are high. And if we don't start now, it's never going to happen. By simply changing the narrative to show that change is possible, that in and of itself will be a huge win.

Melissa Chan, *University of Luxemburg Senior Atlantic Fellow, Global Brain Health Institute*

To add on to that, if we're talking about shifting the narrative, it's also about asking how and the steps we need to take to change that narrative. How do we bring sector players and different disciplines into the conversation by involving them in a room like this? Designers, the neuroscience field, public health, urban planners, educators, people who are experts at digital technology, and even people who have skills like performance marketing — to cut through the digital noise, target, and reach people with very specific messages. How do we leverage the ecosystem? In terms of the industry players, the corporates, the businesses. For example, with workplace initiatives in Germany, workplace mental health initiatives are mandated. Insurers help to subsidise the cost of these programs. In Japan, just a few days ago, Eisai Pharmaceutical and LifeNet launched a dementia insurance program called "Be". They are providing brain health information accessibly and tiering services for the general public and policyholders. Level one offers access to brain health support and education — everyone can get it, even if you're not a policyholder. Level two, if you're a policyholder, you get exclusive services and personalised support. Level three, from the stage of MCI, provides support and non-pharmacological interventions right now. This focus is on journeying with the user and being able to guide them across their lifespan.

Franca Gatto, *Director, Division of Aging, Seniors & Dementia, Government of Canada*

I would just add that from a macro public health perspective, risk reduction initiatives will help. Even without definitive research or regulations, more exercise for example, can help address overall health and wellness. Yes, we need ongoing research, but in the meantime, it is important to communicate those incremental messages we are confident about, and to link them with brain health awareness. People already know they should exercise, and that they should be socially active, but they haven't necessarily linked those activities to brain health. That's part of what we're trying to do now and make people question "Can do something to prevent dementia? What is it?". We want people to link risk reduction to brain health, for example, if it's good for your heart, it is good for your brain. We want people to make those types of links going forward.

Emiliano Albanese, *Professor of Mental Health, Università della Svizzera Italiana*

I'll try to go against the proverbial the neutrality of Switzerland and try and say that there is a contradiction within. We all want to balance the whole population and individual approaches in prevention. And we know at the population level it lags behind. And I would claim that in the individual approach, if you go the FINGER way, it's pretty neutral and it is collaborative with the whole population. If you keep calling things brain health clinics, as a part of prevention strategy, you're actually making an appropriation of something. Because, "clinics" in ancient Greek means "beds", "hospital beds", and in common understanding that is what it means. It recalls, "I have to go to the hospital". This is wrong. It's actually draining resources. It's counteracting the message that we have to cast about brain health, which is a unique opportunity, because at the highest possible level through the WHO, we have established a definition that it is uniting a discourse around brain health. And this is unprecedented. We don't want to waste that opportunity, relabelling memory clinics as brain health clinics. This is a wrong. Thank you.

Johannes Streffer, *Senior Vice President and Head of Global Clinical Development, Lundbeck*

In a way the point was already made. Initially, in the discussion, we talked a lot about research and science. I think we have to make sure that once we start the communication piece, we realise it has to get to the heart and the stomach of the people. And then it's about translating that into something that is real. In the last session on the other side, there was a lady that very friendly offered her view on what would be meaningful or would have been meaningful for her as a caregiver. And I think that is where the messaging has to start. Meaningfulness, what could it be, and then bringing all the science into that, but in a way that people understand it.

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

Thank you. You know I love the value-based conversation certainly and what is meaningful to one person is important to them, period.

Helen Skinner, *National Project Lead for Brain Health Services, Brain Health Scotland*

I just wanted to follow up from what you were saying. In one health board location in Scotland, NHS Grampian, we've worked with public health team there, and we've created a brain health service and brain health clinic. It is on the high street. We have done it as Brain Health Scotland which is part of Alzheimer's Scotland. The clinic is open access. Anyone can come in and have a conversation on modifiable risk factors for dementia. They get risk advice on modifiable risk factors. We have a health psychologist who inputs into that, who has trained the staff who work there. But we also have a brain health clinic within that, on the high street, where we have a clinical nurse specialist working and also a consultant psychiatrist. So if people are sharing risk factors they can go on for further assessment. For us it's really important not to just relabel memory clinics, it's a new service completely that is open access and on the high street for people to attend.

Sarah Lock, *Senior Vice President for Policy & Brain Health, AARP*

It can't be limited to clinic, but I how we label these clinics and treatments are very important in thinking about it. When you're talking about the clinical care for people who have either mental health or cognitive health or behavioural health issues and you're trying to give them tools, I think that that can be part of the conversation around brain health in a clinical setting, but you don't want by all means to take the special care that is very sophisticated at trying to treat memory deficits and assume that these kinds of brain health messages will solve for all of that.

Shibley Rahman, *Honorary Visiting Professor, University of Liverpool*

It is all very well to say more research. In 1952, when there was established a link between smoking and lung cancer. It's very similar to multi-morbidity, multi-factual. I suspect what's happening in dementia is in the 20s, lots of factors impacting on subsequent decades later.

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

Thank you. Really quickly, and I know I'm stealing now time from Philip, just to close off the panel from the standpoint of last thoughts or parting comments in terms of what's next. What would you like to see happen?

Franca Gatto, *Director, Division of Aging, Seniors & Dementia, Government of Canada*

I would say that while we've made progress in some areas, we have a long way to go still. In Canada, we've made progress with some risk factors. For example, rates for smoking have gone down, but the prevalence of some other risk factors, such as obesity and diabetes has increased. So there's a lot of room for us to continue our efforts and to continue to learn from those of you in this room and other partners in this space when it comes to risk reduction and messaging. I would also say that we need to be careful with messaging and we need to be sensitive to how our messages are being received by finding the right balance. As we continue to move forward, we want to make sure people take actions to reduce their risk if they can, and for those who develop dementia, we want them to know more about those behaviours that could potentially slow progression.

Melissa Chan, *University of Luxemburg Senior Atlantic Fellow, Global Brain Health Institute*

My message is one where I see lots of hope. I see a great opportunity to translate things to the lay audience now. I think the complexity lies in the human behaviour, considering the various socioeconomic factors, and ensuring we design for different persona types. So, as we continue discussions on the evidence around what works, I'm also very eager to explore how we can take action now to scale and reach different communities effectively.

Sarah Lock, *Senior Vice President for Policy & Brain Health, AARP*

One of my hopes is that when somebody says, "what is brain health?", people understand what that means. I think that there's a lot of vagueness and still striving despite new, strong definitions, but that it becomes part of the vocabulary for people of all ages. That's what I really hope happens.

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

You know, I think one of the things that certainly we heard and we saw within some of the activity from the audience and from the panellists is that we have to think about this from a multi-sectoral, multi-factorial way of thinking about modifiable risk factors. It does not happen in a vacuum. It happens for each of us, but it also happens in the environment we create for each other and with each other. So, with that, I appreciate all of you.

What can the unexpected deliver: disruption in the decade ahead?


Philip Scheltens
Chair


June Raine
Speaker


Siddharthan Chandran
Speaker


Joanne Pike
Speaker

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

This is now the final panel. We're now actually going to, so Lenny called this very nicely, "what can the unexpected deliver: disruption in the decade ahead?" So, in this last panel session, we're really going to take action. We're going to disrupt and we're really gonna change things and we're really gonna sort of make it happen. I'm inviting my panel members here:

- June Raine is the CEO of Medicines and Healthcare Products Regulatory Agency, better known as the MHRA;
- Siddharthan Chandran, the director of the Dementia Research Institute, and also a clinician in Annenberg; and
- Joanne Pike, my vice chair, president and CEO of the Alzheimer's Association.

So I have three prepared questions actually for each of the panel members, and to see where we go from there. Siddharthan to start with you, you've worked in basic science, you're a clinician as well. What is the disruption we need to change over the next decade? So be very specific. What needs to be disrupted in order to get us there in 2034 of the aims that we all want to achieve?

Siddharthan Chandran, *Director, Dementia Research Institute*

I don't know if this is disruption, but I think the key is to move away from the model which we currently have, which is a separation between research, translation, implementation and delivery. So, I think the key is to integrate care and research. Every health contact is an opportunity for new knowledge. Whether that's in the primary care setting or in the hospital setting. But the principle of every health contact is research, best health care cannot be separated from research and our goal should be to be able to offer people not just a better diagnosis but the opportunity to participate in a suite of studies. This this is key. And these studies need to include the key experiment, the only experiment that matters in the end, and it is called trials our trials. We need to be running trials as the default and at scale and at pace and link those

trials where you need to innovate in terms of adaptive models, multi-arm adaptive models but needs to be crucially linked to bio sampling and digital annotation, high frequency data capture, community-based hybrid trials. And then that will drive this virtuous circle of health care research trials, translation, reverse translation, and you just need to keep that loop on. And then this needs a public-private partnership model where we never move away from the primacy of public health benefit so you can do that and retain engagement with all kinds of stakeholders. But the root of this is tomorrow's clinics, wherever they are, community, hybrid, need to be all about delivering an integrated model of care and research. Thank you.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

You know that is music to my ears and we'll come to that later how the practical implications of that sort of vision will be. June, if I can turn to you, I think many of us won't associate regulators with the word disruption, to be honest, but I turn to you. How can regulators actually be disruptive and help us get ahead of the game and really sort of speed up in the dementia field as to what has been said many times where cardiology is, what oncology is and how do we do this and how can regulators help us here?

June Raine, *CEO, Medicines and Health Care products Regulatory Agency*

Well, Philip, thank you so much for this question. I would like to say how amazing it is to hear this really vibrant energetic conversation and to culminate a day of really productive debate with disruption. Yes. And I would like to perhaps countermand your impression because we welcome disruption, we thrive on it. And these have never been more exciting times in regulation. And I doubt that you hear the words exciting and regulation in the same sentence many times. We don't know. Let's be clear what was COVID the pandemic? What was, let's pass quickly on, leaving the EU? What was we had a major safety review run by government? Disruption is there for a purpose. It is to bring change; it is to add value. And without adding value regulators don't really have a right to exist. So, I would say we start with an end to end model facilitating research, enabling access and then studying safety benefit risk in the real world. And we have the assets to do this now.

I'm proud to say that in my agency, we do span the basic research. We've got a neurodegeneration team looking at biomarkers. We have the approval processes running, if you like, as rolling reviews, as the packages of data become available. And we have real world evidence, albeit largely from general practice, but over a quarter of general practice data. And this is where people's health from birth to grave is monitored in the UK. So I think we are the starting point for a disruptive approach to regulation that will enable access. What is it now, nine and a half years from discovery through to deployment? That needs to be halved or less. We have the 100 days mission for the pandemic agents, diagnostics, vaccines and therapeutics and it is breathtaking to think but it's achievable 100 days for a new pandemic vaccine. I think the therapeutics might take a bit longer but there in terms of diagnostics we need to be driving this.

I think in 10 years' time we'll see a totally different model of regulation. And finally, it will be worldwide. The best question I ever had from an audience was, why do you need more than one regulator, the evidence is there, the patient population, now we can tease apart the genomics, why do you need more than one? I immediately felt very defensive. But I said things about our cultural approach to how health care is delivered, all these differences. Well. But let's think about connecting regulators so medicines can reach the public without unnecessary delay in effective ways where benefit is monitored in clinical use. And if I hear, as I did last week at our dementia mission meeting, that there are 4,000 patients already on certain medicines whose experiences can feed in to our knowledge, for all of us, then we must do that. Thank you. Thank you. We'll come back to that and of course we'll entertain questions again.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

So Joanne is my co-chair and moderator for all day. We know your expertise is in public health, but we also, well, public health systems may not be ready for any disruption. How do you see that?

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

I feel like I'm getting a taste of my own medicine right now, by the way. I think one of the things that we have to think about and consider is how, in an environment where we don't have capability, infrastructure or readiness, consistently, or very much, what does change that? And there are two things that I often think about. Where do we need to make the investments and where do we need to provide the incentive? An incentive can be investment, but on the other side of that, we need to also think about the investments from the standpoint of people, process, and what comes next. So how we create the disruption within


the health care system, so it becomes better prepared, is really thinking about how do we incentivise the behaviour we want to see. And that could be through payment, it could be through reform and regulation, depending on where the health system is making decisions, how they are making decisions. But we need to also think about the investment in the structure itself to ensure that it is ready as well.

We are in this place because of some of those two very ideas, the investment from a research standpoint. Now we need to flip that and make sure that the environment is ready for that research investment that we have been making as a community, as a global community, for decades now.

Sarah Lock, *Senior Vice President for Policy & Brain Health, AARP*

Ryoji, this is really the question for you. I appreciate the regulator's response about learning from people who are on the new therapies and what we have to do. Because so many people who have the need for early interventions with dementia have co-morbidities or at stroke risk or at a variety of things. And I think we don't know yet a lot of the interactions or treatments, how emergency room doctors will be dealing with people who are on these medications who are perhaps trying to deal with someone who's needs to be treated for stroke. So I mean there's a whole variety of things that we need to know more about these medications and how people experience them, although we're anxious to roll it out and have everybody have the benefit. I really want to make sure that everybody can benefit from it and so anything that you have further describe the caution which we need to address it as well as the excitement.

June Raine, *CEO, Medicines and Health Care products Regulatory Agency*

Well, I think your question, which is a great one and very timely, goes principally to the way internationally we can share and profit from information as it is generated. And even more to look for evidence generation function internationally. The recent interactions we have been having with the FDA and the EMA have been very much looking at this. So, let's take this opportunity particularly in the area of dementia to set up platforms that will connect that we will all be able to share and use data in the way that will benefit patients. And I do think it is important that we are able to manage risk. We have had that great panel about avoidable and manageable risk, that we actually take into account patients' views of the data we generate. We don't make rather patronising decisions about avoidable risk that patients actually might be prepared to countenance. So, there's a lot of dimensions to your question, but I do think now is the time for international platforms and collaboration in data sharing.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

Can I be very concrete? Are you saying that you are looking at a certain dossier at the moment and you're incorporating in your decision ultimately the real-world experience already with this specific compound?

June Raine, *CEO, Medicines and Health Care products Regulatory Agency*

I wouldn't go that far. I'm talking in very general terms and please do read my blog about the interaction, very helpful interaction, with the FDA about starting this journey of international evidence generation. And as soon as there is exposure in populations, as Sarah is saying, we start to think those risks that we expected, are they playing out in the way that we predicted?

Tim Ferris, *Consultant, Morningside*

Just on the point that you made June about connecting the delivery of care to registration in trials and so forth, can I just say that is often referred to in the literature, health services literature, as a learning health system. And the first papers about a learning health system were written in the 1980s.

And I would say we are probably just as far away from the vision of the learning health system today as we were in the 1980s. And one of the barriers, not the only barrier, but one of the barriers that the people

in this room can affect is the fact that every vertical cancer, cardiovascular, they are all trying to do it separately. And there is, I would say, no chance of building a learning health system when all of the special interests in a particular vertical try to build something on the delivery system that is vertical specific. Like that's just not gonna happen. It's not realistic to think that it will happen. And so I guess what I would encourage is since everyone who you talk to agrees we should have a learning health system, the life-cycle of evidence and care should be put together. Might people in dementia health work with cancer and cardiovascular to actually say we should do this together because separately there's not enough leverage to make it happen so it's just a thought.

Siddharthan Chandran, *Director, Dementia Research Institute*

Yes, of course, what you say is correct. There's a challenge here because we're unable to boil the ocean. Trying to integrate everything you said is the goal. One way of thinking about this is, in a sense, what we're all trying to do is maintain health in an aging society. And as we get older, various things go wrong, but there are some unitary common features, metabolic, vascular and brain aging. And so, I do think taking a whole body, life course, potentially approach to thinking about maintaining health in an aging society and brain health is the way to go. So, you're trying to, if you like, distil the grander vision of integrating all these verticals around maintaining health in an aging society. All serious governments recognise the public health threat of aging and the economic and health gains to be had. So, we do need to think about how we can bring that together but it's not easy, but it needs to be done. But it has to be done at the level of the earliest contact with health care professionals not tertiary, we have to move away from a hospital-based model, so we've got to be thinking much more about prevention protection promotion and so on.

George Vradenburg, *Chairman, Davos Alzheimer's Collaborative and UsAgainstAlzheimer's*

I just want to call out, June, your agency, which has been involved with us and others around the world in thinking through how to get to an Alzheimer's vaccine. You've done such a great job in the infectious disease world, and now we're beginning to think about vaccines in the chronic disease world. But I just wanna say that you have put into action in all of your work with us exactly what you've said in terms of the coordination among your agency, EMA, FDA, and so on. So, I just wanna thank you for what you're doing.

June Raine, *CEO, Medicines and Health Care products Regulatory Agency*

I have to thank you, sir, for stimulating this, and it shows how the stimulus can come and then internationally people respond to it. So you should feel very congratulated and proud of what you've done.

Mark Roithmayr, *Chief Executive Officer, Alzheimer's Drug Discovery Foundation*

Couple things, as much as I wanna just keep thanking George, I'm gonna start with the thank you and that's Philip to you and Joanne for what you've led here today. I'm sure I'm representative of many. You know, on a day like this, you go on the journey of feeling all this hope and at the same time all this despair, depending on the presentation is! I'm gonna ask you to give me a little bit of space on this and Philip you'll figure out I have a question somewhere in here. I'm struck you know a bunch of us were at ADPD about two or three weeks ago and there was a couple of interesting themes that came out of that and one I think particular for this panel I forget who it was, but we said, science leads clinical guidelines, clinical guidelines lead regulators, and regulators lead payers. And it's in that spirit, I want to talk about disruption. Because if you buy that, or even if you don't buy that, science is the disruptor here. And it was interesting, because at that meeting, what really was forefront, was the biology of aging. That it is nice to have the monoclonal antibodies, as has been said today, it's at the beginning, but it's nowhere near the end. And that three quarters of the clinical trials that are going on are on the different pathways of aging. And what this is really about now is biomarkers, blood assays that back up those biomarkers, combined therapy trials, and precision medicine. And so, and again, this all came out of ADPD, I'm just reporting what was there. I'm curious because, and this will be for you and Joanne, because you haven't talked about this at all today, and yet it's a big part of your day job, and that's about lining up capital so that the science can disrupt. Because that's really where the disruption is. Until the science is proving something, all of this is somebody said it well before. It'll pull the rest through. So, I think an issue that hasn't been talked about today, and Joanne I'd be interest in your comment on this also, lining up the capital. Where does the capital and the science need to be to speed this through so that the regulators say, "hey, I only need one regulator. Here's the science. It's clear."

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

I'm ruminating a little bit on kind of the thoughts around this, because I think it's incredibly important to consider where does innovation come from. And I agree with you in the line of thinking that science is part of the innovation, especially in this place. But I think it's also true that we're seeing innovation in this disease at this time because it is early days. And I think that's where science is the pulling force within it. But I think we have to remember, in 10 years from now, that may not be always the case. Technology could be the driving force of disruption. And that may be true today, right? We've heard many people talk about artificial intelligence and how it is driving some of these things. So I want to respond on that front that yes, science is a major piece of disruption with where we are today. But I think it is not the only force of disruption.

Mark Roithmayr, *Chief Executive Officer, Alzheimer's Drug Discovery Foundation*

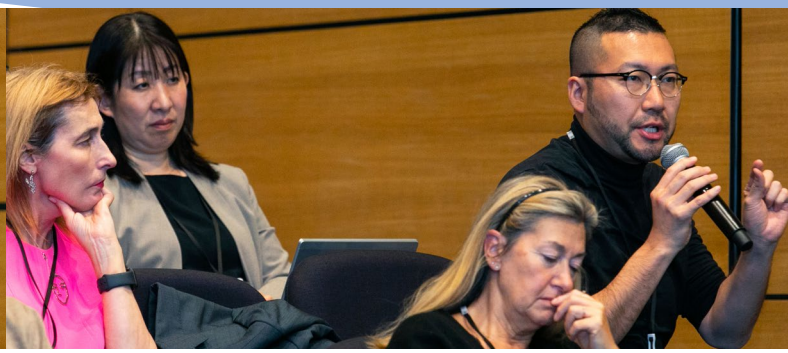
And with that, just to your point, I include the technology with the science. To me, it's ubiquitous across the table.

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

And I think from the standpoint of, you know, back to my original comment on investment, choosing and thinking about where do we drive incentive within there? I think we have to have some conversations around where are there gaps? Where are the opportunities from the standpoint of to what you're saying on this is first generation treatment? What is second generation? By the time we get to 10 years from now, we're going to be on precision medicine and third generation treatments. And so, we have to have a view on what is behind us to know also what are we speeding towards? And there is investment coming from multiple places. And part of that is the regulators who are going to benefit from driving that investment or driving that innovation, so it changes cost conversations long-term. But I think the other piece is passion and people. And that's part of all of this, but it is also from, for instance, the responsibility of non-profits to drive that passion so we change some of this conversation long-term, too. Maybe thinking back to you, what do you think the driver for some of that investment in regulation would be?

Siddharthan Chandran, *Director, Dementia Research Institute*

One thing that's perhaps surprising to me from today is until this question is the absence of discussion around funding. Because let's face it one of the reasons we've got so many interventions and there's been a revolution in cancer medicine in the last three decades is because of funding. It's not the only reason. And I think sometimes we are unnecessarily shy about saying, yes, there's been a lot of progress, but the most valuable investment is targeted funding around human-led discovery with the focus on moving from discovery to benefit. This disease, given the scale of it, and the burden, you can monetise that in any way you want, the proportion of spend on this disease for discovery, and I agree with you, the absolute catalyst to accelerate everything is brilliant human-led discovery, hence that integration of care and research. And we need to invest, but it's an investment rather than a spend, if you see the distinction. And this point is not made enough, and we need to advocate that. And we're fantastically reliant on charities who do a great job, ARUK, for example and others who are here, but we need so much more, and we shouldn't shy away from that. And particularly around building the workforce, there's a real capacity issue around the discovery scientist, the data scientist, and the delivery scientist. We do need money and we need to talk about it and we need to be more confident and make the case of the value for money.

June Raine, *CEO, Medicines and Health Care products Regulatory Agency*

Could I please just offer a regulatory perspective? We always say regulation follows science, but I think the new disruptive era is that regulation should help drive science and the position we are in, as Siddharthan said, the opportunity to fill the gaps. Because we see across the whole piece we have that privilege. We shouldn't shy away from driving science that is needed. And the additional brief point, is that you were mentioning the public-private partnership type context for all of this. It worked very well for the European Commission with the now Innovative Health Initiative. I do think we should begin to think about these models so that it provides this umbrella that the public are aware of the, and quite transparently as they should be, of the interactions that we need to have, and I think we'll take the public with us.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

Well, to answer Mark, yeah, to give my personal perspective in that sense, since I'm now an investor, and I started actually just before June 2021 when the Aduhelm approval was announced, and it was very difficult because people said, well, why would you actually do this? And why would you invest in neurodegeneration? Because nothing works. And the simple fact that there was accelerated approval in June, and now we look back on it and see, we may criticise it, but that helped enormously. Suddenly people said hmm maybe there is a way out, maybe we can do this and then of course in September, the year after that when Lecanbi published their results, we actually got phone calls from people, can we invest can we help drive this forward. So as we saw in multiple sclerosis we see it in Alzheimer's disease now as well the single success or two or three successes really drive forward and then we have to build on the science that is produced in academia, funded by government bodies, by charity bodies and from that on we can build as venture capitalists and you know this very well as well, we can build on making companies, helping the companies to drive them to the next phase and ultimately get better treatments for our patients in the next few year. And that is based single on the fact that there is finally a success. Whatever you may think of the success, how big or small it is, but it really helped to sort of, I would say, liberate the community from this dark veil that was wrapping itself. It will never work. Yes, it will work. It can work actually. And we will show that it will work. So that's my perspective.

Zul Merali, *Founding Director Brain and Mind Institute, Aga Khan University*

I was quite excited about the earlier discussion about disruptive technology to do clinical trials in the communities, but really cutting across the silos of individual diseases. We're setting up a cohort in Kenya where we're going to be doing exactly that. Hopefully we succeed. But in essence, we'll collect information about brain health, about mental health, but also diabetes and hypertension at the same time, in the same population, across a lifespan. And this will be done right in the communities. We're engaging with the communities right at the outset using anthropomorphic studies with them. I hope that this will be a small demonstration project to see whether we can integrate the various components to be really to be disruptive in that sense.

June Raine, *CEO, Medicines and Health Care products Regulatory Agency*

Just a quick comment, I think this is brilliant and I think that there are ways to support your initiative with technology. We've been working on app related safety data collection that's easily used in these circumstances. So, leapfrog all over all the, if you like the stuff, that we've had to deal with and go straight for the best possible tools for this really important work.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

That reminds me of a question. Regulators are open to any kind of innovation in terms of endpoints or safety measurements, be it digital or anything. I mean, please inform us that you're open to that or if not, then please say something.

June Raine, *CEO, Medicines and Health Care products Regulatory Agency*

Absolutely, because we mustn't keep patients waiting. There are ways to rapidly gather data and to make being in a trial a really good place to be. Thinking about how mobiles are so prevalent. There are ways to make being in trials a really good thing to do. So, let's make it a natural data collecting and a learning system that's an international one, not located in a city environment, in a high resource environment.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

So, you'd accept a measure that came out of this?

June Raine, *CEO, Medicines and Health Care products Regulatory Agency*

We'd want to discuss it beforehand, but I think let's all help this important lift that you're doing.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

Siddharthan just to come back to you, I mean you make the point clinical care and research shouldn't be separated it's actually should be one. You may know that in Amsterdam we do this already for 20 years, in the sense that every patient is participating in research by definition. And every researcher is participating in clinical care. So we have operationalised that model a little bit in Amsterdam. And to our advantage because there's a huge data that's coming out of that is not Is that the model that you're referring to? Not the Amsterdam model, I'm not sure, but is that a sort of model that you were actually thinking of?

Siddharthan Chandran, *Director, Dementia Research Institute*

Yes, on steroids.

Ryoji Noritake, *CEO & Board Member, Health & Global Policy Institute*

I think another perspective about the funding mechanism is to include investors. One reason that I think that Eisai, this is just my personal opinion, were perhaps able to stick to this is because it's family-owned company. They don't have shareholders, less shareholders compared to big other pharmaceutical companies. The 21st century capitalistic shareholders stock market, it's so short term and which is very different from long-term strategy on say brain health. So, if we can include investors behind the pharmaceutical companies who actually bring the money like a bank, venture capitals and son on. For example, in green energy, the sustainability sustainable development goals, that's one of the areas where investors are really keen. If some companies have some risk they don't invest anymore. So maybe we can include investors in this meeting for 2025.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

Good point. Questions? When you go back to Kenya, what are you taking with you? I mean, what do you say to the people? I was at this day in London, it was all very nice, there was a lot of disruption, but you go back to Kenya and what do you say?

Zul Merali, *Founding Director Brain and Mind Institute, Aga Khan University*

I would basically say that really we're on the right track. Because what we are talking about is exactly what we're trying to implement in a small way. The advantage of working in developing countries is that the barriers are not all there hard and fast like they're in developed countries because they worked for quite a few years in Canada. Going to Kenya, at least the field is quite open and people are ready for disruption because they're the need is so great that the barriers are not as high as you would see elsewhere.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

Are there any clinical trials running?

Zul Merali, *Founding Director Brain and Mind Institute, Aga Khan University*

Yes, there are. Definitely. We have got a clinical trials unit, but what we are trying to do is not go to the clinical trials unit, but for us to go to the communities and do trials there using a van where we can do the sample collection, the biosample collection, as well as the clinical upfront. So it's a different model.

George Vradenburg, *Chairman, Davos Alzheimer's Collaborative and UsAgainstAlzheimer's*

I just want to say what Zul is doing in Kenya is fascinating because what it says is basically this is not a disease called dementia. It is a series of life experiences with a variety of co-morbidities which ought to be tracked together. So Kenya is developing a model for a brain health plan that contemplates cardiometabolic interventions in mid-life and indeed going earlier than that and then tracking to see how you eventually reduce the incidence or prevalence of dementia. So, he has got a model here so I'm going to compliment him. He's bringing resources from all over the world.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

So, let's assume that we are here together in the Crick in 2034. Have we sort of solved the whole issue? And if so, what are we celebrating? And if not, what are we then discussing in 2034?

Siddharthan Chandran, *Director, Dementia Research Institute*

So the answer, unfortunately, is no. It will be just further along in a journey. We're taking a global perspective here. So just to move away from what you might call pockets of elite neurology and elite practice, the acid test is, is what we're discussing relevant to the majority of the world. I suspect by then not yet. And if you just use MS as a pathfinder. So MS is 25 years in since beta interferons. I can tell you from a UK perspective, massive advances, but there's still a long way to go. What people want is obviously faster precise diagnosis, personalised prediction, and this wider democratization where they are able to take control in terms of lifestyle choices, and then targeted treatments, which may or may not be combinatorial, and at home-based monitoring. It takes a long time even to say that. I don't think we will have got there, but it will just like cancer there has been spectacular advances and a lot to be done, in 2034 there will still be lots to do. We need to be optimistic and plan for success but we need to think about it over decades but achieve significant and meaningful advances in this decade.

June Raine, *CEO, Medicines and Health Care products Regulatory Agency*

I am really in the same space as you are. But I hope we will have banked a number of successes. And the pathway will be very early, pre-emptive, steps so people can then make informed decisions about the risks that they want to take. And maybe we'll be looking at some really international data sets of experience of those patients that tell us of the choices that are now available to people. So, I'm sure we can book our seats, our tickets to London, for 2035. But I think it will be a very different picture as the MS journey has been. And that I think there'll be more smiles, even more.

Joanne Pike, *Vice Chair, WDC; President & CEO, Alzheimer's Association*

I think it's a little bit of a blend of what my thoughts are with what has already been said. I think there are things that we're celebrating and there are certainly things that we are still considering and grappling with and that may be worse than where we are today.

So, let's start with the worst and let's end with the celebration. I think that where we are in the life cycle of our cause in Alzheimer's and all dementia and in brain health generally, I think we're still going to be grappling with access issues. I think that in terms of how we need to change the health system, how we deal with inequity, does not change in the next decade, but instead we need to think about the next century and how we build a world that is more accessible, more trustworthy to all of us instead of some of us.



The celebration, I think, is instead of debating value, the way we debate value today, I think we're going to have an understanding of what person-centred value and meaningfulness is within the landscape of treatment and diagnostics and how we provide and need to provide care. And that's the moment I'm looking forward to from the standpoint of being in this trajectory of innovation, being in a place of understanding what this means for a person living with or that could be living with dementia, early Alzheimer's, preventive care within this space, that we allow them to define what meaning is and that we listen. And, that instead of a dollar assigned to them, happiness and outcomes are assigned to them. Thank you.

Philip Scheltens, *Chair, WDC; Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund*

Hear, hear. We have to end the session. I'm going to thank the panel very much for your willingness to be on the stage and share your thoughts. One official photograph will be taken now. I want to thank the audience for the participation, but I mainly want to thank also Melanie who is over there and Lenny who is over there.

World Dementia Council
Leading the Global Action Against Dementia

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

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