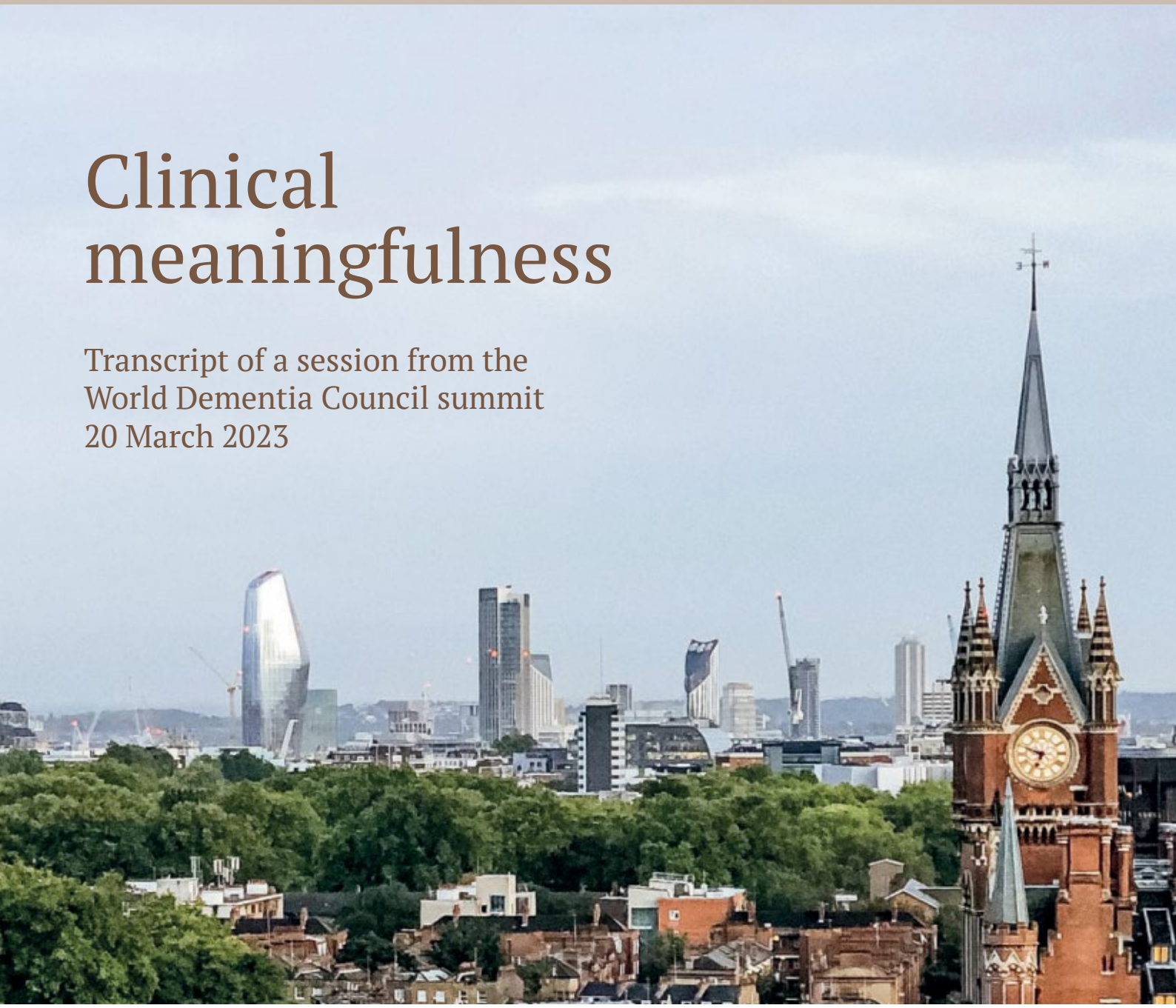
Summit 2023

Dementia in a new era:
prevent, diagnose, treat

World Dementia Council
Leading the Global Action Against Dementia

Clinical meaningfulness

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



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

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Chair

Philip Scheltens

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

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

Speakers

Professor John Harrison

Chief Scientific Officer, Scottish Brain Sciences

Professor John Harrison is an acknowledged cognition expert whose principal professional interest is in helping people understand, maintain, and enhance their cognitive skills. He is Chief Scientific Officer at Scottish Brain Sciences practice where advises on the selection and successful integration of cognitive testing into therapeutic development programs. John is an Associate Professor with the AUmc Alzheimer Center and Visiting Professor at King's College London. He holds Chartered Psychologist status and has authored/co-authored more than 100 books and scientific articles, including a popular neuroscience book 'Synaesthesia: The Strangest Thing'. John's wider professional activities include conference hosting, professional voiceover acting and podcasting.

Professor Gillian Leng

Dean for the Royal Society of Medicine and former CEO National Institute for Health and Care Excellence (NICE)

Gillian Leng spent over 20 years in senior roles at the National Institute for Health and Care Excellence, becoming only its second Chief Executive. She published a new 5 year strategy for the organisation aiming to put NICE at the forefront of evaluating new medicines, devices and diagnostics, and delivering dynamic, living guidelines. Gillian has close knowledge of the health and care system, both as a frontline clinician and through her work to improve patient access to effective new treatments and interventions. She has worked closely with government on new policy developments, including the Office for Life Sciences, BEIS, DHSC, the Department for Education and the What Works Centres. Gillian trained in medicine at Leeds, worked on clinical trials and epidemiological research in Edinburgh, and was a public health consultant in London. She is now the Dean at the Royal Society of Medicine, on the Board of Radar Healthcare and a trustee of the Cochrane Collaboration and the Guidelines International Network. She is also a visiting professor at King's College London and an affiliate professor at the National University of Singapore.

Professor Mark McClellan, MD, PhD

Professor of Business, Medicine, and Health, Duke University, Director and Robert J. Margolis, M.D., Professor of Business, Medicine and Policy at the Margolis Center for Health Policy at Duke University

He is a physician-economist who focuses on quality and value in health care, including payment reform, real-world evidence and more effective drug and device innovation. Dr. McClellan is at the center of the nation's efforts to combat the pandemic and the author of a roadmap that details the steps needed for a comprehensive COVID-19 response and safe reopening of our country. He is former administrator of the Centers for Medicare & Medicaid Services and former commissioner of the U.S. Food and Drug Administration, where he developed and implemented major reforms in health policy. Dr. McClellan is an independent director on the boards of Johnson & Johnson, Cigna, Alignment Healthcare, and PrognomIQ; co-chairs the Guiding Committee for the Health Care Payment Learning and Action Network; and serves as an advisor for Arsenal Capital Group, Blackstone Life Sciences, and MITRE.

Dr William Reichman

President and CEO, Baycrest Health Sciences Center

Dr. William E. Reichman is President and Chief Executive Officer of Baycrest, among the world's premier academic health care organizations focused on seniors' health and residential care and aging brain function. Dr. Reichman has an appointment as Professor of Psychiatry on the Faculty of Medicine at the University of Toronto and is a recipient of an honorary degree of laws from OCAD University. He is a noted global authority on the delivery of innovative medical, mental health and dementia services in geriatric care settings. Dr. Reichman is a former President of the International Psychogeriatric Association, the American Association for Geriatric Psychiatry, and the Geriatric Mental Health Foundation. He has been a special consultant to the Civil Rights Division of the United States Department of Justice on dementia and mental health-care delivery within nursing homes and has advised the WHO and the governments of Canada and China on health policy. He served as the weekly Senior Health columnist for the Star Ledger, New Jersey's highest circulation newspaper and has been widely interviewed and quoted by all of the major media outlets in the United States and Canada. Recently, he also served as Co-Chair of Canada's Ministerial Advisory Board on Dementia and was instrumental in the development of Canada's National Dementia Strategy.

Discussion transcript

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

I think the first topic of the day is one of the toughest ones, I think. That's why we chose it to be the first one. It's clinical meaningfulness. Although I'm a clinician, I don't even know what clinical meaningfulness exactly is. For me it's different than from the patient in front of me, from the payer perspective it's different from the regulators it's different as well. And from academia or industry it may also have a different meaning. So, what is clinical meaningfulness and how do we define it?

And it's an important discussion because as you know we have the Lecanemab results, 27% difference in 18 months on the CDR: is that meaningful or not? Is it all in the eye of the beholder? Ultimately patients want to be treated with something that's meaningful for them.

So, we have a very distinguished panel for you to kick off the discussion on this particular topic. We have not really briefed them to say this or that or what do you expect me to say. Just say what you want to say and be open and also provocative if you want as we know there is no single interpretation there will be no right or wrong at the end of the discussion, but we will have an exchange of views on this important topic.

So let me introduce the panel to you and I'll ask them on the podium:

- **Professor John Harrison,** who needs no introduction, but anyway, he is Chief Scientific Officer at the Scottish Brain Sciences. Welcome John.
- **Professor Gillian Leng**, Dean for the Royal Society of Medicine and the former CEO of NICE
- **Professor Mark McClellan**, Duke University and a Former Director of the FDA and Medicare
- **Dr William Reichman**, President and CEO of Baycrest Health

So, very diverse panel already to start with. I'm looking forward to the discussion. Thank you for accepting to be on the stage here and to be in front of a very critical audience and an audience that will also be engaging with you.

So, who is first? Who wants to kick off with a statement or an opinion or a question?

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

Thank you, Philip, and thank you for the invitation to be here. This is a glorious opportunity. I was thinking on the very early train that I took this morning, while listening to the owls hoot, what I should say today. And I thought I would just revert to type and draw from my clinical work.

So, the people that you would see Philip in Amsterdam, the people that I see in Edinburgh, and the people I've seen over the years are all diverse. I spend a lot of time with people, and I learn what is clinically meaningful for each person that I interact with. To take Lenny's point from the introduction, I know what's clinically meaningful for me, the preservation of my intellect, arguably my sole virtue would be the thing I'd really want to hang on to. So, at a personal level, and in the interaction, I have with patients, I have a very good understanding of clinical meaningfulness.

But then I get to opine on clinical trials, and I find that I've got a very poor data set to work with. What we use to select people for a study an almost 50-year-old test of memory. Even though we full well know people can present with executive dysfunction, difficulties with concentration and so on. Then we measure it all with a decades old memory test, which is essentially all the ADAS-Cog is. I get rung up after every trial reads out and get asked "so where do you think the action is going to be cognitively"? I say, well it's got to be memory and they say, "how do you know that?". I say, well, if I look at the ADAS-Cog in mild patients, on most of the tests of praxis and language they perform perfectly on, so it can't possibly be that. And there are no tests of executive function or attention or the other things I'm interested in. So, I'm left with memory. And when the data reads out that's typically the case.

So, I find this mismatch. At a clinical level I have a very good understanding of what clinical meaningfulness is to my patient and to my caregiver and at a personal level I do too. But when I look at clinical trial data, I've just got insufficient data to make a judgment. So, I think what we need to do is to address that mismatch because then we'll be much better informed about what clinical meaningfulness might actually be in the context of a clinical trial.

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

Thank you John. We'll hold off the comments for now, we'll just let the panel go first.

Professor Gillian Leng, Dean for the Royal Society of Medicine and the former CEO of NICE

Good morning everyone. I think all of us when we think about dementia, we draw on our professional lives don't we, but inevitably personal experiences that we have as well?

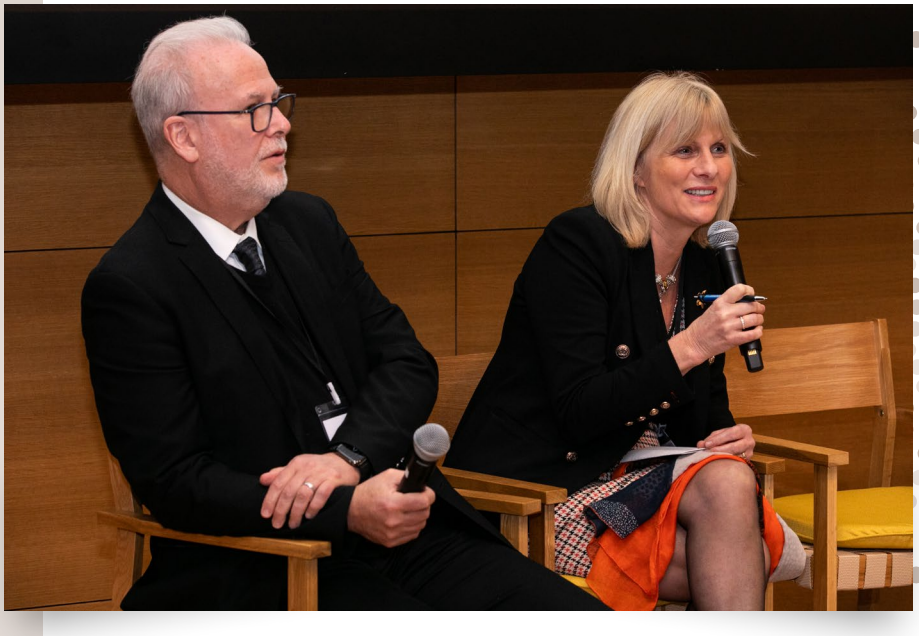
I think I first came across a patient with dementia as a medical student, but as my career developed through public health dementia took a higher profile. And of course, during my 20 years on the board at NICE, dementia was one of those tricky areas that we dealt with through our appraisals and guidelines.

But in relation to clinical meaningfulness, I think that was first drilled into me as a junior doctor. Treat the patient, not the x-ray. And that's the same philosophy, isn't it, here with outcomes and trials. I spent several years doing research into cardiovascular disease. And the trials there, they were always looking at the disease through an angiogram or a scan. But actually, what mattered to the patients with that condition was whether or not they could walk to the shop or the pub without getting pain. And the relevance of the trials was really quite limited.

I spent many years working with the Cochrane collaboration, who did a lot and have done a lot to try and address clinical trials and make sure that the outcomes are meaningful. But I still think we've got quite a long way to go. And dementia is particularly complex, not least because of the time frame that you need to see the clinically meaningful outcomes.

And I also want to just add a personal story, because my mother had Alzheimer's. And she had, I think, really quite a high threshold for what, for her, was going to be meaningful for her life. And she said, I don't want to be here if I'm no longer myself. For her, it was all about her identity. Her identity was someone who was organised, smart could cook, capable hostess, and if that went, she didn't want to be there. She didn't want to be someone. It didn't matter to her if she could live independently, if she couldn't be herself.

So by way of conclusion I would say it is not easy to answer this question but I do think an important element to answer it is by talking to people, talking to people with dementia and their families and their carers.



Dr William Reichman, President and CEO of Baycrest Health

Good morning everyone. So for about 30 years of my career, my main sources of data to answer the question of how is my patient doing was asking the adult daughter, who typically accompanied her mother to the clinic visit. Or it was the results of pencil and paper tasks, that are now done on a tablet or a laptop computer, things like the mini mental state exam or the MOCA and so on.

I firmly believe that a decade from now, maybe sooner, but a decade from now, an audience like this is going to look back on how we appraised clinical effectiveness and say, oh my goodness, look how primitive they were. We're on the threshold of a new age in access to data, which is going to provide us with such a more comprehensive understanding on the functional integrity, the well-being, the level of social and recreational engagement of our patients, than we ever imagined was possible.

So today in the clinic I might ask an adult daughter, so how's your mother been doing? Does she safely drive a car? Is she able to prepare meals for herself? Does she wander out of the house at night? Is she taking her medication? All the questions that all of you are quite familiar with. But I suspect that in the near future I won't be directing that question to the adult daughter. I'll be requesting that question from Siri or Alexa. Because of the convergence of three main technological advances: big data, which you're all familiar with; the Internet of Things, the connectivity, the wireless connectivity among many different types of data gathering instruments; and then ultimately artificial intelligence to help us to make use of what are all of these data sources, what are they telling us about the well-being of this individual and where we should focus our attention to mitigate risk.

So I do believe we're on the threshold of the new age, and it's going to be my mother's car, not a bystander who's going to tell me whether she operates it safely or not. It's going to be her pharmacy or the grocery store, which is going to tell me whether she's eating the right foods, eating enough of them. It's going to be her technology-enabled smart home, which is going to tell me whether she's had some near misses or falls, or whether she's left the stove on. It's going to be all those different sources of data which will converge, be analysed by artificial intelligence platforms, and so much better inform us on the status of individuals who are undergoing treatment or are in need of treatment. Thank you.

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

Thank you very much for this insight into the future.

Professor Mark McClellan, Duke University and a Former Director of the FDA and Medicare

And let me just add into this. First of all, it's great to be part of this distinguished group at such a timely gathering in the midst of what I think is a really hopeful period for dementia. This is a condition with your leadership that can be right at this cutting edge of bringing new biomedical technologies along and bringing along the data and analytic methods we've been talking about in this panel.

Now, my own work is mainly on the policy side. I don't see as many patients as you all do. But I gotta tell you, from the standpoint of the US FDA and CMS, there are no issues bigger than trying to find more effective ways to deal with dementia. It is such a burden, both financial and personal.

So, we're gonna see, in the next few months, pivotal studies for lecanemab and donanemab reported out that I think if everything stays on track, are going to lead to FDA full approval for these treatments. Followed, probably shortly, by approval in other countries as well. And that's going to be based on their judgment of clinical benefit from 18 months of data showing up to, maybe 20 to 30 percent, as you said Philip, incremental slowdown in the measures of cognitive function that are included in these trials. Now, there's a reason to think that that is worthwhile, because those measures are predicted to translate into the stuff that really matters for patients, how well they can live independently, do the things that make to them. The things, as Gillian said, that are important for their identity.

But there were only 1,700 patients in the trials, and in conditions that are probably not anything like usual clinical practice. These trials may not have included very many people like you, or like many of the other people who have been affected by dementia. So, given all of that if you think about it there are a lot of unanswered questions still around with these treatment approvals.

And that's where I think we're seeing some of the controversies involving CMS and other payers. A lot of people would like to say, well, if FDA determines a treatment is safe and effective, it should just be available and paid for. But as CMS and others have noted, a safe and effective determination by the FDA for such a broad and heterogeneous population of patients for treatments that are gonna be used potentially for a long time in very diverse settings of care may lead us to think that we really need to get better evidence. Exactly as the other panellists here has talked about. So based on the trial results, I think what you're going to see is many of the payers listening to experts who say that specialized care capabilities are going to be needed for the initial diagnosis and management of patients using these new monoclonal treatments.

The U.S. Veterans Administration did recently announce that they are covering lecanemab based on the accelerated approval results, but they're excluding a lot of patients. Following the trail criteria, excluding people under 65, people who have other conditions such as immune conditions and other serious illnesses, APOE4 homozygotes and so on. And there are significant requirements on the prescribers. The treatment can only be prescribed by a VA board certified neurologist or geriatrician specializing in dementia care. There need to be regular screenings with MRIs, a proper diagnosis, ongoing monitoring and so on. The prescribing doctor needs to update the patient's status before any single infusion occurs, make sure they're still on track, monitor for complications or side effects and so on.

CMS has said there are lots of other questions that they'd like to see answered. Are there downstream benefits that really are meaningful for patients? Are there differences in the adverse events that occur in different kinds of subgroups, people with coagulation disorders or other comorbidities and so on? And what practice capabilities are really needed? Because there aren't that many practices that can do the kinds of monitoring and ongoing oversight that I just described and that we're likely to see in the early use of these treatments.

We really need to get ahead of the game here. Registries can be very helpful in producing real-world evidence. But the sources for this real-world evidence can be much broader than they are now. And I don't think we fully got those capabilities in place.

And then, just a final point about all of that. To get to clinically meaningful benefits, we need to support new ways of delivering care to patients. Lenny started out by noting this this morning. Most dementia patients are not treated in a coordinated care setting with ongoing monitoring, shared decision making about treatments that may have benefits, but also may have risks, in a way that brings together the medical, increasingly, as well as social and other supports that they need. That's not the way we pay for dementia care. That's not the way we set up teams. If we could make progress on that as well, that would also create much better ways to develop and learn from the kind of evidence that we've just been talking about this morning.

So I think there's a tremendous amount of potential for realizing clinical benefit, but our systems, our supports, are not set up to make that happen easily, even as these new treatments are coming along. And that's gonna force some of these changes, hopefully leading to faster progress on actually delivering meaningful clinical benefits to patients. Thank you.

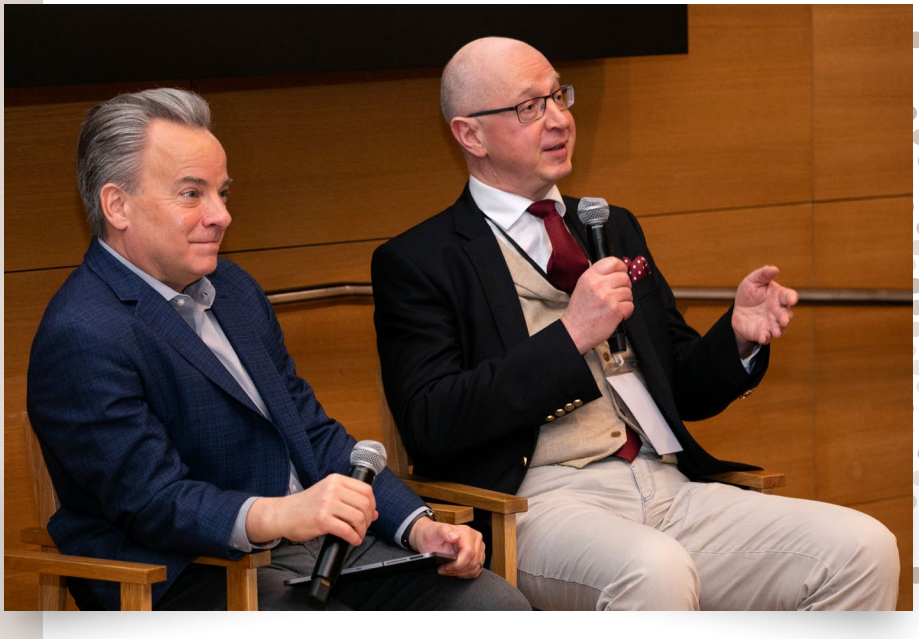
Professor Philip Scheltens, chair of World Dementia Council, Professor Emeritus at Amsterdam University Medical Centers and head of the EQT Life Sciences Dementia Fund

Thank you very much for your opening remarks. Is there already somebody in the audience who wants to directly sort of interrogate or respond or comment? Yeah, there you go. We have Tetsu over there and one here in the front. Can you raise your hand again? Tetsu, go ahead.

Participant | **Tetsu Maruyama**, Executive Director Alzheimer's Disease Data Initiative (ADDI)

Thanks, Lenny and Philip. So, two things. First, thank you very much for mentioning data! As the head of the Alzheimer's Disease Data Initiative, a data sharing platform, I think a lot of the answers we're looking for are gonna come from getting more people access to more data to analyse in different ways. But secondly, I'd like to ask a question I hope isn't too uncomfortable! Major depression,

schizophrenia, bipolar disorder are all conditions for which we've had barely adequate treatments and barely adequate diagnoses for a very long time. And for these conditions the incentives seem not to be there to improve either the measurement of clinical meaningfulness or the treatment. What are we going to do to make dementia different?



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

Yeah, thank you. I've worked on MDD and schizophrenia and the interesting thing from my perspective is I think we do a far better job actually of assessing cognition in MDD studies than we do in Alzheimer's studies. Which is a very sad reflection of where we're at! To make progress in dementia means I think to catch up very largely with the kind of approach that we took in MDD studies. And the answer is to emulate much of what went on. I think when one works in an area outside of Alzheimer's disease, there's very rarely a legacy in terms of expectation of what one tests. We tend to take the assumption if we just pick really good, reliable, valid, sensitive measures, they'll deliver for us. And in those other disease areas you mentioned, that's exactly what was done. The Matrics Initiative in the US, I think is a really good example of that.

I have a client who's run a cardiology study, and we were looking at cognition for safety purposes, and the same client does a lot of Alzheimer's disease research. And I mentioned to them the huge irony, they do a better job of measuring cognitive safety in a cardiology study than they do efficacy in an Alzheimer's study. So I think it's just beholden upon us as a community to up our game and match that level of assessment.

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

Yeah. You want to respond as well?

Professor Mark McClellan, Duke University and a Former Director of the FDA and Medicare

Sorry. I do hope this turns out to be different, but the track record for most conditions where there are good diagnostic criteria and effective treatments available is not that great. Depression, other behavioural health conditions, low rates of treatments. Hepatitis C, we have a cure, easy diagnosis test, or pretty easy diagnosis test. Yet still millions of people living with the disease. I could go on, hypertension, diabetes, etc.

Getting to early diagnosis and intervention, I think, requires a different way of both organizing care and paying for it. It means think about how you have a system where you're paying not just for use of a drug, but paying for actually tracking how patients are doing in these very important measures others have mentioned. The impact is what matters, but that's not what we're paying for now, for the most part at least.

And there are good potential models. CMS in the United States is in the process of developing one in Medicare that would pay something like a per-person amount for each person with dementia who's diagnosed appropriately and then monitored well with an emphasis on slowing that decline and progression and improving how that person is doing with these kinds of outcomes that are increasingly measurable. But we're not there yet.

Professor Gillian Leng, Dean for the Royal Society of Medicine and the former CEO of NICE

It's a really interesting question! Not least thinking about the schizophrenia parallel. We had such a raft of new antipsychotics, didn't we, 20 to 30 years ago, and it's kind of stopped.

We've seen some progress in a separate area antimicrobial resistance. I don't know whether there's any parallels, but we were not getting any new antimicrobial treatments. But that has changed largely because of international interest in the issue, concern about population health, concern that there was going to be some dreadful new bug that would kill us all. The work that's happened there, NICE has led with NHS England, in relation to a new funding model, because it's fundamentally an area where if you have a new drug you don't want it to be used a lot, you have to protect it. That of course is different with dementia, there is clearly potential for lots of people to have access to a new dementia drug, but I raise this parallel because my thinking was we got this level of progress in antimicrobials because of concern of governments.

So I think if we're going to make a difference here to funding both diagnostic tests as well as then supporting industry to continue the quest for finding drugs, we do need international interest from governments to provide some research funding, to provide incentives, and to encourage those drugs to continue to be developed. I think the lever for this is the impact on the cost to society both in terms of productivity, carers and all the rest. It is a huge societal cost and that should be the lever to drive change and investment.

Dr William Reichman, President and CEO of Baycrest Health

I think there have been two streams of thought within the collective zeitgeist that have distinguished how we think about dementia and the opportunities before us versus how we think about cancer and cardiovascular health.

The first is, for so many years, it was commonly believed that dementia's just a part of getting older, so there's nothing you can do about it, there's nothing you need to do about it, it's just something you accept as you get older. Just like your joint ache when you get up in the morning. Something that happens for no apparent reason. The second is the lack of an effective treatment. Why should I even be concerned about this? There's nothing anybody can do about it anyway!

I think now that we know it's not an inevitable consequence of aging and a sizable proportion of dementia can be prevented, and now that we're on the threshold of a whole new generation of therapies, I think the collective zeitgeist is going to change.

And the difference, I think, between dementia and say cardiovascular and cancer, versus the example of bipolar illness or schizophrenia, is that if you ask those most at risk, my generation, the baby boomers, what are you most concerned could happen to you in terms of your health as you get older, we're not going to say schizophrenia or bipolar disorder. We're going to say cancer, a heart attack like my father, or God forbid, dementia like my grandmother. So, I think that we're on, like I said, the threshold of a very different way of thinking about all of this in the very near future. And I think that's cause for optimism.

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

Okay. You see, this works. One question, four answers.

Participant | **Chris Edgar**, Chief Science Officer at Cogstate

Thank you. We've heard a lot of really interesting perspectives here on clinical meaningfulness and how there may be different audiences for what is clinically meaningful, how we might think about content validity and actually measuring what matters for individual audiences as well as the size of an effect that might be achieved.

Is part of the problem that we face, a lack of pressure that we as a field are putting on our colleagues, on our peers, in terms of the way that they report clinical meaningfulness? We're not making people sufficiently articulate what they mean. Allowing the phrase to become a kind of jargon whereby, you know, they're not truly articulating why they think the content of what they measured was relevant, why they think the size of the change, or the threshold of difference, was meaningful and so on? And how do we change that?

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

Intriguing comment. John.

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

Yeah, thank you, Chris. I think it is fixable. And I think probably the first step is to build in and contemplate clinical meaningfulness in the design of your trial. So, I've had the good fortune to go through the Biogen data, Lilly data, a whole host of trials that are read out. And we're always trying to reconstruct clinical meaningfulness after the fact. What we end up concluding is, we can make some progress, because we can look at the content of a clinical dementia rating scale, or a clinical global impression of change scale. And we have to go back to the CRF to find the nuggets of evidence that we actually did have that relevance.

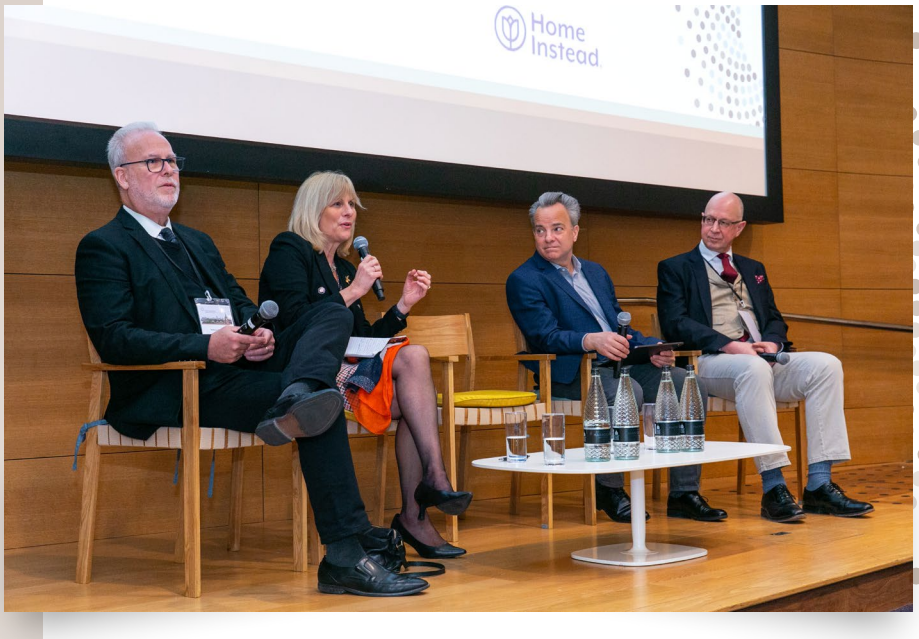
So I think the role of other third party stakeholders is critical. In fairness to the FDA, in 2018 they published a draft guidance which I read with glee, nothing short of delight. I mean, it seemed to me to be saying all the right things, sensitive neuropsychological testing, the dichotomy between function and cognition was arbitrary, and actually probably not defendable. And yet in the intervening five years, I see no difference in the protocols that land on my desk from week to week.

So, to answer your question Chris about how we get there, I think there is pressure that can be applied, which is subtle, draft guidance and so on. I think probably even pressure from considering the ethics of a trial. Is it ethical to be testing people on an outcome measure where you know you can't show improvement because people are at ceiling? I think a responsibility falls to ethics committees to ask difficult questions. I would also like regulators to take a more proactive role in dictating what we use, that would be really helpful, because there is a lot of uncertainty. But I think constructing measures that will inform us and incorporating them into protocols to begin with, that would be a really good first step.

Professor Mark McClellan, Duke University and a Former Director of the FDA and Medicare

Yeah. Just to add that FDA is in a tough balance position. They want to encourage the better measures and so forth. But they also recognize that performing these clinical trials is really expensive, takes a lot of time, you need to follow patients for at least 18 months in these pivotal trials. And as a result the FDA has to balance pushing for better measures against the fact that manufacturers, product developers may be a little bit slow to change and to adopt new measures as their primary endpoints for approval. Now, like you said, there are a lot of these nuggets and additional data buried along with the primary endpoints for the studies, which are the more traditional ones, and which look like they're showing some improvements here.

But I do think that puts this whole issue back on the community. We're not going to see those trials, those pivotal trials that are being done in the next 18 to 24 months, switching to the kinds of measures John that you're talking about. That means we really need to learn from the real-world evidence and the methods that could be applied to rigorously collected data from these new electronic systems to learn more about what treatments, and in what combinations, are really mattering for different kinds of patients. That's the phase we're at right now, given the clinical trial results and that no new clinical trials are going to come to settle these issues anytime soon.



Professor Gillian Leng, Dean for the Royal Society of Medicine and the former CEO of NICE

I'll just be brief. I really feel we should be running some good quality focus groups with lots of patients, different stages of disease, and their carers, and getting some really good data that we ask everyone to use in their trials. And regulators could definitely do more. Over the years, NICE did sometimes make statements around, we need to see this questionnaire or we're not going to take a look at your new drug. But more often it's, we would like this, not we have to have this. And I think there could be a stronger pushback.

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

So input from the patient themselves and the carers as well. But I must warn you, I've been in this field for 30 years in the sense that I've watched it being very resistant to new measures, that's why we still use the ADAS, and it is why we still use the MMS, because nobody actually dares to do anything else, although there are many other out there! But that's my personal hobby horse. There's a question from someone that has actually come to the microphone instead of the microphone coming to them, which is a very good initiative, so, go. You first and then George.

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

So I want to embrace the idea that we don't have the will to make the change that we all know needs to be made, right? We all talk about, everybody has talked about now, the fact that cognition is really hard to measure. And yet what do we try to do? We try to reduce it down to a single test, a single measure, et cetera. And at some point where do we just embrace the complexity of the behaviour? We

talk about it, we know it's heterogeneous, we know it changes. When we do an early intake, do family members, do people, do they test themselves? They never test themselves, but they know that they have an impairment, right? Why aren't we doing that? Why aren't we taking sort of all the technology and combining it in a way to let us measure this in the way Bill you say?

The only thing that I would add is because we have the word world in the title of this meeting, if we think about technology, we've got to think about the smartphone because that's the only way we get to world. So, I like your comment about why don't we do this because we all know we can and why don't we have the will?

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

So why don't we have the will? Why don't we do it?

Dr William Reichman, President and CEO of Baycrest Health

Well, I think we've fallen into a common trap where you miss the opportunity. It feels to me like, you know, we're a bunch of automobile manufacturers trying to figure out how to get goods across the continent by building faster cars, when in fact the answer is airplanes. And so, you know, we're trying to take our old machine from 1975 and we're trying to contemporize it. And what I'm saying is, no, the 1975 machine is obsolete and there's an opportunity now to build a 2025 machine. And that's what we need to be focusing on right now, not optimizing our obsolete car from 1975, but let's build our 2025, 2050 method of gathering data to help us understand the status of the people we're committed to care for.

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

But I would say the 2025 instruments are already here. We have them! But they are not being used. I think that's one of the problems.

Dr William Reichman, President and CEO of Baycrest Health

Well, they're not being used in our sector. They're being used for consumerism, right, and to sell us things. But those same technologies can be adapted to our purposes. But we're the ones who are going to have to adapt those technologies to our purposes. They're not going to be done by others. That responsibility is with us in our field.

Professor Mark McClellan, Duke University and a Former Director of the FDA and Medicare

Now that they're getting to be diagnostic tests and treatments that really could matter, I don't think you're going to get there by waiting for the clinical trials, the randomized clinical trials to be done. I do think that there are a lot of healthcare payers around the world, NICE, NHS, the VA in the United States and CMS that are struggling with these issues right now and that would very much like to pay in a way that encourages the measurement and better understanding of the outcomes that really matter to different segments of this very diverse population being treated under very diverse types of clinical practice. That working with the payers is something I think this community could find some very constructive steps for. Pay for the outcomes that you want, and you'll hopefully get the airplanes.

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

I have several people in the audience who want to respond. You are next.

Participant | **Russ Paulsen**, Chief operating officer UsAgainstAlzheimer's

So, Philip started this thing by saying, it's in the eye of the beholder. We've been doing work on what I would argue is the most important beholder for the last four years patients (John and I have been on a panel about this in fact).

Often when you get into this conversation you do exactly what's been happening here. We start talking about how do we measure, what are the possible things we could measure, what are the technologies, and then we also talk about anecdote and then we focus on, if we're talking about the Lecanemab trial, we talk about one single primary endpoint, and the average group changes as if that affects everyone in the group equally.

What we've learned is, in talking to patients over the years and doing rigorous research, we've talked to 370 patients roughly and asked them specifically what matters to you. At the macro level, what we learned is that it's about progress in the disease. Progression or lack of progression is what matters most to patients. So, if I were to urge us to look at one measure on the Lecanemab data or any other data, it's the Kaplan-Meier curves about progression to the next phase. That's what's clear, unambiguous, in our patient data. What matters to patients is progression or lack thereof.

At the granular level then, the stuff like CDR measures and ADAS-COG, patients care about 42 specific items. CDR sum of boxes measures 12 of them. The ADLs are more frequent and more often. So the ADL measures matter a lot. I think when you're evaluating what's clinically meaningful to patients to try to get at this heterogeneity, you can't just look at one primary endpoint. That measures just a small fraction of what matters to patients. You can't just look at any one measure. You've got to look at the concordance of measures, and you've got to look at progression. And by the way, when you talk about minimal clinically important difference, it's defined literally as the difference that's important to the patient, not in the eye of any other observer. Thanks.

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

Thank you. Comments, reactions, thoughts? Yeah, to both those themes.

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

So, Rhoda, Russ, Chris, I mean, we've sat in rooms endlessly, in my case, for three decades, saying there's a much better way. We really should get around to doing this.

I had supposed that this was going to be the role of government. Back in 2013, I was very optimistic after the G8 summit with David Cameron speaking as eloquently on the topic as he did. And then last year we were promised a strategy for dementia which we still don't have. So, I think I've sort of given up on the idea that, at least in the UK, government is going to take the lead on this because it's clearly not done so. Part of the reason for forming Scottish Brain Sciences is to demonstrate by example. I think we've gotten to the point where it's clear we're going to make no progress through argumentation, so by providing an alternative model and offering that as something for consideration, we think that might be a fix.

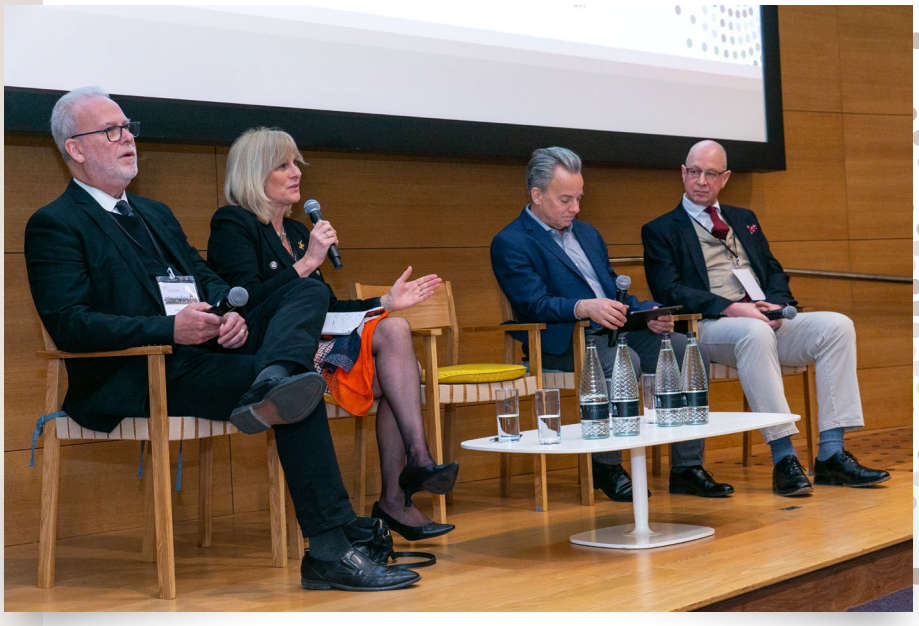
Professor Gillian Leng, Dean for the Royal Society of Medicine and the former CEO of NICE

Just a slightly broader point around data, because I do think a way forward around using real-world data and probably having a lower threshold for introducing some other drugs could be a really good way forward. Some of you will be familiar with the Cancer Drugs Fund that we had in England. It's now been expanded, so it's now innovative medicines rather than just cancer. The fund lets you introduce a drug with less data and lets you then evaluate it with real world data collection. And bearing in mind, I think we need a longer time horizon for demonstrating the impact of anti-dementia drugs. I think that could be a new model.

But am I alone in the room worrying about people with dementia living in smart homes? Because although my home is quite smart, I'm quite good with all the technology. I see all my older friends not living in those sorts of worlds and my mother was dreadfully resistant. She could use the video recorder, and then she couldn't. So the video recorder was put in the shed to stop her remembering that she couldn't use it. She used to be able to text, then she couldn't. And the phone went in a drawer. And she used to be able to follow a recipe, then she couldn't. All those sorts of things. I worry that to imagine we're going to have people with dementia living in a smart environment might not be realistic unless we provide lots of support to make it work. But you were advocating that Bill so I should let you reply.

Dr William Reichman, President and CEO of Baycrest Health

Well, you know I think where are we at it you know as a field well you know in clinical meaningfulness is not only with people with moderate or more advanced stages of dementia. I mean we're going to be treating people with preclinical Alzheimer's disease and a lot of them are going to be walking around with smartphones and are going to have access to technology. As will people with MCI. So, I do think there is a cohort where this could be useful. And then other kinds of technologies could be leveraged for people with more advanced disease.



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

You did mention that that was 10 years from now that we would look back. So I think the point is right that it's still future in that sense. George.

Participant | **George Vradenburg**, Founding Chairman, Davos Alzheimer's Collaborative (DAC); Convener, Global CEO Initiative in Alzheimer's (CEOi); Chairman, Global Alzheimer's Platform Foundation (GAP) Chairman and Co-Founder of UsAgainstAlzheimer's (UsA2); Founding Member, World Dementia Council; Founding Member, US NAPA Advisory Council

I'll be brief. Where is our Elon Musk or Steve Jobs? I mean, where are those kinds of disruptors in our field. I don't think it's coming from academia. The sort of disruption we need is not going to come from government. It's not going to come from health care systems, which are so entrenched. Where are these new revolutionaries going to come that adopt all these magical new technologies and apply them around the world, as opposed to just the 5% of the upper class i high resource settings?

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

Good question. Who has the answer on the panel?

Dr William Reichman, President and CEO of Baycrest Health

I think the demonstration that it creates value. So, if it creates value for technology makers, if there's a market for these kinds of technologies to be brought to bear in healthcare, then the technologies will be brought to bear in healthcare.

Professor Mark McClellan, Duke University and a Former Director of the FDA and Medicare

Just related to that, it is a little bit harder here to demonstrate value than maybe with your Tesla. I mean, we're talking, as you were just saying Gillian, about a chronic disease, takes time, other factors besides the treatment may influence it.

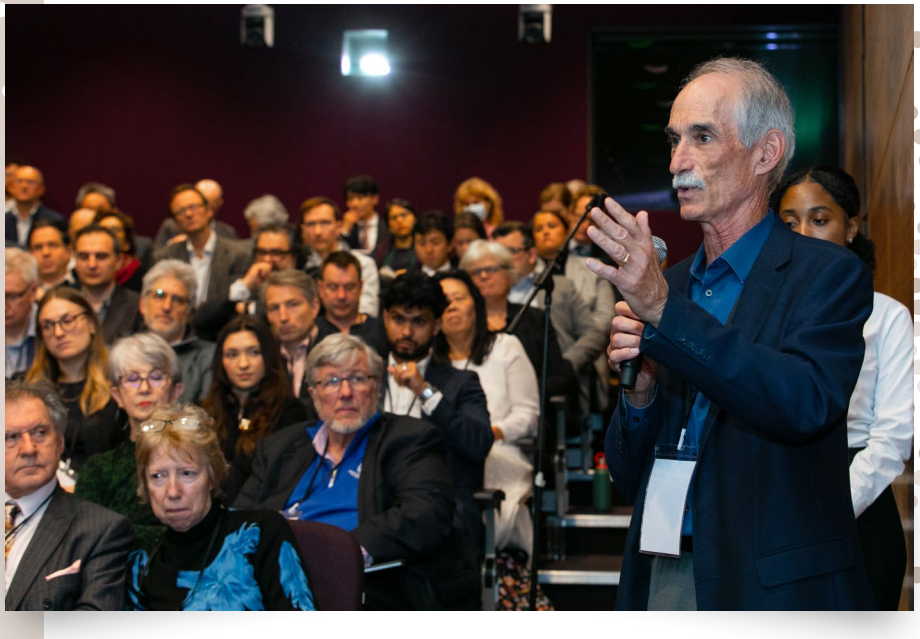
But good data and good methods can definitely help. And the other part of value is these are treatments that, for better or worse, are largely paid for under public systems. And if those public systems aren't reformed in a way that recognizes the outcomes that you all care about, it's gonna be hard to create a sustainable growth model for these kinds of innovations.

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

Philip, just really quickly, I think as a community, we probably need to be a bit less polite and a bit more cross, is my honest response. And I think Lenny's opening conversation was a very helpful one. I think the reason why we developed HIV drugs with the speed we did is there was an advocacy group that was not going to be silenced and I think we just need to be a bit more vocal.

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

Here you go. Harry, you're next, but first Steve. I was thinking to myself, we have clinicians in the room and I haven't heard them yet and then Steve stood up.



Participant | **Steve Salloway**, Associate Director of the Brown Center for Alzheimer's Disease Research, the founding Director of the Memory and Aging Program (MAP) at the Butler Hospital, a Professor of Neurology and the Martin M Zucker Professor of Psychiatry and Human Behavior at the Warren Alpert Medical School of Brown University, Providence, RI

Thanks, Philip. So as a clinical trialist, I have a lot of experience with the new drugs, really across the board. And in my experience, we had over 100 people on aducanumab, some for eight years. And so, I really got a sense about clinical meaningfulness for them. And the problem is these are small effects as a mean. But what has been clinically meaningful for people is, as Russ said, and I think as Gillian said about her mother, is people who stay in a milder state longer.

So, there is a subgroup of people, at least within the aducanenab trial because we follow them long enough, that progressed very gradually or minimally. And the families noticed it. Their tests stayed the same. It was very gratifying for them. It was easy for us, for the clinical staff, to see. That was clinically meaningful. They were still able to function pretty much as they were. That's a subgroup.

We need to get better at identifying responders. We are much too sort of global in the way we approach these things. Lilly tried to do this by using biomarkers to nail down who might be most likely to respond, and I know we will get to biomarkers later today. So, we need to get better at responsiveness.

Rhoda's point is, and what I think George was getting at, is we really need to partner with AI specialists and get people who are really smart, really good at AI, and apply it to Alzheimer's. I know it's not going to come from us. I don't know enough. Rhoda maybe knows enough about it. I don't know. But I'm not a specialist in that area in bioinformatics. So anyway, we need to partner there.

And the third thing is for Gillian, I have a question. I know you're probably not at NICE anymore, but I know in the old days NICE had concerns about the clinical effects of cholinesterase inhibitors and memantine. The effects with these monoclonal antibodies aren't any better, and they cost a lot more and they have a more serious risk profile. So, I don't know what the climate is at NICE, but how is NICE going to deal with that?

Professor Gillian Len, Dean for the Royal Society of Medicine and the former CEO of NICE

Yes, it was a controversial period! It was something we approved, and then the new data came along and suggested that the effect wasn't as much as we'd originally thought, and the decision changed. So, it remains tricky, to use a technical term!

And NICE has published, it did when I was there, you're right I'm no longer there, an update in the methods guide, which hopefully provides a bit more scope to take into account wider factors that might impact on the decision. However, the opportunity cost is always in the background of the committees that are sitting and looking at new drugs. If we are spending all this NHS resource on this new medicine what does that mean in terms of the overall spend across the health service? And there is an equation that NICE plays to which is listening to clinicians, listening to the views of patients, listening to industry and listening to the NHS funders. And it's a circle that's impossible to square, there's always somebody that isn't comfortable.

Over recent years, as some of you will know, NICE did a lot of work and continues to do so with NHS England. So that there is a negotiation with drug companies that the NHS can have the drug at a discounted confidential price. So that gives us potential for a way forward. And if we can link that with the data collection that I was speaking about, that might give us a way forward. Because as you say, it doesn't look like a brilliant equation if we've got more side effects and we've got higher costs, but it might be possible to do that through some cost sharing and through some data collection.

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

I'm going to go to Harry who was first actually to respond probably to John's out cry.

Participant | **Harry Johns**, immediate past CEO of the Alzheimer's Association

Well, I think the most recent conversation is exactly where I would go. Lenny said it is not a new era across the world. And he is absolutely right about that because it won't make a difference for many people across the world in the immediate sense.

I would contend though that we are entering a new phase. There are different kinds of detection possibilities, that are already emerged or emerging rapidly.

And we do, and Steve's done so much work on this, as he just commented, have new technologies now in treatment. Now, they are imperfect. I worked in cancer more than two decades. The newest treatments were imperfect. And yet they've been paid for around the world. But for Alzheimer's, we have this presumption that the answer is no.

So, the most recent part of the conversation is crucial here because what's different is that people with Alzheimer's who are converting by the thousands every day from mild cognitive impairment to a point that's beyond what these treatments will do are not getting access that others with other diseases have.

So, on the policy side, we have the things that are coming over the years, and I agree and completely embrace those. But it's for the people today that we do have to get even more cross than we are with those who are in a position to change these outcomes. Because there are ways, I believe, to demonstrate these things, show more data, but not create access barriers that are inappropriate and specific to people with Alzheimer's and not other diseases.

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

Thank you. Brief comment from the panel and then we go. I have a few people in the audience that still want to talk. John you want to respond?

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

I'll happily if I may. I agree entirely with the comment that we do need to do something for people right now. And just in terms of legacy, we have Donepezil which on a good day has a 0.3 effect size on the things we measured in the trial. It is a remarkable observation. But interestingly mild patients on Donepezil tested on the kinds of measures that we've all been talking about today have an effect size of 0.8. So, we've always understated the true value of the drugs we have because we've never

really tested them in a rigorous way. So, I think we can do something for people today even based on pushing through some of these technologies a little more quickly and they're not that new because we've been using them for about three decades. So, I think there is a fix.

Professor Gillian Leng, Dean for the Royal Society of Medicine and the former CEO of NICE.

It's a slightly trite remark to that, but what people actually want is hope. And when we look at these drugs, people want us to approve it to give them hope. Any change will make a difference.

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

Good point.

Participant | **Sube Banerjee** MBE, MBBS MSc MBA MD FRCPsych, Executive Dean and Professor of Dementia in the Faculty of Health at the University of Plymouth

The hope point is fundamentally important. We should perhaps think about what makes for an outcome that is valuable for people with dementia and potentially for their family carers as well. Luckily we've got 20 years of experience speaking to large groups of people with dementia and their carers, trying to understand what makes for good and bad quality of life for people with dementia. And quality of life is a great outcome if we are looking for what matters to people with dementia and carers overall.

A major issue is that the things we always measure are cognition and functional limitation, and while these are really important they are not what drives quality of life for people with dementia. Decreases in cognition and function happen slowly in Alzheimer's disease and this allows for adaptation because human beings are brilliant machines for adapting to difficult problems.

So, we should remember to look at what does drive poor quality of life, and what is seldom included in the way that we have constructed our trials, we measure cognition and function because we think that's what dementia is. There is potentially much to be gained from measuring quality of life itself, as we do in just about all other illnesses. It would also be helpful to measure the things that drive quality of life, like behavioural disturbance and social interaction. It is really quite likely that we are missing positive effects from the medications we have coming on line now. It would be great to measure those things that actually matter to people. And we have measures to do just that. It's just that we choose for whatever reason not to use them in trials.

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

Thank you for the comment. It goes with the mismatch that you also indicated John. I have just one minute to go. Now, Jetske, you are allowed to ask the last question, and then we'll wrap up this.

Participant | **Jetske van der Schaar**, PhD Student Amsterdam University Medical Center

Well, thank you. I'll try to make it a good one then. I would like to add to the previous comments on quality of life, because I think it's very important to measure cognition and function and independence and all those things. But I think some trials, for example Lecanemab showed what I thought were quite impressive effects on quality of life. And I feel like somehow this is left out of the discussion. And even here, it's only brought up in the final moments. But I think you can argue quality of life is perhaps one of the most important aspects for patients.

And to come back to a prior comment, we need strong advocacy groups to stress the importance of this. So, I think my point is we need to pay more attention to quality of life and also include that in the discussion. Because I think ultimately that is what is most important for the patients or the future patients.

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

Thank you very much. We need to wrap up because otherwise we have no second panel anymore. Just a brief one-line comment from each of you to end of the session. John?

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

Let's educate people about their cognition so they can take control of it, measure it for themselves, and protect their cognitive health.

Professor Mark McClellan, Duke University and a Former Director of the FDA and Medicare

I think there's a lot of potential alignment between what the payers for these new technologies want, the kinds of outcomes that you all are saying mattering, and the interests of this group. If we can just get some of those models going, like yours it sounds like Gillian, that would be great.

Professor Gillian Leng, Dean for the Royal Society of Medicine and the former CEO of NICE

Some great comments and it feels to me like we need to re-energize and reset and move forward.

Dr William Reichman, President and CEO of Baycrest Health

It's clear to me that it takes a village and the solution to these challenges is going to require novel partnerships with those outside of our sector, whether it's technology developers, whether it's others, that also have the same commitment to the public good that we do.

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

Thank you very much. Give a big round of applause for the panel. So, while everybody is sort of resetting themselves, thank you very much for the lively discussion. This is actually the way we want the day to go.

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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