Alzheimer's Disease International (ADI)

End of Year Forecast 2025 Transcript

The diagnostics revolution; are we ready?

End of Year Forecast 2025
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Photography:
Robbie Appleton-Sas

Event summary The Diagnostics Revolution: Are We Ready

Dementia diagnosis has reached a pivotal turning point: after decades of research, reliable tools for earlier and more accurate detection of Alzheimer's pathology are emerging alongside the first disease-modifying therapies. The central challenge, however, is translating these advances into routine clinical practice worldwide. The End of Year Forecast stressed that this phase requires not only ongoing innovation in biomarkers and treatments, but also reshaping diagnostic pathways, workforce capacity, and policy frameworks to ensure these tools reach people living with dementia and their families promptly and equitably.

Hosted in partnership with Edelman, the event had a full-house for in-person attendees in London and 1,400 virtual participants. Dr Alireza Atri, keynote speaker, placed the moment in the broader context of Alzheimer's complexity, noting that whilst amyloid and tau remain central, vascular changes, neuroinflammation, and co-pathologies are frequent, with widely varying individual trajectories. He emphasised that progress depends on person-centred approaches, compassionate disclosure, integration of technologies such as AI and blood-based biomarkers, and global advocacy to ensure earlier detection supports planning, autonomy, and access to emerging therapies.

The discussion addressed challenges including diagnostic delays, system readiness, ethical implications of early biomarker disclosure, and lessons from oncology. Paola Barbarino, ADI's CEO, and Dr Atri highlighted the need for workforce training, clear referral pathways, and a societal shift to treat cognitive symptoms with the same urgency as other health concerns.

Watch the event recording

Speakers

Carolyn Paul, EMEA Chair of Health, Edelman

Carolyn Paul is Global Managing Director and EMEA Health Chair at Edelman, with over 30 years' experience in public relations and healthcare communications, specialising in central nervous system disorders including Alzheimer's disease, oncology, and global campaigns.

Paola Barbarino, CEO, Alzheimer's Disease International

Paola is CEO of Alzheimer's Disease International. Prior to this, she was CEO of LIFE and occupied senior positions with Cass Business School, Tate, British Library and IIED. She is a Board Member of the World Dementia Council, and a Trustee of Lauderdale House. Previously she was a Non-Executive Director of the Non-Communicable Disease Alliance (NCDA), a Trustee of Shelter, the housing/homelessness charity, and of MLA London. She holds a degree cum laude in Classics from Federico II Napoli University, an MA in Field and Analytical Techniques in Archaeology and an MA in Library and Information Science both from University College London.

Alireza (Ali) Atri, PhD, MD
Cognitive Neurologist and Medical Director at the Banner Sun Health Research Institute

Dr Alireza Atri is an internationally recognised cognitive neurologist and clinician-scientist specialising in Alzheimer's disease and related dementias. As Director of the Banner Sun Health Research Institute and Chief Medical Officer at Banner Research, he oversees research, clinical care, and education programmes focused on early detection, biomarkers, clinical trials, and person-centred care. A former chair of ADI's Medical and Scientific Advisory Panel, his work advances understanding and treatment of neurodegenerative disorders.

Opening Remarks

Carolyn Paul *EMEA Chair of Health, Edelman*
Thank you very much, everybody. My name's Carolyn, I head up the health sector at Edelman. Edelman is delighted to host this event for the second year. We have a long-standing partnership with ADI, which is hugely valuable to us, and I'd like to thank Shaun, who is our Edelman lead on that relationship, because without him, we would not be here. So thank you, Shaun. We're delighted to be able to host you again, and our CEO has just said to Paola that he's delighted to host again next year, so that's all taken care of.

Just a few facts and figures. We have around 70 people here in the room. And then online, we've got 1,400 people listening in, so an amazing turnout. Thank you to everyone who's helped with that. Thank you to the team at ADI, and our marketing team as well.

Without any further ado, I would like to hand over to Paola, ADI's wonderful CEO, and Dr. Atri, who is our speaker, to take us through the presentation today.

Paola Barbarino *CEO, Alzheimer's Disease International*
Thanks so much to Carolyn, to Shaun, for having us here for the second year running, but also for a partnership that has lasted 8 years and has been incredibly fruitful.

I should not forget to thank my amazing team at ADI. This is the last of our external events for this year. We have had an extraordinary year. In particular, I should thank Chris Lynch, Deputy CEO of ADI, whose idea was first to have this lecture yearly, and it's been a great success. Thank you so much, Chris.

We have had a welcoming introduction, but who I have with me today is Ali Atri. Ali, who has been, until a few months back, the chair of our medical and scientific panel, and is one of the luminaries in the world on Alzheimer's disease.

Today, he is kind enough to speak to us about diagnosis, but this will intersect with treatment as well. And also the issue of the continuum of the disease. So it's going to be a very open conversation. We have some questions that we had been sent in advance, but we are very interested to hear from you in the audience. As usual, you will be able to introduce yourself, but also send questions online that Chris, who is here with us, will consolidate and pass to me, and magically I'll be able to read these questions.

We are going to start with the presentation by Ali. But before I do that, I'd like to thank all of the sponsors that have enabled us to run this forecast this year, and in particular, Eisai and Roche, but also GE Healthcare, Acadia, Johnson & Johnson, and Re:Cognition Health Brain and Mind Experts. All of these have made this possible, and all of our sponsors continue to make ADI possible.

In particular, I remind you that we are a charity, so should you feel generous at Christmas, please remember to make a donation to us. Everything we do is thanks to the work of our volunteers. Everybody that speaks at ADI is a volunteer. A lot of the people that work at ADI, like our wonderful partners Edelman, do it because of the kindness of their heart. We couldn't do what we do without volunteering and donations.

Opening Remarks

ADI was established in 1984. We are the umbrella organization of 105 Alzheimer's and dementia associations around the world. We also have 15 members in development on top of that. We have one member per country.

Today, we also have the pleasure of having one of our board members, Bill Yeates, coming all the way from Australia, and our board member, Ameenah Sorefan, coming all the way from Mauritius. It's nice that we are in London, because people do come and see us.

We represent our members at the WHO, at the UN, at the OECD, G7, G20, all the multilateral bodies, but we are also the promoter of the World Alzheimer's Month and the creator of the World Alzheimer's Report. Our mission and our motto continues to be that the vision is prevention, care, and inclusion today, as we wait for a cure tomorrow. Though the cure is coming, we are very, very excited by this.

Final thing for me, please join us in Lyon in 2026. Our global conference that happens only every two years is going to be from the 14th to the 16th April in Lyon in France. It's a huge conference, it's very broad-ranging, and all the actors in dementia will be there, so please consider coming and registering. And now, we are getting into the thick of things, so I'm going to hand over the slides to Ali, and we're going to commence this conversation. But before we do that, Ali is going to give us a little introduction.

Right now, everybody is quite confused by the diagnostic space. We have biomarkers including blood-based biomarkers that are finally coming into action. We've been promised them for years, and then it never happened, and now they're here. What are we going to do about it? And for the other biomarkers? But in diagnosis, we also have a number of new things happening: AI now is reading diagnostics in a completely different manner. Even the cognitive testing now is being delivered in a completely different manner, and online, and anyone can access it. What does this mean for everybody? For the person in the street, for the practitioners?

So this is what Ali will try and explain to us. And a warning, this is not super easy, but you will have a chance, when you are at home, to re-watch it on YouTube, and stop and frame every of the slides. Every slide is a little mine of knowledge. So, we are aware that in one hour we won't be able to cover it all. But we will try our best also to make it available to you. We'll do another webinar on diagnostics in February, where some of these questions can be brought forward.

Dr. Alireza Atri's Presentation

Alireza Atri *PhD, MD Cognitive Neurologist and Medical Director at the Banner Sun Health Research Institute*

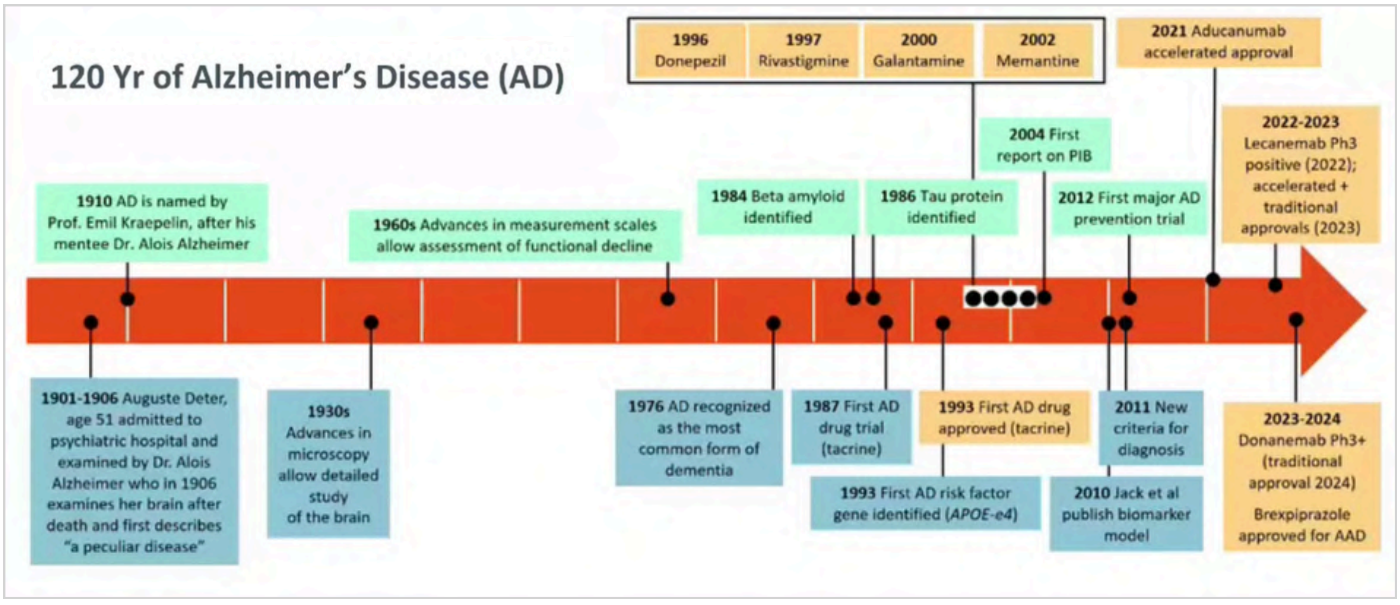
It's a pleasure to be here, and as Paola mentioned, I've made some slides, and they'll be available to you, and I made a bunch of them, so they'll be available online and, for you to take a look at. And I always start with this quote just to center us, so bear with me for a second:

> **Human beings are members of a whole. In creation of one essence and soul, if one member is afflicted with pain, other members' unease will remain. If you have no sympathy for human pain, the name of human you cannot retain.**

This is as true now as it was in ancient Iran, 850 years ago. And I put that in there because we're going to hear a lot about biomarkers, and PET scans, and proteins that go wrong in Alzheimer's disease, and p-values, but ultimately it's about a person. A person who's impacted, and the family around them. And, their personhood, what it means to them, and what we can do with them and for them. And them is us. We're not separated. So, as we march towards personalized medicine, we have to really keep our eye on that. AI–these tools–are incredibly important. They are tools; they have to be wielded wisely. The risks and benefits of them, the person-centeredness of describing these to them, having a compassionate diagnosis, and having it be done in an accurate way are very, very important.

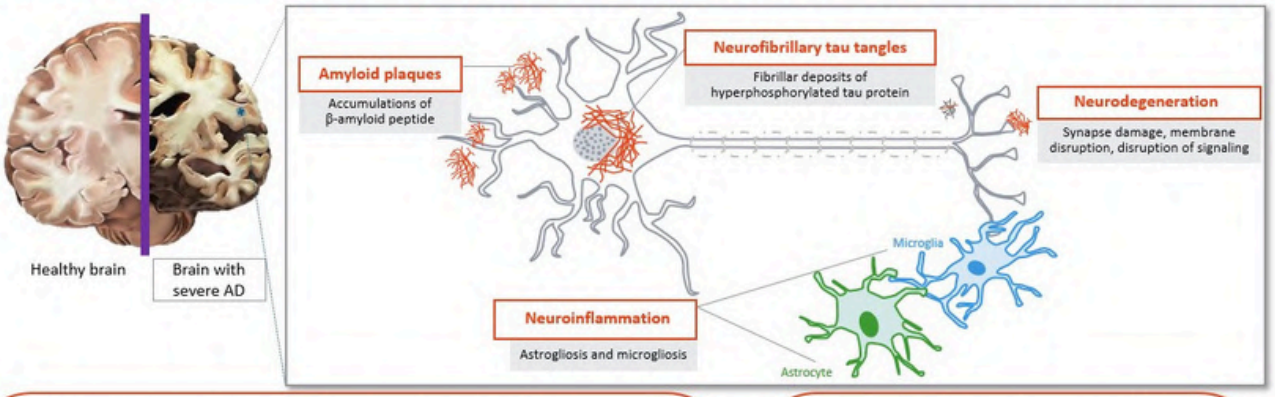
So, the slides are just for a guide, but it's a hopeful time, and hopefully you'll appreciate that there is a rational basis for hope in where we're going. I call this the end of the beginning. It's not the beginning of the end. We have a way to go. 120 years ago, when Professor Alzheimer described this in a 51-year-old woman who had early onset, and those are the people I generally take care of, young people–40s, 50s. And we know that there's late onset, and, during this time, we realized that this wasn't something rare. We appreciated what the proteins are that go wrong. And if you notice, what we call biomarkers, we started learning about these back in the 90s and 2000s. And ultimately, a few years ago, the first two disease-modifying drugs were approved. These are foundational, they're not cures. Before that, we had these symptomatic drugs, which are still important.

But the important part about the foundation is that, I think, as Dr. Cummings explained, is that we finally have a toehold where we can do something about one of the core pathological changes in the brain, and with it, we're changing the slope in a group–in a population. But we don't treat populations, we treat people in front of us, in person. And, the first-generation drugs have some potential side effects, and so they have to be unrolled in a very systematic, careful way, and this is part of what AI's going to help us with. It's going to help us detect some of these things early on, and be able to tell us, in the next generation drugs, which people respond, who's going to get more benefit, who's going to have potentially more side effects.



AD pathophysiology is complex and the dynamics of different factor contributions to neurodegeneration and dementia, particularly at the individual person-level, are incompletely understood

Pathologically defined by amyloid plaques and neurofibrillary tangles—but affect much more in the brain

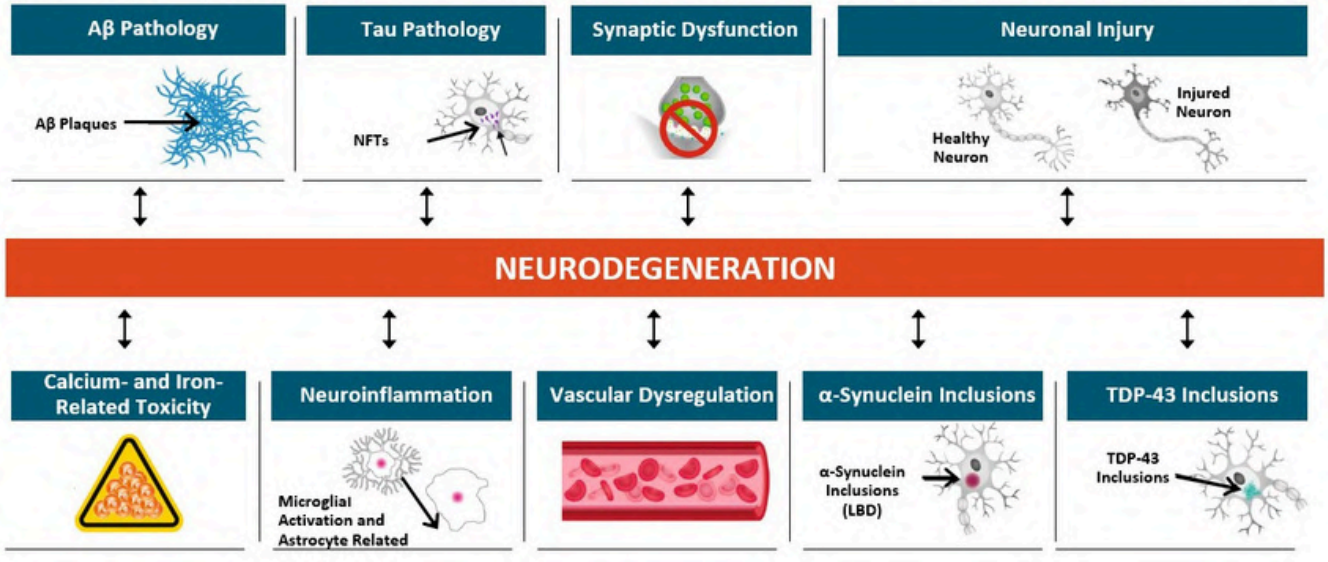


- AD has preclinical, pathobiologic disease stages (span 20-25 yr)
- The disease phases include abnormal amyloid-beta plaque deposits in the brain, neuronal and synaptic injury, tau tangle deposits, neuroinflammation, damage to brain blood vessels and more

- AD has clinical illness stages (span 5-20 yr)
- In the illness (clinical) phase, there are usually slowly recognized symptoms and progressive impairments in cognition and function

de Castro. Intl J Comput Intell Sys. 2011;4:89. 2025 Alzheimer's disease facts and figures. Alzheimers Dement. 2025;21:e70235.
Kinney. Alzheimers Dement (N Y). 2018;4:575. Atri. Med Clin North Am. 2019;103:263.

Multiple Mechanisms Implicated in AD and ADRD Pathobiology and Co-pathobiology AND Copathology is the rule, not the exception, in brain autopsies of persons with AD dementia

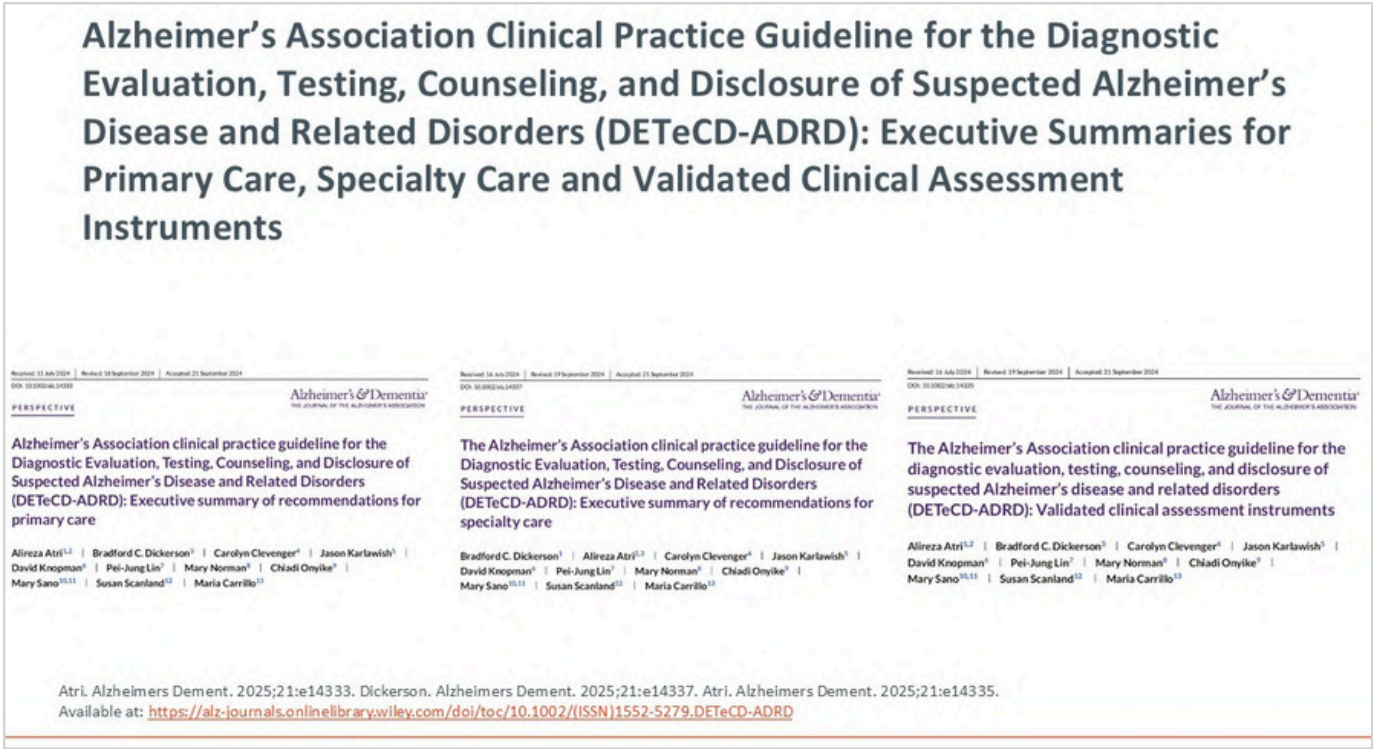


Hampel. Nat Rev Drug Discov. 2010;9:560. Molinuevo. Acta Neuropathologica. 2018;136:821.

Dr. Alireza Atri's Presentation

The other part that I wanted to put in is that, and again, these are for your slides, is that I'm not going to sit here and pretend that we know everything about Alzheimer's disease. It's a very complex and dynamic condition in the brain. It involves not just those two proteins, amyloid and tau, plaques and tangles, but neuroinflammation–vascular changes in the brain. It has phases that are relatively silent for 20, 25 years, and anyone's individual course can be very, very different. And again, that's another opportunity for us with AI and machine learning, and with big data.

The other part is that if you donate your brain in your 70s and 80s, and you've had Alzheimer's disease or dementia, chances are, it's going to be very uncommon for you to have just Alzheimer's disease in your brain. Once the machinery starts breaking down, then other proteins that become sticky. Parkinson's proteins, like alpha-synuclein, Lewy bodies, TDP43, vascular changes, are all going to be important. And removing just one component relatively late in the disease isn't going to affect those. So going forward, we need combination therapies, and we need prevention, and we need to understand these things earlier. But nobody presents to you with their brain and brain tissue in their hands, right? People come with symptoms and changes. And so for us to appreciate whether it's Alzheimer's disease, or the other cousin proteins, or a combination of those things, or vascular changes, which are so common. Or is it that people are maybe drinking too much, taking medicines, or something more rare? Requires a really rigorous and systematic approach. And it requires this: biomarkers. We've been trying to push that door for a long time, and we're going to be able to pull it at least open, and we've been able to do that now, little by little, with these biomarkers.

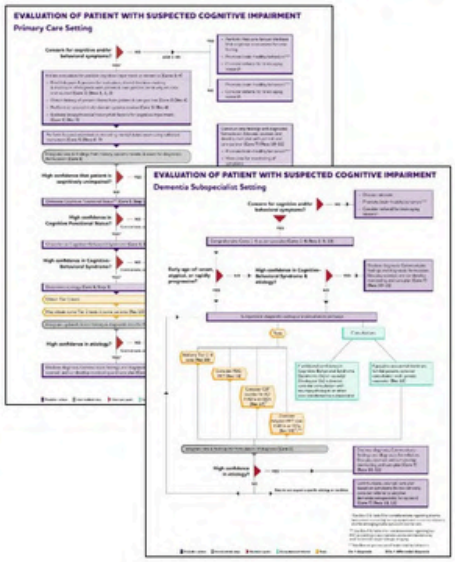


I put this in here as a guide because every country needs their own specific guidelines to think about how do you approach the evaluation process in every setting. This took us 7 years. So I was the co-chair of this, along with Brad Dickerson.

We had not just kinds of neurologists like myself, we had geriatric psychiatry, we had internists, we had neuropsychologists, ethicists. And this was a systematic approach. It took 7 years, 10,000 papers reviewed, and why? It was foundational to try to outline things for somebody who has symptoms, or if you have a concern, what the process is. And this process here tells you in a very systematic way, where you put in the biomarkers.

Alzheimer's Association DETeCD-ADRD Clinical Practice Guideline

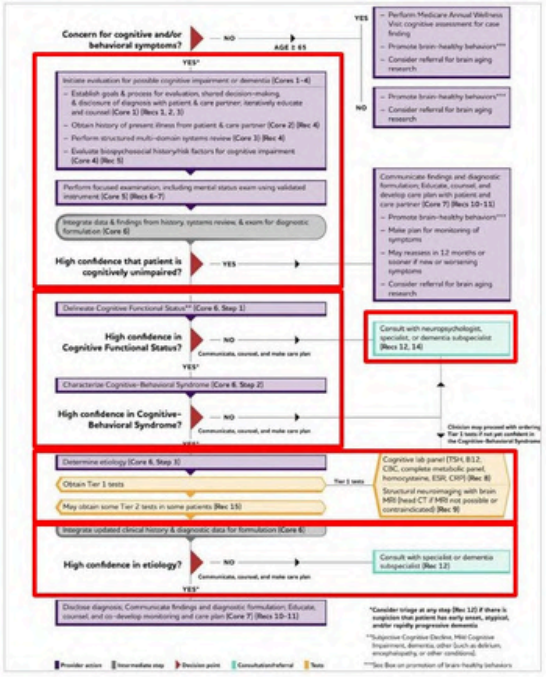
- For persons who may be exhibiting concerns, symptoms, and/or signs of cognitive impairment suspected to be due to AD or ADRD
- 7 core elements comprise a diagnostic and disclosure process (based on 19 recommendations) and achieve 3 steps of a diagnostic formulation:
  1. Is something wrong and at what level? **(Cognitive-Functional Status)**
  2. What is wrong? **(Syndromic Diagnosis)**
  3. What is causing and/or contributing to it? **(Etiological Diagnosis)**



Atri. Alzheimers Dement. 2025;21:e14333. Dickerson. Alzheimers Dement. 2025;21:e14337.
Available at: https://alz-journals.onlinelibrary.wiley.com/doi/toc/10.1002/(ISSN)1552-5279.DETeCD-ADRD

Evaluation of Patients With Suspected Cognitive Impairment: Primary Care Setting

- Flowchart for implementation of the 7 core elements of the diagnostic evaluation process within typical workflow in a primary care setting
- Goal: to evaluate a person with cognitive and/or behavioral symptoms:
  - Determine whether they have cognitive impairment
  - If so, what impact on daily function and behaviors (cognitive functional status, ie "stage"), cognitive-behavioral syndrome, and likely etiology (and contributing factors
- Includes clear and compassionate disclosure



Atri. Alzheimers Dement. 2025;21:e14333.

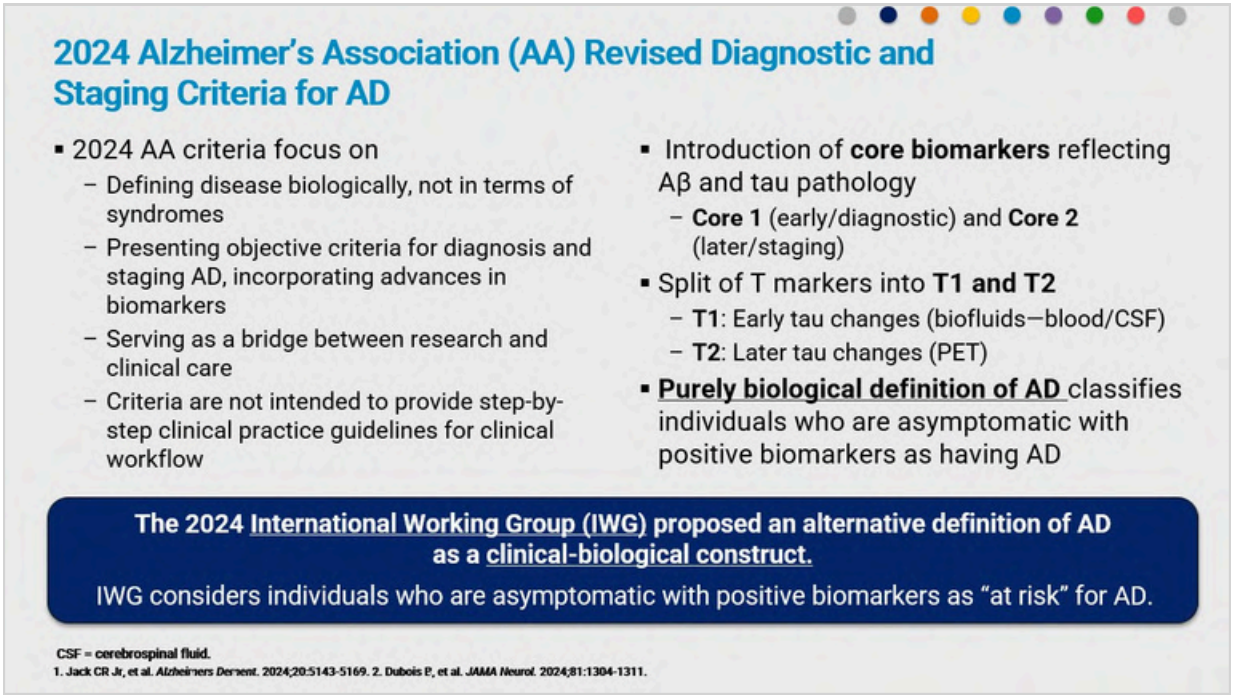
Dr. Alireza Atri's Presentation

So you're not shotgunning it, you're doing tiers– you're treating the person in front of you, not the protein. So it's not protein first, and then person. No, you have to get to know the person. And that's important. And these, all these steps here are steps, whether it's, doing a cognitive test, like you mentioned, so we can talk about the digital biomarkers, or gathering the information, or sifting it through, those are going to be helped, but they're not going to be replaced. We need to integrate it in the context of a person.

And then, of course, we're going to hopefully get to this, but how do we define Alzheimer's disease? The Alzheimer's Association in the U.S. said, you know what, I think we're at a point where we can think about it biologically.

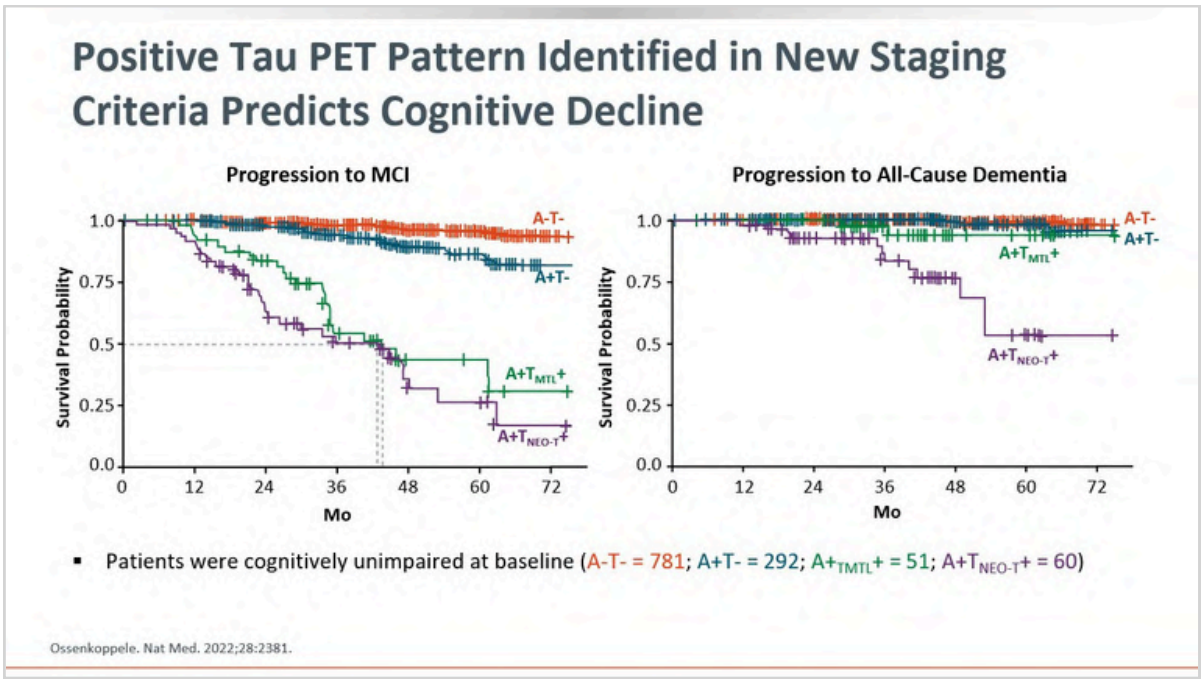
Kind of like, if you have cancer, right? If you have lung cancer, we don't have to wait until you're coughing blood or short of breath to say you have lung cancer. If we take a biopsy and it looks like cancer, we can say that. And that was the idea behind these core biomarkers. Now, the International Working Group said we still can think about it as maybe a clinical biological construct. We can think, if you have biomarker changes, like high amyloid, we can think of you as at risk, potentially. When somebody who's at risk may develop symptoms, we still want to call it in maybe a softer way. That's still a debate in the field, but as long as we're taking care of the person in front of us, and in a patient-centered way, doing right to them, and giving them the autonomy of justice, I think that's what's important.

> **"If you have lung cancer, we don't have to wait until you're coughing blood or short of breath to say you have lung cancer. If we take a biopsy and it looks like cancer, we can say that. And that was the idea behind these core biomarkers.**

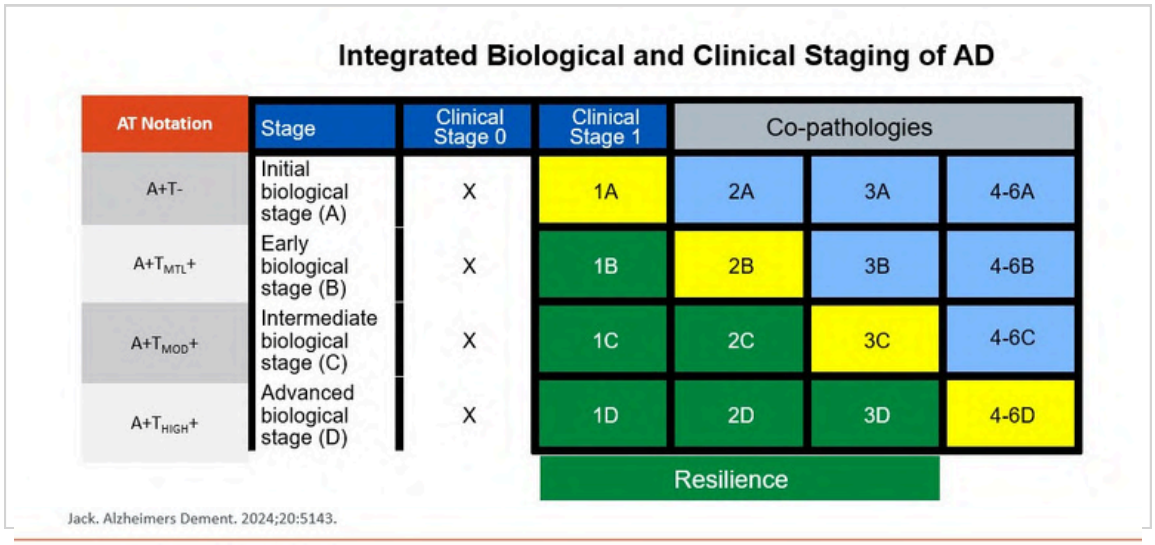


Dr. Alireza Atri's Presentation

What's true, though–and these graphs show you–is that if you have amyloid changes in your brain, so these are graphs on the y-axis is the probability of remaining cognitively unimpaired. The x-axis tells you how many months out. So if you're older, and you don't have any cognitive problems, but your biomarkers start changing, if you have no amyloid and tau biomarkers that are negative, you can see that over 5 or 6 years, your likelihood of having cognitive impairment, MCI, or dementia, is very low. But once you start having amyloids, that probability becomes less. And particularly once you have tangles–and the tangles are starting to spread outside of what we call the medial temporal lobe–you can see that the chances of being amyloid positive and having substantial tangles on the left side, only about 20%, 25% of people, are not going to become unimpaired. So, it is a high-risk state.



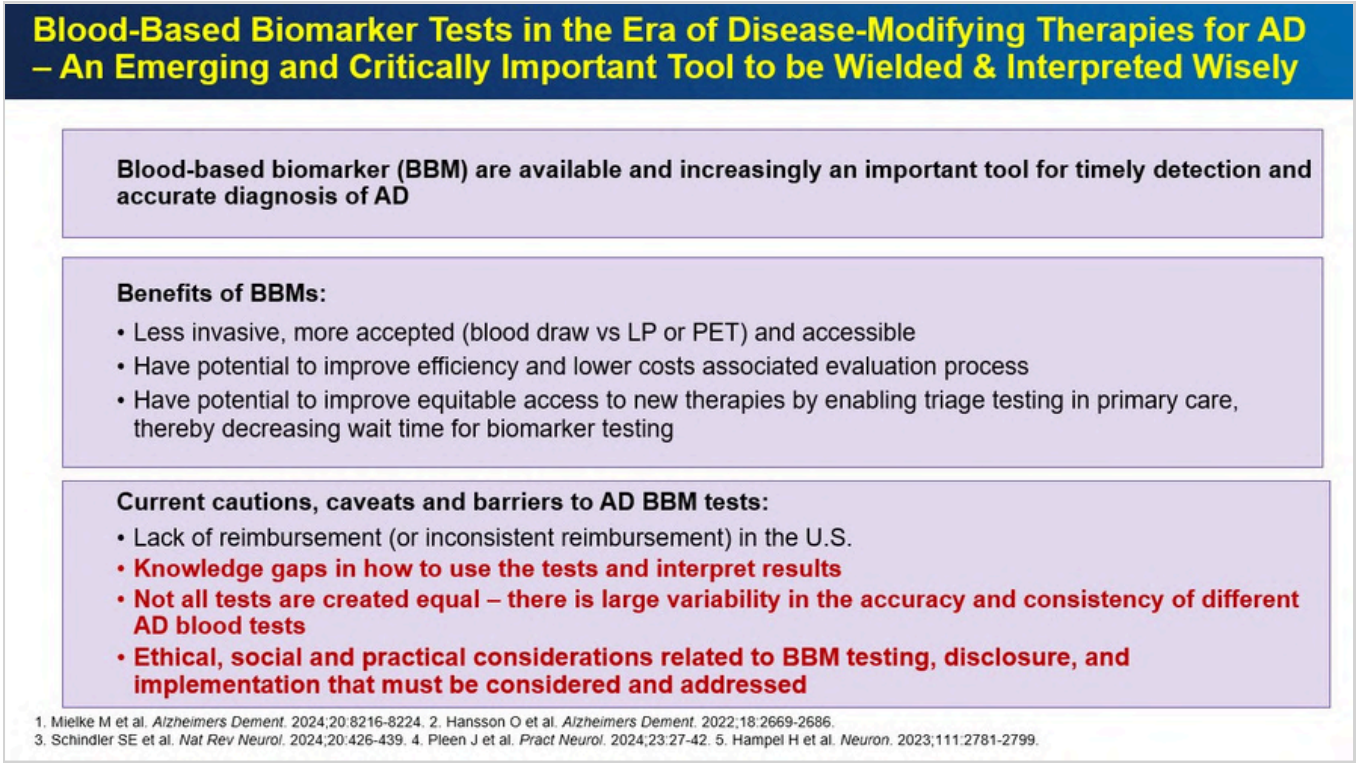
This is where the idea is: we're going towards precision, and saying that you have a clinical stage of where you are, whether you have a biomarker change or not, whether you have subjective kinds of decline or not. MCI is stage 3. Stage 4 and through 6 are dementia stages, mild, moderate, and severe. And they are clinical judgments. So one person doesn't wake up one morning and says, "oh gosh, yesterday I think I had subjective cognitive decline, and today I have MCI because my testers are low, but I'm functionally independent". And then next week, "oh, I have dementia because I'm now dependent on an activity".



Dr. Alireza Atri's Presentation

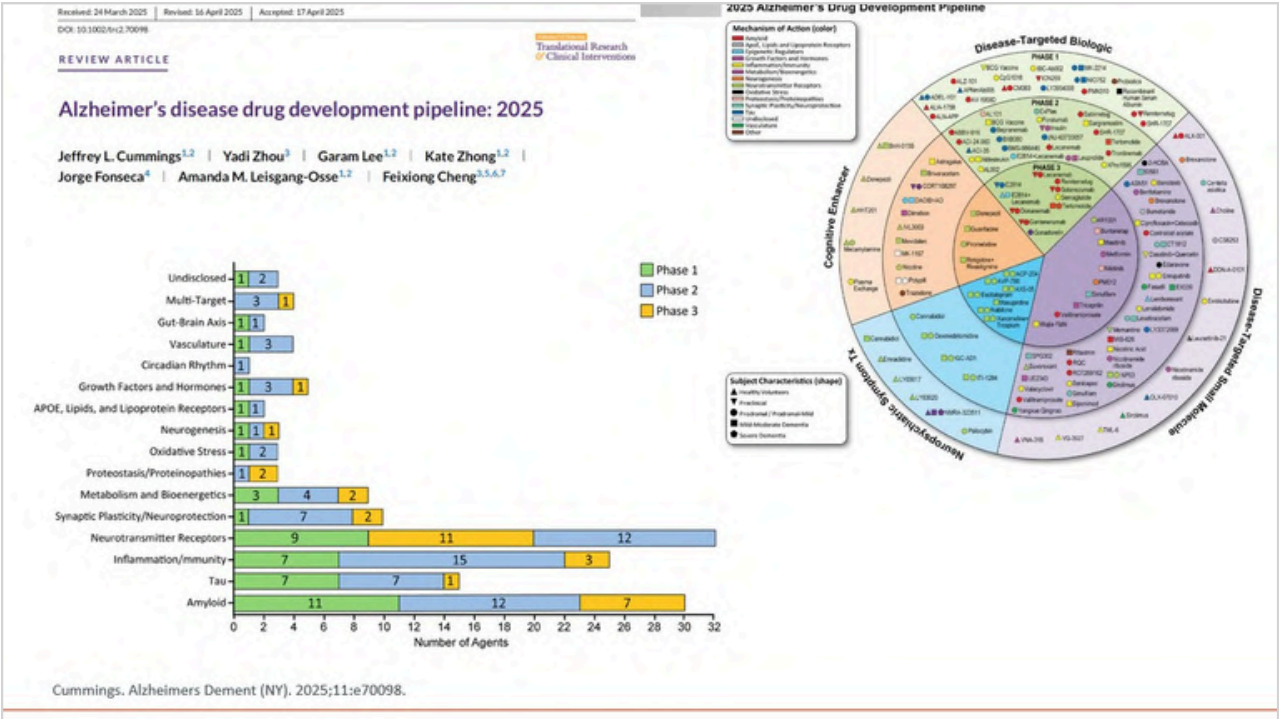
That doesn't happen, it takes time, but if you're biomarker positive, basically, the people in that quadrant are more impaired cognitively than the biomarkers tell you. And so that means you probably have co-pathology. So you have vascular changes, synuclein. The people in this quadrant are actually less impaired than the biomarkers tell you. So they have reserves. Whatever that reserve is, whether it's higher education, taking care of their blood pressure, we want more of it, and we want more of it in your brain.

So, it comes down to the blood biomarkers. But basically, they're a way to democratise things and get people in the pipeline faster. They have lots of benefits, but it's early days. They're obviously going to be more accepted. They're going to probably be at a lower price point. But there's some cautions and caveats. In the U.S. right now, reimbursement is still early days. There are incredible knowledge gaps about how we use these and how we communicate the test results. And not all tests are equal. In the U.S, we have two that are FDA cleared, but there's another dozen in the pipeline that you'll hear about. And in Europe, you already have some. And they're not the same. They measure different things, and they have different sensitivities and specificities. So, there are a lot of ethical, social, and practical considerations about those.



Dr. Alireza Atri's Presentation

And then finally, at the last minute, I want to say to you that the pipeline is very rich, and it's not just amyloid. It's tau, it's neuroinflammation, and it's going forward. And, I think we've passed the tipping point, where these things are going to progress over time.



These are tau drugs; some of them have not progressed, but there's still vaccines and other things in the pipeline.

Anti-Tau Agents Recently Investigated or Currently Under Investigation for AD

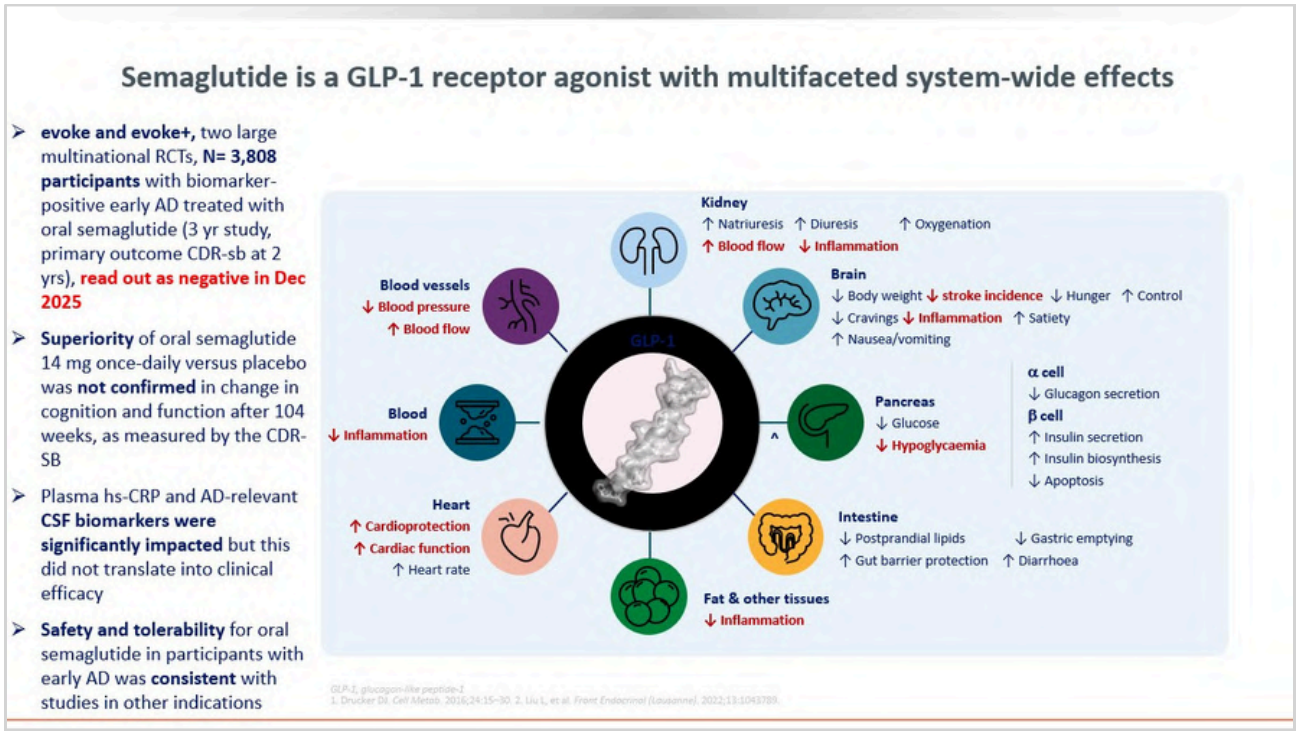
Study Phase	Agent	Therapeutic Purpose	Mechanism of Action	Clinical Trial	Start Date	Primary Completion Date	
Phase II	ACI-35.030	Biologic	Active tau-targeted vaccine	NCT04445831	Jun 2019	Sep 2023	
Phase II	Bepranemab	Biologic	Anti-tau monoclonal antibody binding to central region of tau	NCT04867616	Jun 2021	May 2024	X
Phase II	BIIB080	Biologic	Antisense oligonucleotide that inhibits translation of tau mRNA	NCT05399888	Aug 2022	Nov 2027	
Phase III Phase III Phase II	E2814	Biologic	Anti-MTBR tau monoclonal antibody	NCT01760005 NCT05269394 NCT04971733	Dec 2012 Dec 2021 Jun 2021	Oct 2027 Jul 2027 Jul 2025	
Phase III	HMTM*	Small molecule	Tau protein aggregation inhibitor	NCT02380573	Jul 2015	Apr 2022	X
Phase II	JNJ-63733657	Biologic	Monoclonal antibody targeted at soluble tau (midregion of tau)	NCT04619420	Jan 2021	Mar 2025	X
Phase II	LY3372689	Small molecule	O-GlcNAcase enzyme inhibitor	NCT05063539	Sep 2021	Jul 2024	X
Phase II	PRX005	Biologic	Anti-tau IgG1 humanized antibody	NCT06268886	Mar 2024	Aug 2027	

*UK Marketing Authorisation Application (MAA) currently under review for HMTM for the treatment of MCI-AD and mild to moderate AD.

X = Read out as NEGATIVE

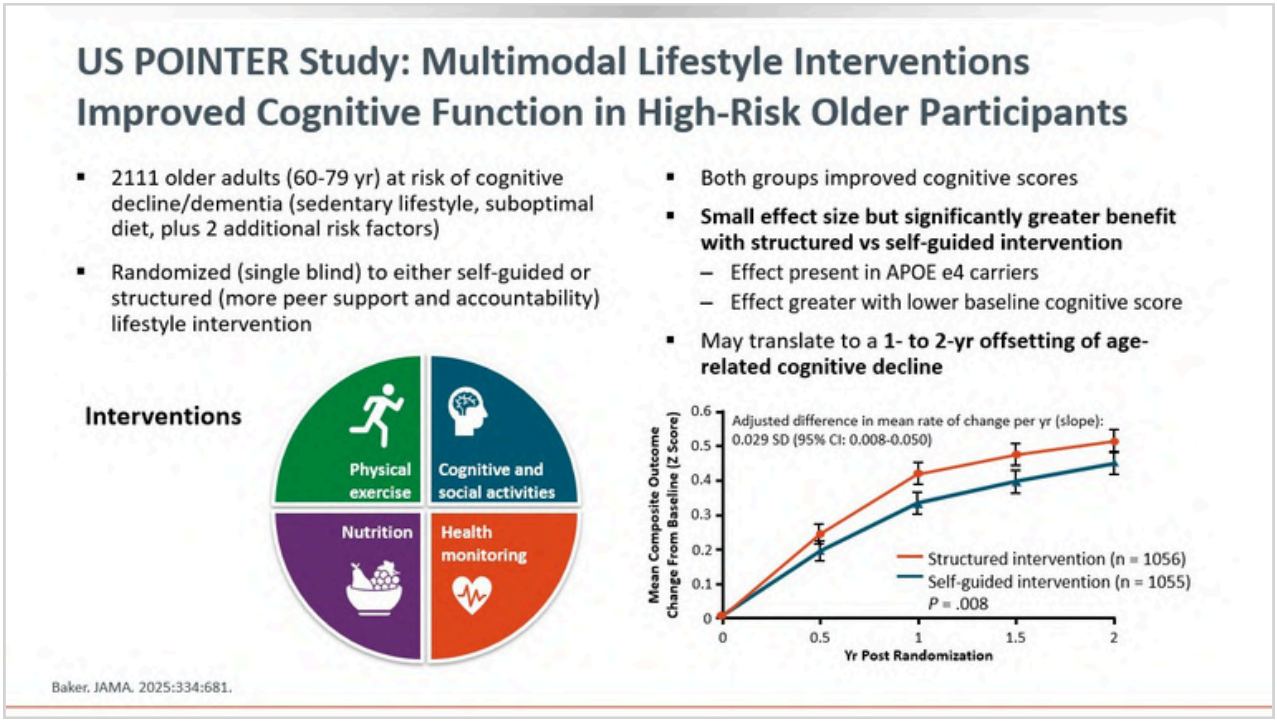
Cummings. Alzheimer's Dement. 2024;10:e12465. Younes. Brain. 2023;146:2211.

Dr. Alireza Atri's Presentation



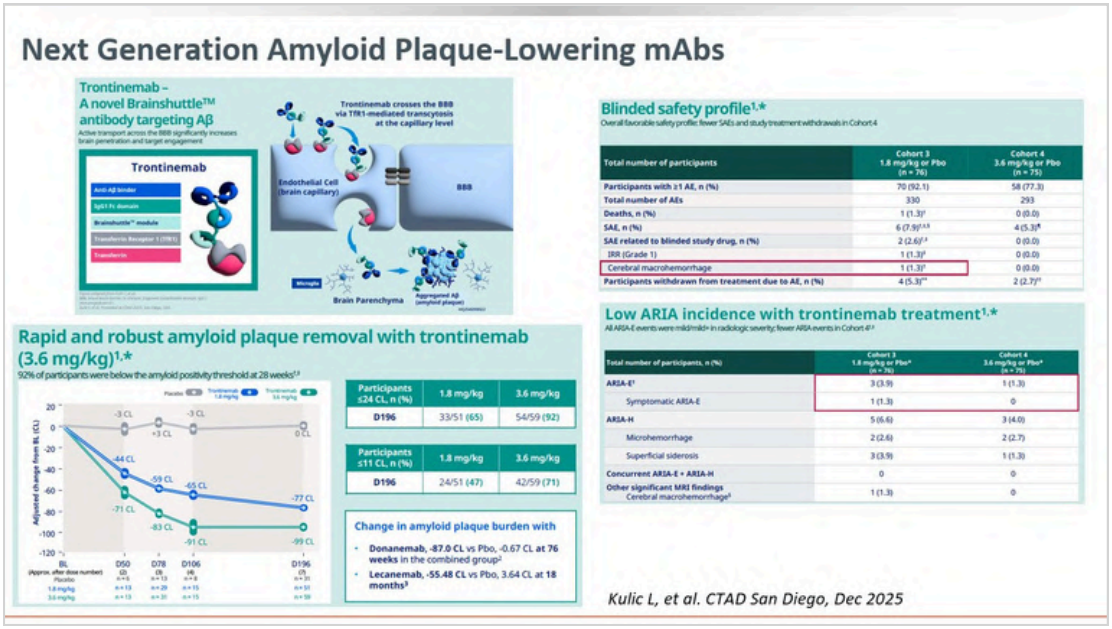
This is semaglutide that if you've been in a cave for the last 5 years, then you don't know about GLP-1. But if you haven't been in a cave, you know that there are amazing drugs that help diabetes and help people lose weight. And people who have vascular risk factors of diabetes are having less strokes. Now, we tested this in Alzheimer's disease, it just read out just a week and a half ago. I've been involved in that for 7, 8 years. And it was a negative study, clearly a negative study. It wasn't a failed study, it was indeterminate.

But it was done in people with basically Alzheimer's disease when they are symptomatic. The question is, does anybody think that some of these drugs may not have brain health benefits if given earlier, particularly if you're at high risk of cardiovascular changes? Probably not. So, that question still is unanswered.

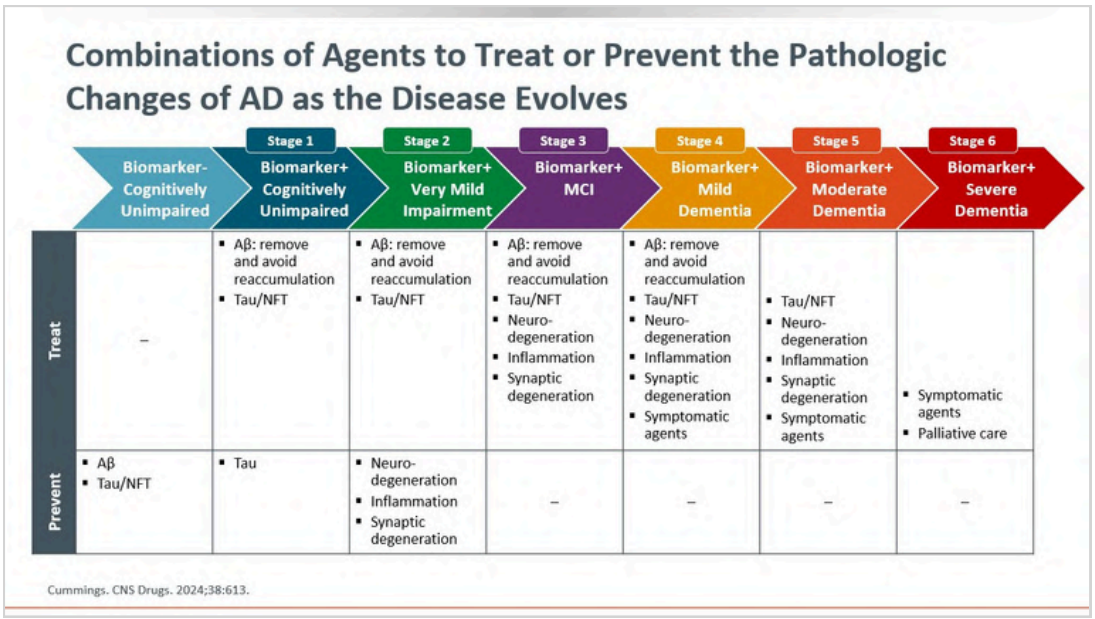


Dr. Alireza Atri's Presentation

And then, it's not mutually exclusive that you should take care of your vascular risk factors and exercise, and things like the World Wide Finger studies and Pointer studies read out and suggest that whether you're in self-guided, or you're doing intense exercise and mental activity and reducing your risk, it's good for your brain, and it could delay your brain aging.



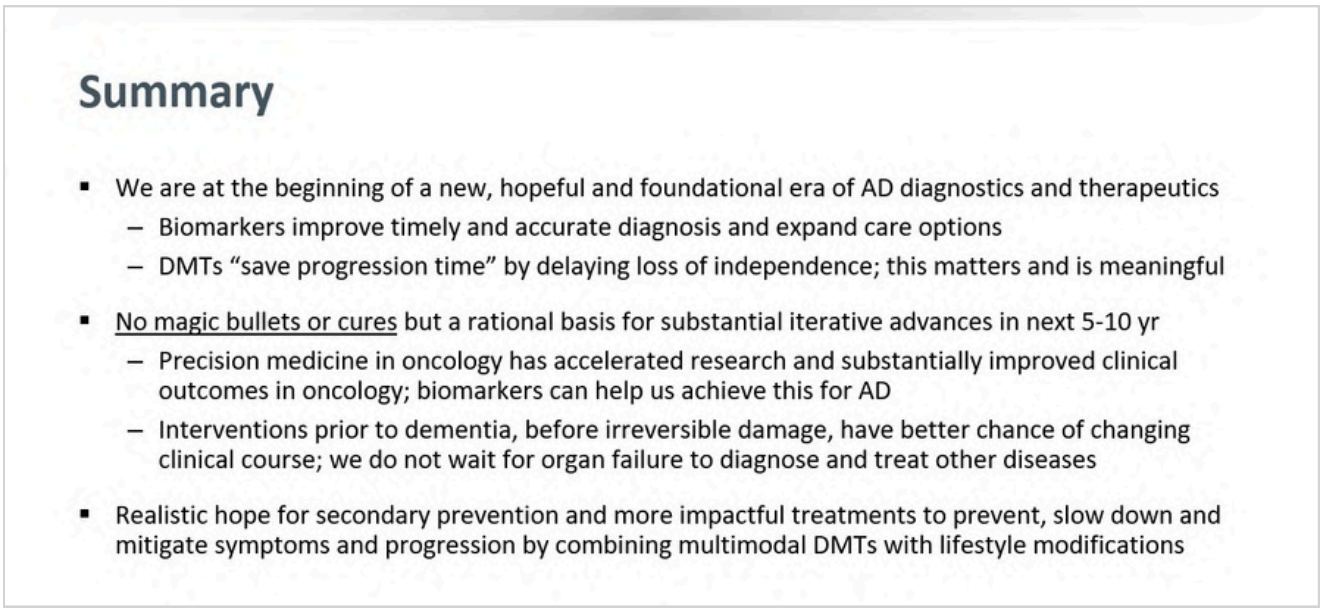
And ultimately, we have next-generation drugs coming. So our first monoclonals were first generation. Now we have drugs like this one that are still being tested, this is Trontinemab, and they're using an iron receptor to get it into the brain, and it looks like it can clear amyloid much quicker with less side effects.



And so, we have to have an approach for every stage that requires combinations, and we can talk more about that. But ultimately, I think it's a hopeful era, and biomarkers are going to help us with that. The disease-modifying drugs right now are a good stepping stone, and they can be meaningful.

Dr. Alireza Atri's Presentation

They have efficacy, but what we don't know is which people respond better, and which people may have side effects, and there's no magic cure. We're going to learn more about it, and we're [already] learning more about it in the U.S, because it's been a while. We're trying to get real-world data. But ultimately, we need precision. In the U.S, at night, when I watch TV, the ad comes on for breast cancer. It doesn't say, if you have breast cancer, take this drug. It says if you have ER positive, HER2 negative, node positive breast cancer, and you've been on this medicine and that medicine, this medicine can help you.



If you had tested that same medicine 20 years ago, you would have got maybe a sliver of a signal, because you're doing it in a pool. You're not giving it to the people that are responding. We're going to go like that for Alzheimer's in the future, and it's the biomarkers that are going to help us.

And ultimately, we don't wait to say, "Gosh, let's wait until you have something, you have a node here, let's wait until it metastasizes", right? But we do that about cognitive changes. We say, "Oh, well, you know, you're older. Let's wait". No, it should be driven by the person who wants to know. And ultimately, I think there's a real basis for hope for secondary prevention.

And no person's an island. I can tell you that I've been affected by this condition, by this disease in my family for many years. I took care of my aunt at home, I took care of my dad at home. It was a privilege for over 10 years. These are our problems, and I think that we've taken many steps already, and I think the glass is more than half full. I've been very hopeful for a long time. Those are my license plates in different countries, and I really think that, even for us, there's actually realistic hope. I know for the next generation, there's a lot of hope.

Q&A

Paola Barbarino

Thank you, Ali, and thank you, everybody, for listening. And as you know, these slides will be available. We can't expect you to have taken everything that Ali talked about in. Eight years ago, when I started working in this field, I often equated it to a tesseract.

I don't know if you're familiar with the shape of a tesseract. The idea is that you have something very dense together. As you unfold it, it becomes more and more complex, and it shows you routes that go to the left, to the right, to the top, to the bottom. This is Alzheimer's. Every time something happens and something is discovered, it seems to me that we open a room to something that we hadn't thought of before. And in his presentation, Ali tried to place the diagnostic issue in the big issue we have around treatment, but also anchor it around risk reduction, which may well be the topic of our end-of-year forecast next year. Because all of this cannot be taken separately. It's part of a whole, and in order to find solutions, we have to look at the whole.

But the whole is three-dimensional. And if you remember our World Alzheimer Report in 2024, 65% of medical professionals still did not understand that Alzheimer's and related diseases are diseases. They are not a natural stage. By doing what we are doing, we are trying to open up people's minds, we are trying to say, you really need to look at this. How are we going to deal with pre-symptomatic stages? How are we going to deal with it in the context of risk reduction, of all those resilience factors that could help us make someone's decline a lot slower. And we do have people here in the room that have a diagnosis, and for whom this has been their life. And so, we do need to think that there are 55 million people right now that have it. But the predictions of how many we are going to have in 15 years is much bigger. So, it's not something that we can sit and do nothing about. It's something that we need to do something about and talk about.

Our first question of this long conversation is going to be, what we've titled the event: **are we ready?**

Alireza Atri

"We have no choice. We have to get ready. These advances are coming. I think the tools are going to be very important, but we have to educate ourselves and communicate to all the different stakeholders how to use them, why to use them, and who, and give the power to the people, to be able to choose for themselves how to do it.

Now, there's risks and benefits to that, but I think we can negotiate it. But it does require a fair bit of education at every level, including, actually, our colleagues in healthcare because it's a completely different paradigm for diagnosis, disclosure, and even therapeutics. Completely different.

Paola Barbarino

We've got to change the way we think. But, let's get into the deep end of the presentation and get a little bit more in detail.

Can you tell us a bit more about the development of blood-based biomarkers? What are blood-based biomarkers, and how do you use them?

Q&A

Alireza Atri

So we've had fluid biomarkers from spinal fluid and they're pretty accurate, and we've had imaging biomarkers, let's say, from PET scans. And usually with PET scans, you can see a nice picture. Sometimes you can quantify it, but it's usually only one thing so an amyloid PET scan only tells you about amyloid plaques of a certain level. Now, the fluids have a lot more information for us–we can measure many different things. But the concentrations between the spinal fluid and the blood are orders of magnitude different. You have to detect things of one part in 10 to the minus 9th–it's very, very small. But because of the advances, we have them now and would you rather have a lumbar puncture, or do a $6,000 scan, or give blood–if that's possible? Again, these are just for background. You can download the slides and look at them.

But, from the blood, you can measure things like amyloid, so if you think about this framework–the ATXN framework–what is it? A for amyloid, T for tau, N for neurodegeneration. It doesn't tell you whether you're looking at an imaging biomarker or blood, etc. And the X are things like inflammation, vascular, and copathologies. So right now, it's an S for synucleinopathy, that's Lewy body, basically. When you take a fluid, you can potentially measure these different things in different ways. So even for amyloids, this chart shows that, for example, there's many different ways: you could look at the A beta 42 over 40 ratio, or you could look at this p-ta181, or 217. It turns out that probably the percent 217 is the best marker, and it's going to win out. And, just last week at Clinical Trials AD, there were a lot of presentations about that. So, what does this percent 2017 do?

Even though it's got tau in the name of it, it's really an amyloid marker. It's a very sensitive to amyloid. It's not a direct measure of tangles, but if you have enough amyloid, if you have tons of plaques, the chances are your neurons are secreting some phosphotau. And so it's very sensitive. Now, if we want to think about T markers for tau, we don't have good ones except for TauPet right now. Which, again, is our first generation, it's expensive. Now, MTBR-tau243, is probably a specific marker. It's low when you have amyloid. If amyloid's low, then that is low. So it's probably not going to be high, and it's probably better correlated with symptoms so this is a promising marker to decide whether somebody has Alzheimer's changes in the brain that are going to derive symptoms. That's important to know. I'm not going to go through this kind of stuff, but I put it in there because it's really important to appreciate that when you have a test, you have a reference standard. So if I'm taking your blood, and I'm saying your blood is high, when we're developing, we have to have a reference standard. Are we testing it against spinal fluid, PET scans, or brain tissue? And that is test characteristics: sensitivity, specificity. The predictive values come with how likely you are to have it. So

The best tests of double cut-offs: a high cutoff is going to tell you whether somebody actually has it, and a low cutoff is going to rule it out. And then we're probably going to have an intermediate zone for now, that requires confirmation. And the two tests in the U.S. that are passed, one of them is for specialty care, and one of them is for primary care. And this primary care one is a pTau181. It's probably going to be replaced soon. But the issue with this one, it's a rule-out test, not a rule-in test, so you only should be giving this to people who are have symptoms after a workup.

If it's negative, you can say, there's a 98% chance that you don't have amyloid in your brain. But if you have symptoms, it's something else, so you have to figure out what that is. So you can't let go of the person in front of you. And if it's positive, you shouldn't tell people, because the specificity is low, the predicted value's only about 22%. So you shouldn't tell people you have amyloid in your brain. You say, "you know what, this first test gets you ready for a second test, so let's look further".

Q&A

So, we shouldn't tell people they have Alzheimer's disease based on tests that are rule-out tests. So that's a really big lesson for all of us. And ultimately, we have to figure out what tests can and can't do. So they're very good at identifying amyloid pathology. They can't tell you, based on the level, where you're going, so my level may be, you know, very, very high, but it doesn't tell me if I have symptoms or not. Or what my course is going to be. And ultimately, you have to do it after an evaluation. And there's all these other concerns, ethical concerns, informed consent: communicating accurately, complex results, what are false positives, what are false negatives, making sure that stigma isn't reinforced, and making sure that the psychosocial impact on persons is actually mitigated in the right way.

Paola Barbarino
Thank you. I think everybody can appreciate how complex this is. We are at the beginning of something very big. There will be more of these tests. In this year alone, there have been two approved. So things are coming up thick and fast.

They will be for different things, they will be suitable for different people, but even those that need to administer them need to learn a lot about them. As we hear, there are many pitfalls to this. Let's now move to a completely different area. We've talked a lot of biomarkers, blood-based biomarkers.

So this is a double question. What, in your opinion, is the changing role of cognitive tests, for example, the MoCA, in the new diagnostic world? Now we are hearing more about those digital and online cognitive assessments–what are they? How are they being integrated? Who should use them? You were talking right now about who should use the blood-based biomarkers. How would they be best used at this stage?

Alireza Atri
They would be best used before you do these other biomarkers because you want to know about someone's changes or status. So, we've had things like Mini-Mental, MOCA for a long time–these are validated tests. There's opportunities to make these things more streamlined,

to be able to do things at home, potentially. I can imagine a world where, a few years from now, you can go online, do a few tests, maybe even do a little blood spot, send it away, and then they say, "well, you know what? Come in. Come in for the next level". Not saying you are impaired, not saying you have Alzheimer's disease, but catching people at potentially risk stratifying at higher risk, for example. So, digital markers are very, very important. They just have to be validated and the level of confidence needs to be pretty high. So, the tests that we have, like MoCA or MMSE, we've used for many, many years. The issue is that primary care and specialty care–especially primary care–they don't have enough time. So we need to make this easier for them, and easier pathways for referral, or knowing what to do next. So I think the digital biomarkers are coming, but they're not completely integrated yet into EHRs and still need some validation. But tremendous potential for clinical trials and also clinical care in the future.

Paola Barbarino
Thank you, Ali. When we did the World Alzheimer Report on diagnostics a few years back, I remember at the time, my great ambition was to come up with recommendations on how governments could implement a test in their health system.

Because people at the moment are doing online tests and those online tests, as Ali says, often are not validated at all. And therefore, that can create anxiety in people that actually have no reason to be anxious. So, these tests could be wonderful. In a way, the market is responding and creating these, and I have seen things that are really interesting. Language is one issue, though. Some people have done fabulous things, but only in a limited amount of languages, for example. Some others have done them with pictures, trying to overcome the problem.

But again, pictures can be misleading in different cultural contexts. So for us at ADI, it's been a fascinating field, and we are hoping to see more.

Q&A

Alireza Atri

So I was going to ask you, in your capacity with ADI and liaising with 120 different associations and countries: **What is the level of understanding and knowledge and appreciation by the associations in the different countries? And is this on the radar for the governments you speak to for the blood tests and other markers?**

Paola Barbarino

I think it's so interesting, isn't it? Because we deal with so many countries. Some are in very wealthy parts of the world, some in less wealthy parts of the world. I sat recently with a Minister of Health who asked me, "in your opinion, how many MRI scans should we buy"?

And I was like, that's interesting, you know, you've got several million people, are you aware that actually MRI scanners may not be the right thing, particularly for Alzheimer's? Maybe you want PET scans. It's very interesting, because I can see that people in countries where they would have not thought about it at all are starting to think about it. So I think this is a sobering thought, that people are starting to look at their capacity. Having said that, we are in England, and even in England, as we all know, there is not enough capacity for diagnostic care. And we also know that after you've had a diagnosis, often there is nothing for the family to do. And so, as we keep saying, diagnosis should go hand-in-hand with post-diagnostic care. You can't just tell people that they have a diagnosis, there's got to be something that they can do about it. And there is plenty that you can do about it. So, I think the members of ADI need more information. They all are super curious about this. And certainly, the things that are most readily available are the ones that are most fascinating, but this is why we are doing this lecture. Some things are suitable for certain situations, some other things are suitable for other situations.

It's important to try and understand what is suitable for what, at what stage, at what point, and also to keep looking, because there are things coming up all the time. Healthcare systems, they are not ready. I mean, we've been talking about the fact that they are not ready for ages, we've been trying to get healthcare systems to be more ready, but alas, I just don't think there is an understanding of the scale of the problem.

Even in this country, at the Alzheimer's Society's latest conference, I was there and the minister in charge at the time said that they were very happy that they were going for their diagnosis rates of 60%–not having reached it yet. And I just stopped and thought, gosh, if this was cancer, there would be riots in the streets. So, how can we still have this in a country, that is one of the wealthiest economies in the world, where dementia now is the first killer? Now we know that people in the street–because there's been a lot of publicity about that, rightly done by the Alzheimer's Society in England–people in the street know it's the biggest killer, and it's the thing they most fear. And yet, if you are looking for a diagnosis, you can't have it.

Alireza Atri

Yeah, you know, it's interesting. I think, there is denial, and there is a focus on the very immediacy and kicking the can down the road, and kind of ignoring these bigger problems, hoping that it'll go away. Now, I've talked a lot about hope. The hope that I'm telling you about is backed by data. So there's data, and you can see where it's going–there's a rational basis for it. But the systems still have to be prepared. And so this is why you're here, and you're listening. We're all nodes in this, to be able to take this forward and take it to the stakeholders for them to appreciate that something has to be done.

Paola Barbarino

Can you tell us a bit, Ali, especially from your point of view in the US–which of course has been more advanced where some of these things have been approved–**with the new blood-based biomarkers, how are clinics and hospitals integrating them into practice? And how is the data and the experience being shared so that more people can learn?**

Q&A

Alireza Atri

Well, it's very early days, because we've had tests available, but they haven't been reimbursed. Now, even though FDA clears something, doesn't mean in the U.S. that it's going to be paid for. And the US is a very fragmented system with insurance companies, etc.

So it's still really early days. One of the ways we're trying to learn about it is, we have this thing called ALZNET, which is a registry in the U.S, and it's going to now become, hopefully, global. And for the first time, we have a mechanism– and I'm part of the steering committee with the Alzheimer's Association for that in the US - to get real-world data, to be able to think about how these tests are used. And will it improve outcomes? Will it be cheaper? Will it help people get into the diagnostic pathway better and get the treatments earlier if they wish? But it's really, really early days, and, right now, reimbursement is an issue, and it's a hodgepodge, and so some people pay out of pocket, some companies actually have assistance programs, but it's not something that's uniform. So, I think just like the DMTs (Disease Modifying Treatments), by the time it spreads to other countries and other areas more, I think we'll have a little more learnings from that.

Paola Barbarino

Now, we are about three-quarters of the way through, so I think for a moment, I will stop some of the questions that we've already received, and I will ask the audience if they have any question they would like to ask Ali.

Audience member

Thank you, Ali, that was really informative. **I'm a carer for my wife, who was diagnosed at the end of 2013 with young onset Alzheimer's disease. She was 57. It took 4 exasperating years to get her diagnosed, including a misdiagnosis. And in the end, she was diagnosed based purely on pencil and paper testing. And I thought to myself, if that was cancer, that would be wholly unacceptable. So, my frustration is, if we fast forward now, we've got blood biomarker scientific breakthroughs, and they are quite amazing.**

But I want to focus on the back end of your presentation. I can envisage a time when people will be stuck in the diagnosis hopper, waiting for MRI scans, waiting for the psychological and cognitive tests, and still not getting confirmation of that diagnosis. And to the point that Paola made, if we don't engage with our healthcare systems sooner, and make them see what's coming through the pipeline, we're not actually going to progress any further forward at all. We're just going to be stuck, and I find that very, very exasperating

Alireza Atri

Yes, you're completely right. And this is why the different stakeholders and the work that ADI does is so important, and we need workforce development. There are not enough geriatric older psychiatrists, cognitive neurologists, and we need a different pathway for that.

Now you can see our disease-modifying drugs have benefits, but they also have to be managed in a certain way. So, right now, it's not something that should be done, I think, in primary care for these drugs. And an accurate diagnosis really matters. So, I put that up there just for you guys to see that if you have a 90% sensitive and 90% specific test. Which is actually, for the field, that's probably adequate for a blood confirmatory test. If you get that same test to two different people, in two different clinical contexts.

One's a 75-year-old, you've done the workup, and you think they have typical memory-impaired Alzheimer's dementia. And the other one's a 60-year-old that maybe they're complaining of stuff, you can see their pretest probabilities are very different. You give that same test, if you get a negative in that first gentleman over there, it's a 40% chance, almost, that's a false negative. If you get a positive in that 60-year-old, there's a 31% chance that's a false positive. So, that's why I'm putting this nuance in front of people. We can make it simpler, but it's not simple. And we need workforce development. We need investment, we need people to go into the field, and we need to have groups that can actually work with primary care to make this bottleneck easier.

Q&A

Audience member

Thank you, Dr. Atri, that's very helpful. And I liked your metaphor for breast cancer, which I thought was very useful. And if I think clinically, when we pick up people and diagnose them with Alzheimer's disease, sometimes it's a memory deficit, but more and more, it's a deficit of language, or praxis, or working memory, or executive function. And then we do clinical trials, and then we don't measure those things, or we do so really, really badly. To improve and to deliver on that idea of precision, don't we have to move away from the ADAS-Cog and Clinical Dementia Rating Sum of Boxes (CDR) to make sure we actually fix the things that people come to us with.

Alireza Atri

Thank you for that question. I think there's a lot of different flavours. I think people can have the same protein in the brain and manifest their symptoms very differently because of resilience and vulnerabilities. And, some of those things are really pushed by, and mandated by regulators.

And that's the issue, going down the very, very standard pathway of being pushed a certain way. And, we have to open our eyes a little bit, and be open to measuring things in different ways also. As you know, even the disease-modifying drugs that are available now in the U.S. and now–I know you're having some difficulty here, less so in some parts of Europe. Canada just approved it, for example. You know, they were tested in only the memory-impaired flavour of Alzheimer's disease. And yet, I'm a part of a group called the Appropriate Use Recommendation Group. It's an ADRD working group, it's an independent group. And when we looked at this, we broadened it out and said "why should it just be for people with memory impairment"? We have to be more practical about it when we institute those kinds of therapies.

Paola Barbarino

I should tell the audience that the World Alzheimer Report next year is going to be on clinical trials. If there is one thing that I have learned from following this debate, it is that the design of a clinical trial is so critical to what's going to happen, and often the design, it's not flawed,

but people haven't thought about all the possible repercussions, and also it's super difficult. As many people tell us in the industry, it's very hard even to follow people for such a long period of time and recruiting, that there are just so many elements around it that can make a trial fail. And for each one of those failures, there are people like Ali that have dedicated their life to finding a solution, and it's so disappointing for all of us when that happens. So, be aware that in September we'll do that. But, before I pass the question to the audience, I want to make sure that we don't miss the role of artificial intelligence. So, we've been talking a lot about artificial intelligence in the last couple of years. We know it already plays a role in diagnosis. How do you think this is panning out? Do you see something positive coming out of that?

Alireza Atri

There will be, but like anything else, I think there's a fair bit of excitement that needs a little bit of tempering first. But, things like reading images, for example, even for very experienced readers, looking at fluid shifts in the brain that can come with some of these monoclonals,

you've heard of as ARIA. They're imaging changes, they're not symptoms. And if it's very big, and I showed you that picture early on, anyone can see it. But they're small. And AI can help identify these things for an experienced reader to pay attention to it, for example. The other thing it can do, it could raise the floor for workforce development and allow people with less experience to get to the point where they can deal with more common issues, and then bring attention to the less common issues to other folks. So showing them pathways in the electronic health record, for example, what to do, getting through a bunch of information. The bane of our existence right now is not just insurance in the U.S, but also the notes that we have to, we have to dictate. Half the time, we're treating the computer, not the patient. So I think AI's going to help with all those things. And I think in big data, potentially sifting through some markers and identifying for primary care clinicians and others, hey, maybe this person is on a trajectory, on a high-risk trajectory, maybe they deserve to come in. So you have to have carrots for that, not just sticks. So I think AI's going to be good for that, but it requires the will for people to appreciate this is a big issue that needs to be addressed.

Q&A

Paola Barbarino

Good point, and very interesting, these are other possible solutions. And other things will come up, that's the other thing. People are thinking of ways of using this all the time.

Audience member

We often look to cancer innovation for inspiration. I presume cancer clinics all over the world are now used to using blood tests for different types of cancer as part of their diagnosis pathway. What can we learn from oncology in terms of introducing these new tests into clinics in terms of training and speed of introduction?

Alireza Atri

Yeah, we can learn a lot, and I think the idea of having specialised centers where you can get potentially really quick, accurate diagnosis and a plan and then having that with multifocal care, so you have information for the person who's involved, with the care partners.

And then having a sort of that hub, and then having the spokes where things could be done locally. Also with cancer, there was a movement towards that, There was an awareness. People valued that.We have to change the idea that this is just because you're older, therefore you have this. If we don't value it, if we don't put those resources into it, we're not going to get the results.

Paola Barbarino

We've got to have a movement. This is clear. If we don't do something, nothing is going to happen. There has to be willingness behind all of us to raise awareness.

Alireza Atri

Imagine if you go to a clinician and you say, "gosh, I've got this pain right here". They don't say, "oh, you're 75 years old, everyone's got some pain over here". No, they know exactly what to do down that pathway, take it very seriously, but there's no urgency about cognitive changes.

Something that's common doesn't mean it's normal. So we have to change that fact, because earlier means better, not just to get treatment, it's patient-centered. You have to give the person involved the autonomy to make their decisions for them, their agency to do that themselves.

Paola Barbarino

You have mentioned vascular dementia and Lewy body. So, obviously, in Alzheimer's disease, there is more innovation. But what do you think are the treatment breakthroughs for others, like Lewy body, Frontotemporal dementia, etc, looking like?

Alireza Atri

So, I'm not going to go through these slides, but I have some slides for you down here, too, that tell you about tier testing. Basically with Alzheimer's, these are proteinopathies. Some proteins become sticky, so we know that in Alzheimer's disease, 15-30% of people have some amount of Lewy bodies. When you have Lewy body disease, about 60-70% of people have Alzheimer's changes to some degree. So the co-pathology is there. Actually the European specialty societies that put their own guidelines out that, you can look at it by yourself, but you see different levels of biomarker testing. So we're having a roadmap now with Alzheimer's disease for Lewy body, for TDP-43, for vascular. We're looking into biomarkers for those. For Lewy bodies, we have this synuclein seeding assay, you can get it from spinal fluid, and you can get it from skin biopsies. Actually, it's pretty accurate, it's pretty good. They're looking for PET scans for those. For TDP-43, they're looking for blood. And then once you can identify people pretty well, then you can follow things along and then use some of the same approaches we've done with monoclonals and hopefully vaccines, and small molecules for that. So, there's actually a roadmap that, because of the investment in Alzheimer's disease, I think is becoming available for the other conditions.

Q&A

Paola Barbarino

That is a fascinating field, and it is true. There is a feeling at times that Alzheimer dominates the discourse. It does not. There's a lot of people that are working on a lot of types. Let's remind ourselves that dementia is the end condition for a number of diseases, so a lot of them require further study. This is why it's so difficult, what we are trying to tackle here.

Alireza Atri

What are some of the ethical considerations? When you're thinking about diagnosis and what it means, both the persons involved and care partners are really central, and we're talking about biomarkers and diagnostics, but should we call it amyloid elevation?

Tau elevation? Should it be Alzheimer's disease? Do people need to be at risk or have symptoms? How do you think about that? Because there has been a debate in the field. These are tools, and we need to talk to the people in front of us, but I'm interested to hear what your thoughts are.

Paola Barbarino

This is so interesting, and it dovetails with another question that we got from an anonymous person that was saying that we know that identifying someone in their 50s as being at risk, if they test positive for amyloid or tau, is going to open a whole can of worms, about employment, legal rights, finance, right to drive, who is tackling these? So, these ethical questions are really the work of Alzheimer societies all over the world. This is what our members need to bring forward. But it's not easy. We went to speak 6 years ago with the International Labour Organization, the ILO in Geneva, to see whether they wanted to discuss with us, for example, the employment rights of people living with dementia, and Trevor and I have talked about this in the past, but also of carers. So, we were arguing that because carers often find themselves in the position of caring for children and caring for elderly parents, how could we try and make their work lighter? For example, could you have care leave, like you would have for maternity leave? And at the time, also, we wanted to talk about if a modification be made in a work environment that would enable people that are diagnosed to work for longer?

Because it can be done, and there are a lot of people around the world that are working on the environmental issue, and I remind you, our World Alzheimer Report in 2020 dealt with that, how you can make the environment more dementia friendly. These are all ethical questions. But right now, there is still not a great appetite in these bodies. We were having this discussion this week in ADI, so this year, we made progress with the non-communicable disease issue, and we have made massive inroads. What should we tackle next? Should we tackle labour rights, migration? Should we tackle more the ageing spectrum in general? But then again, our movement is moving to include a lot more people than people that are of a certain age. It's becoming bigger and bigger, all these issues, this ethical point of are you diagnosing people early? What are you going to tell them? How are you not going to scare people? This could be really worrying. People could think they have Alzheimer's, as Ali says, but actually, they don't, or may never progress to Alzheimer's. So, we do need, as a group, to spend a lot more time on that. In Lyon, I hope that this will be something that we will tackle in a particular roundtable, but we've asked some of the greatest brains in the world today to start putting some dots on the i's of this big ethical question, and give us a pathway of how to go tackle this. This is where science and policy really need to work together because this is a massive issue. If you don't understand one bit, you won't understand the other bit. We do need to take the road together.

Alireza Atri

Interesting you mentioned AI earlier. On the way over here in the Uber, I was talking to the driver about this, and what's going to happen, and some of the predictions are that a lot of jobs are going to be taken over, and there may be people that work less, or there's going to be universal income. Well, guess what? If there's less work for people, it would be amazing to have young people and other people be with people who are, who are having changes as care partners in some ways. So I think putting the seed of the idea that AI's not going to take care of people and be with people. We need people to be with people, and to de-stress carers and care partners.

Closing Remarks

Paola Barbarino

And we need an equitable and just society to enable people to do all of this so that they can afford doing that. I think we are at the end of our time. It's been an absolute pleasure to host you, Ali. I'm sure that you will agree. And it's been an absolute pleasure to host you and everybody online.

We have tackled so many things. Thank you, Ali, for being with us. Thank you, all. Thank you, everybody.

ADI thanks sponsors Eisai, GE Healthcare and Roche.

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Published 2025

Alzheimer's Disease International