Zoom in on **Dementia & Alzheimer's**

Artificial Intelligence and Alzheimer's: How AI Is Revolutionizing Dementia Detection and Treatment
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Transcript of Zoom with Timothy J. Hohman, PhD, Professor of Neurology, Vanderbilt Memory & Alzheimer's Center

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Please note: This transcript has been edited for clarity and brevity.

NANCY LYNN: Welcome, welcome, everybody. It's great to see you all. It's amazing to see so many people over the age of 40 interested in AI and joining us. I'm one of those people that actually had to do a lot of homework for this session. So welcome to Zoom In on Dementia and Alzheimer's from BrightFocus Foundation. We're delighted to bring this live program to you with support in part by educational funding from Biogen, Lilly, and Genentech. So welcome.

As often happens, we've received a lot of questions that are not actually on the topic of this episode. So I just wanted to remind everybody of the prior episodes, which are available online at BrightFocus.org/ZoomIn. If you sent in questions, if you're new to the program and you're interested in learning about any of these other topics like "The New Alzheimer's Drug: What is Leqembi?" or "How Is Alzheimer's Disease Diagnosed?" these are available free to you anytime. And we'll probably start circling back to some of these as some new drug approvals come through in June and July this summer. So please take advantage of those.

And now I'd be delighted to introduce Dr. Timothy Hohman, who is a professor of neurology, cognitive neuroscientist, and computational geneticist-- hope I got that right-- at the Department of Neurology at Vanderbilt University Medical Center with secondary appointments in the Vanderbilt Genetics Institute and Department of Pharmacology. Dr. Hohman's research leverages advanced computational approaches from genomics, proteomics, and neuroscience to identify novel biomarkers of Alzheimer's disease risk and resilience. And don't worry, we're going to put this into English. He leads the biomarker core for the Vanderbilt Memory and Alzheimer's Center. His research aims to bridge the gap between fundamental science and medical applications by developing cutting edge methods for studying the brain and the nervous system. Dr. Hohman's areas of interest include resilience to Alzheimer's disease, the study of genes associated with the disease, and the analysis of brain changes during aging and Alzheimer's disease progression. Dr. Hohman's programmatic research focuses on understanding how certain individuals are able to accumulate Alzheimer's disease neuropathology without showing clinical symptoms of the disease. His team takes a precision medicine approach focusing on characterizing the best predictors of risk and resilience given an individual's age, sex, genetic, and neuropathological context. That was the best I could do at putting this in lay language. Welcome, Dr. Hohman.

And I know people are starting to put stuff into the chats, but I wanted to start with my own personal question here because I noticed you received your bachelor's degree and your master's degree in psychology and then you earned a doctoral degree in neuroscience and clearly, you've gone in a totally different direction from just general neuroscience. So how did you go from starting with a strong interest in psychology to doing AI and the kinds of work that you're doing now and how do they connect?

DR. TIMOTHY HOHMAN: Yeah, great question. Yeah, I became really interested in dementia early in my life. So when I was 15, I was working at a veterans home in my home state of Vermont and I was in the Alzheimer's disease wing there. So I actually went into undergrad knowing that I eventually wanted to study Alzheimer's disease. And I was actually a triple major at the time. I was a music major, a psychology major, and I had a computer science major as well. And I think of neuroscience, especially

the computational work that I do as the intersection of computer science and psychology. So yeah, so I did a lot with psychology early on and cognitive psychology for my master's degree, but I did always have the goal of studying Alzheimer's disease and using those tools to have an impact and move towards therapeutics.

NANCY LYNN: I'm curious about it because some of the applications of AI, as I was looking at them, have to do with caring for people and many of them are completely dry of anything psychological or emotional.

DR. TIMOTHY HOHMAN: Yeah, absolutely.

NANCY LYNN: Really interesting. So let me jump into the topic with a basic question from Deborah from Baltimore, Maryland, "What is AI?"

DR. TIMOTHY HOHMAN: Yeah, great question. So a lot of the methods that we use for artificial intelligence approaches are based off of methods that have been around for a really long time. And often you'll hear people use the term machine learning. And usually what we're trying to do when we're using an AI approach is to build a model that is more complicated than we could make with a standard analytical approach. So a lot of times the best way to think about it is if we could have a network that represents every combination of individuals or variables in a model, that network could give you insight into what's actually happening. And with AI, we're able to do lots and lots of layers of these networks that we couldn't do in a simple analytical approach. So a lot of times we're doing abstractions at orders of magnitude that allow us to get more precise definitions of an individual person or an individual disease. I always think about this in terms of the way the brain works, but realize not everyone can think about it that way, but our vision works this way, the way that our neurons talk to each other and represent the world that's around us, works this way too through complex network interactions. So with AI, that's what we're trying to do. A lot of times we'll use what's called a convolutional neural network and that's going to have a lot of nodes or pieces of information in it that allow us to make really precise definitions. So yeah, that means that any time that we're building an AI model, it's really important that the input to that model is accurate and reflects the world. And if it doesn't, then the output of the model isn't going to make

a lot of sense either. So hopefully, that's an OK description of AI, but happy to dive into the details.

NANCY LYNN: Yeah, I'm going to dig a little bit deeper because I think what you were describing was interesting because the term artificial intelligence and then when I think about collecting, think of it as being able to collect data from millions of people, let's say, and then it doesn't sound like intelligence

DR. TIMOTHY HOHMAN: Right.

NANCY LYNN: Or it doesn't sound artificial, but when you talk about it like the brain where all these neurons are detecting all these different things, it can learn from them, I guess and create a scenario based on a lot of data that you couldn't consciously put together, then it makes sense as intelligence.

DR. TIMOTHY HOHMAN: Yeah, exactly. Yeah, if you can think of it as like a feature. So if I were trying to categorize something that I was looking at, how many features would I need to be able to differentiate that item from another item that may look like it? You can imagine as your definition becomes more complicated, it's going to take more and more features for you to be able to differentiate things. And these neural networks allow us to do that, to increase the complexity, to represent more complex figures. And that application in a visual world can be easily pulled into language, or cognition, or subgrouping for clinical trials.

NANCY LYNN: OK, we'll get to clinical trials. So before I get into really how it relates to dementia, so is there-- because we hear these terms all the time, what is the difference between artificial intelligence and machine learning? Because it's used a lot if you're into the subject.

DR. TIMOTHY HOHMAN: And a lot of times they can be used interchangeably as well because really AI is a machine learning application. The overall approach is very similar between the two. With machine learning, what you're trying to do is teach your model something so that it can then apply what it's learned in a novel scenario. And in AI, we're doing the exact same thing. Typically, what differentiates it is

the level of complexity of the model. Often with AI, it requires higher computational load and more complex networks that underlie the analytical system, whereas often with machine learning you can use a pretty basic analytical approach and just do it a thousand times, or 10,000 times, or 100,000 times to tune your model parameters. At the end of the day, both of those approaches are doing the same thing. They're trying to tune the model to accurately reflect whatever you're trying to categorize and then apply that model in a novel scenario to make sure that it still works outside of the data set that it was trained. So both of those. AI is just another type of machine learning, but typically, what differentiates those when someone says you're using an approach versus an ML approach is the complexity and depth of the network model that they're using.

NANCY LYNN: Thank you. I haven't heard it described that way. I'm being told I'm hard to hear. I'm going to move closer. So in very broad terms-- and I'm going to go into the different ways that AI could potentially be used for Alzheimer's and other dementias, but Anna from Lake Forest, California, "Broadly speaking, how is AI going to help in the dementia world? What are the types of ways it's going to help us?"

DR. TIMOTHY HOHMAN: Yeah, think there's a lot of incredible opportunities here and it's almost overwhelming to try to think of every way that this could have an impact. So I'll pick a couple of my favorite ways, but certainly happy to dive into other ways as well. I think one of the primary and most fundamental challenges in the Alzheimer's disease space is that the disease carries incredible heterogeneity.

NANCY LYNN: Could you explain what that means?

DR. TIMOTHY HOHMAN: Yeah, so a lot of people in the population actually carry features of this disease. So you may have in your brain and not know it, pathology of Alzheimer's disease. But the amount of time that you go on with that pathology in your brain differs dramatically from person to person. And within your brain there are a lot of other processes that are going on that have to do with aging or with other disease processes. So it means that when we're tracking an individual patient it's really challenging to know where they currently stand in terms of likelihood to progress onto dementia and whether or not they're going

to respond to a therapeutic in the way that we hope that they would. So I think one of the things that AI is really going to help us do is deconvolve or reduce some of that complexity to try to identify in the population, who's the most likely patient to respond well to this approach that we think is important or who's likely to go on to show cognitive decline in the next two to three years? AI models are really helpful for that type of approach, and you can feed them layers of information to help the model figure out what the best prediction is going to be. So I think that's a huge opportunity in the field, is trying to identify who's likely to benefit from a therapy, or who's likely to go on to dementia, or in my case, what I'm really interested in, who's likely to remain cognitively normal for a long time? So AI is going to be really helpful for that type of complex scenario.

But there's other applications too that I think are really exciting. I think the drug development side of this is really important. And a lot of times we might have a target that we're excited about that we think there's potential for, but finding a molecular agent that can actually impact that target is very challenging and takes a long time and AI can help a lot in that space as well. Even something as simple as defining the protein structure of the thing that we're chasing after, AI has huge applications in that space. So yeah, you can go down the list. There's a lot of ways that I think this is going to be helpful and impactful. Everything from the way that clinicians care for patients to the way that we identify and develop and move therapeutics through the stages of development are all currently being impacted by AI and it's going very fast with the recent applications of large language models that have become in the popular press. We've seen a lot of this with ChatGPT. That's really changed the way that we can do science and move things through to hopefully therapies. So yeah, very excited about where we are right now as a field.

NANCY LYNN: Well, so I stayed up late last night trying to categorize to make this a little simpler. And I actually will send this to everybody who registered as a resource after looking at the different applications of AI to understanding the whole world of dementias, including the family's journey. And I'm just going to quickly read down the list for folks, but I can send this to you. So for people like Sandy who have their pen, if you can't get it all down, I'll send it to you. The broad categories, and I may be missing some, I thought it was prediction, to predict who's going to get it, when they're going to get it, the rate they're going to progress at. And

even I read something about predicting how long somebody could be expected to live rather than just a broad thing. It could be five to 20 years or whatever with more precision. We're talking about precision medicine, I suppose, predict how long somebody will live and how they will progress. So prediction was number one. Number two was diagnosis. And I think you mentioned these in your discussion just without labeling them.

DR. TIMOTHY HOHMAN: Yeah, absolutely.

NANCY LYNN: Which is identifying what proteins you have. And your, I think particular areas if you have this protein or this pathology, how come you haven't developed cognitive issues? And hopefully, using this computing power will help researchers diagnose disease earlier and determine how different types of dementia are related or not related. So diagnosis was the second area. Understanding the diseases, actually, I wrote the diseases because we know that even Alzheimer's disease is not just one thing. We don't understand enough about it to all these different types. So understanding it. Drug development, which you also mentioned specifically. So you can't develop a drug unless you know what your biological or physiological target is. And so AI can help determine what to target and then what kinds of drug molecules may be able to help. I'm putting this in very basic terms, of course. Clinical trial recruitment, which is actually something we don't usually talk about in general with families, but it's critical that people become more familiar with, clinical trials, why they're so important and why it's so important to participate in research. Health equity, and I know that may seem a little esoteric to some of us, but having people with different ancestral backgrounds in the research. A drug may not work for somebody with a one background versus another based on genetics. So it's actually really important to be studying people of all different ancestries so that they have treatments and therapeutics that work for them. And then there's a whole huge world of post-- I was going to call it caring/ caregiving, but call it post-diagnostic support, the use of robotics for people who have dementia, whether it's to give them exercise classes, or reminders to take medications, or wearable sensors on your socks that can say, tell people where you're going, or if you have fallen, or all of those types of things. And then I have a whole bunch of subcategories AI and nursing and AI and end of life decisions. And so

that's a lot, that's a lot of stuff. And I'll encourage the audience if there are particular aspects since this is such a big world, where to begin, Dr. Hohman, and what's relevant to people on this call at home. Maybe we can start with prediction and diagnosis.

DR. TIMOTHY HOHMAN: Sure, that sounds great.

NANCY LYNN: How does it help make prediction of and diagnosis easier?

DR. TIMOTHY HOHMAN: Yeah, absolutely. So maybe we'll start with diagnosis. So I think that's a huge and very important challenge. So as therapies are developed, they're developed for a particular diagnostic stage of the disease. And often that means that you need to know whether or not an individual has a particular type of proteinopathy in their brain and also whether or not they reach criteria for clinical dementia, which means that they're having a problem with their cognition and their activities of daily living, driving, doing your finances. So most often in the community, the people who are doing workups to figure out whether or not someone has dementia are people in primary care settings who have-- or are doing your work up for everything else and don't necessarily have specialized knowledge about neurology, or about dementia, or about Alzheimer's disease biology. So what you're starting to see already and I think you're going to see a lot more of is AI tools that can help the clinician who's in primary care setting or in a memory clinic and may not have as much dementia expertise to make an accurate decision based on the clinical information that's available to them.

So one example of this I think that was sent around was this new FDA-approved approach called BrainSee. So what BrainSee is doing is it's using clinical information that has been used in the field for diagnosis for decades and brain imaging that has been used in the field for decades as well. But what it's allowing a clinician to do is very rapidly see, what's the best diagnosis given the clinical information they have available to me? Meaning how is your cognition doing? And the way that your brain scan looks that you may not have as much experience looking at a T1 image to see whether or not there's enough atrophy to define someone as Alzheimer's disease or is likely to progress on to Alzheimer's disease in the next five years, which is what BrainSee is doing. So these types of tools can be rolled out and simplify the process for a clinician to standardize

and ensure that you're receiving the most accurate diagnosis possible. That example is with brain imaging and with cognitive data. But I think what you're going to see come out more and more is approaches like this that use blood. So you do a blood draw. And from the blood draw, we can look at your genetics and we can look at the proteins that are in your blood that tell us something about what's going on in the brain. And then we can combine that with clinical information to make a really accurate characterization of whether you need additional workup or eventually I think it'll actually be whether you should be diagnosed with disease. So I think that's a really exciting application for AI approaches that make essentially complex, multi-layered decisions for a clinician achievable even if you don't have specialty knowledge around dementia. Yeah, I think on the diagnosis side you're going to see more and more of that coming out.

NANCY LYNN: So let me ask you, because people did send in questions about BrainSee.

DR. TIMOTHY HOHMAN: Sure.

NANCY LYNN: Is BrainSee available to anyone in general?

DR. TIMOTHY HOHMAN: So I have to look. I'm not an expert on BrainSee. But I think for the FDA approval, it's specifically designated for individuals who have an amnestic mild cognitive impairment. So that means that you don't have a full dementia, but you're starting to show problems with your memory specifically and it does have to be memory specifically. And if you reach that criteria, then it can be used to basically give your clinician a knowledge about the likelihood that you're going to go on to dementia in the next five years. And that can help them make a treatment decision to try to slow cognitive decline with some of the therapeutics that are available already.

NANCY LYNN: So that's actually critical because the one drug so far that's approved to potentially slow down the progression and help you retain the ability to do activities of daily living has to be administered early in the disease. So this could help with a more accurate detection of whether you're a candidate for that drug, is that right?

DR. TIMOTHY HOHMAN: Yeah, that's exactly right for that particular drug. So for the amyloid therapeutics, this probably wouldn't be used for that because they're targeting amyloid specifically. So for that, you're going to need to have a scan that tells you whether or not you have amyloid deposition in your brain. But this would be really helpful for if you've gone on memantine, or Aricept, or something like that. This might tell your clinician earlier, yeah, this is a good time to start that therapeutic that also only works for a window of time and then stops working. So starting that therapy early is important as well and this will help make better help the clinician make a better decision about that type of therapeutic. There's also a lot of therapeutics coming down the pipeline that target this pathway specifically. So I think you'll see applications like this become more common as better and better therapeutics targeting cognitive decline come to light.

NANCY LYNN: And I know there are a few scientists who are on and writing. So for one of them I'm going to quickly ask you, will BrainSee be able to detect the integrity of the locus coeruleus?

DR. TIMOTHY HOHMAN: Yeah, that's a great question. I think the answer is no.

NANCY LYNN: Explain that to us, OK.

DR. TIMOTHY HOHMAN: Yeah, I think the answer is no just because locus coeruleus imaging is really challenging. And typically, well, actually always this particular software package is developed for standard clinical T1 images that wouldn't have the spatial resolution or contrast necessary to image the locus really as well. So yeah, great question.

NANCY LYNN: So back to what you were just saying. So it seems to me that even if it's not to detect amyloid, so it's not to get you on the path to get Leqembi or donanemab if it's approved, it will tell you earlier whether you are going to or likely to progress. And so I know people don't always love to talk about this, but it's also an opportunity while you're still pretty cognitively sound to make life decisions with your family.

DR. TIMOTHY HOHMAN: That's right. And knowledge is power for sure.

NANCY LYNN: And I want to just respond, Burton. Someone named Burton sent in a question. "Have there been any published scientific papers yet reporting on the application of AI to the diagnosis and treatment of Alzheimer's disease?" And I know, of course, there have been scientific papers published. So I'm just going to ask you while everybody's here, if you would send the best ones and potentially the suggestions for the best ones, we can send them around to everybody as resources. And maybe in one or two of those are not so much scientific publications because those are very difficult for regular people to understand, but both because we do have scientists out here. OK, so you're talking about detection. And is there anything else you wanted to impart about what's unique about using AI for detection?

DR. TIMOTHY HOHMAN: Yeah, I think maybe building on one of the points that you brought up, which is the importance of inclusion and diversity in these diagnostic models, one of the challenges we have as a field is so much of our research data has been collected in non-Hispanic white populations in the United States that don't reflect the global population of Alzheimer's disease and people at risk for Alzheimer's disease. So now as our AI models are being built and developed, it is absolutely critical that the data that lay the foundation for these models is inclusive and represents global populations even when you think about something as simple as the APOE4 genotype. So this is common. You probably have or could get this in your 23 results. You can know whether or not you're a carrier of APOE epsilon 4, but that gene has dramatically different associations with disease based on the genetic ancestry of the individual and based on the context. So the layers of complexity with just that one example for how APOE4 carriers do or do not progress on to be amyloid positive, meaning have one of these proteinopathy in their brain. The complexity of that modeling alone requires layers of consideration that are challenging, but AI can help us with those, help us figure out, OK, given your complex genetic background, what's the likelihood that your amyloid positivity is going to predict where you're going to go? But also, what's the likelihood that this particular biomarker, for example, accurately reflects the amyloid deposition that's in your brain? So we really need to use these tools to help us make sure that our modeling is

representative and can really be applied to the individual patient, which I think is the big challenge for the field as a whole as we're moving towards trying to get biomarkers into prime time and try to use them clinically.

NANCY LYNN: I want to respond to Marcia in the chat who says, "Where does one begin to get diagnosed? What type of doctor?" And well, that doesn't relate to AI and I want to say to Marcia that we did an entire episode, a really wonderful episode with Dr. Randy Bateman on how to get a diagnosis. So please take a look at that on our website. But basically, and I'll ask you this anyway, Dr. Hohman, and I don't know if you're in the clinic, but it is: While you guys are doing all of this incredible AI science and putting together complex data sets and so on, we the people have so much trouble getting diagnosed, this is a getting an accurate diagnosis. And so many of the time, so much of the time, if you go to a primary your average primary care physician, they don't have enough understanding of the disease to even know what the journey, what the pathway is to get diagnosed. And then ultimately, have to get to a neurologist. And in some states there are very few neurologists or there's a nine-month wait list just to get an appointment with a neurologist. So maybe the question to ask for you to further from Randy Bateman's episode is, can AI help this torturous process ultimately? What do you see in the future in terms of somebody-- because we know there are so many other conditions that can mimic dementia, Alzheimer's disease.

DR. TIMOTHY HOHMAN: Absolutely.

NANCY LYNN: It could be a medication-- you're taking the wrong medications together, there's all kinds of things. So how can this help people understand how they can get an accurate diagnosis.

DR. TIMOTHY HOHMAN: Yeah, absolutely. Yeah, so in the field, you've seen a move towards a biological definition of disease where we try to use information about what's happening in your brain using things that we can measure in life to decide whether or not you have the disease and AI is going to be very helpful in that regard. So I'll just give one example. So just a few years ago, if you wanted to know whether or not you had amyloid in your brain, you needed to get an amyloid PET scan or you had to get a lumbar puncture. More recently, there's been an advent of blood-based biomarkers for Alzheimer's disease where we can measure

these things in blood. But the applications of these are really challenging for the reasons that you just mentioned. One thing to think about is kidney function. So it's the case that often these blood biomarkers don't reflect what's happening in the brain in the same way if you have kidney disease. And you can just imagine taking all sorts of co-morbid conditions and thinking about how they might modify the way that you interpret that particular biomarker. So think as we start moving towards what think will likely be these types of biomarkers in the primary care setting at some point having tools that can help a clinician make an informed decision very quickly on a complex disease background is going to be really important, but very possible. It's absolutely feasible to do that. It's just a matter of making sure that you're putting the right information into the models as you're generating them, making sure that your model is learning the right things. So that's something we're thinking a lot about, how can we layer in information from health records, other disease processes to aid in the interpretation of these biomarkers? But yeah, right now it's a huge challenge to put so much pressure on specialty clinics, whether that's neurology or geriatric psychiatry, what have you. That puts a lot of pressure on those specialty clinics to do a lot of the heavy lifting. And certainly a big goal in the field is to try to make it achievable to get a diagnosis faster in a primary care setting, hopefully.

NANCY LYNN: But I think this could be an entire episode on its own because I think that given the complexity of these conditions I can't foresee a time where a primary care doctor is going to be able to manage this. And so it seems to me there's going to need to be a specialty for diagnosing dementias and that it's going to have to be AI-driven because it's so complex. So keep us posted please on when we're getting there. I'm looking through the questions. What type of doctor? So we didn't really answer, but you are, in theory, starting with a primary care physician and/or a geriatrician or a geriatric psychiatrist sometimes and going to a neurologist. So that would be currently the typical pathway. And if that becomes difficult, there are a lot of resources. There are websites that the National Institute on Aging offers for helping to navigate how to find a provider that actually is dementia savvy. And you can always write to us and we can try to help you find either an Alzheimer's Disease Research Center that has the capabilities of doing a good workup, or a memory

center, or some specialty organization that's nearer to you, hopefully. And I wanted to move since Kathy- Thank you for putting what you put into the question, into the chat box. She wrote, "If you sign up to do studies on Alzheimer's, then you get some tests given. So sign up." Go, Kathy. Participating in a research study or a clinical trial, we say this all the time, is one of the best ways to get really good care from people who know what they're doing. So let's talk about trial recruitment. And there is also-- we're about to launch in June, I should tell everybody, an additional series of Zoom Ins that focuses on clinical trials. We're actually going to take an hour for each of these and walk you through a clinical trial. And the first one is going to be-- it's on June. Amanda, you can help me with the date. I don't even remember. But it's going to be a research study that's not for drug, but something that almost anybody can participate in that's for lifestyle interventions. But you could sign up and participate in a study. And then you'll be sent a lot of information through that study, so we'll encourage-- and then we're going to start doing episodes on clinical trials for different drugs, clinical trials for different diagnostics. So we're going to get more into that.

But Dr. Hohman, how was AI going to help us with-- there's two issues, recruiting people for clinical trials. There's hundreds of clinical trials for dementias being carried out right now. And we did an episode in January with Dr. Jeffrey Cummings where he talked about this year and what it looks. So you need tens of thousands of people to volunteer. That's number one. But number two is it's very hard for people to navigate all of the sites. And we have one. We have on our website, a clinical trial finder, there's clinicaltrials.gov. Different advocacy groups have them. So how is AI going to help people find these trials? How will it help us find people for the trials?

DR. TIMOTHY HOHMAN: Yeah, great questions. How it's going to help people find trials I'd probably less about, but I can think of some ways that it could potentially do that. But certainly who would go into trials think I can comment on. I think one of the big challenges for clinical trials is making sure that the participant who's coming into your trial is likely to benefit from the therapeutic and actually that they're likely to decline if there's not a therapeutic. So one of the big challenges that we see in the

clinical trials so far when you have a cognitive endpoint in particular is if your cohort happens to not show much cognitive decline--

NANCY LYNN: I'm sorry I'm just going to stop you. When you say when you have a cognitive endpoint--that is trying to show to actually affect your cognition, make you decline less quickly or something right?

DR. TIMOTHY HOHMAN: Yeah, Exactly. Yeah so if we're measuring your memory performance, for example, our clinical trial may be deemed successful if we slow the rate that your memory is declining over time. But you can imagine if the cohort that you recruit into your clinical trial doesn't show much memory decline, then there's not much room for you to show a benefit of the therapy. So it makes it really challenging on the trial because now there's less room for you to save, if that makes sense. So one of the things that you can do is try to prioritize individuals who are coming into the trial who are likely to benefit from that therapy and likely to show a more rapid cognitive decline. And that's going to help give you more sensitivity to disease modifying effects. So any time you're thinking about stratifying in that way, that's, when I say stratifying, I mean, selecting a group of participants that is likely to have those features. It's really a challenging thing to do. So in the early amyloid trials about a decade ago, they recruited participants into the trial and at the time we didn't have amyloid imaging to do screening. So where they ended up was that about 25% to 30% of their enrollees into those early trials targeting amyloid didn't actually have the proteinopathy in their brain that the drug was trying to target. So you can imagine you're starting out of the gate completely behind because you already know, well they didn't know that, 25% of your participants aren't going to benefit at all. So just bringing in amyloid imaging into screening dramatically changed the game because now we know that the target is present and we can measure whether or not the target has been engaged. Well, now you can start thinking about the complexity just of that. So what if we could identify people who have really high levels of amyloid and have the genetic makeup that is most likely to benefit from this particular therapy. Now, it changes the game in terms of what you're able to do from a clinical trial perspective. So I think that's where you'll start to see some benefit from it.

The other thing that you could think about is starting with a large pool of participants who could theoretically be eligible and prioritizing that pool, of a lot of times we think of those as registries. From that registry, these people who have signed up and said they're willing, well, what would be the best therapy for them given their biomarker profile, their genetic makeup, their cognitive profile? Using these layers of information, not only to benefit the trial because it's important for the trials to be successful so we can move towards successful therapeutics, but also to benefit the individual participant who's enrolled into this trial, that they're more likely to benefit from the therapy that they signed up for. So that's a hard task, but I think those are the areas where AI can be really, really helpful.

On the other side of identifying trials, that's a really cool point that I haven't thought a lot about, but absolutely I could imagine ways that these types of models could make that information more available and easier to access for people who are interested in trials. Yeah, that's a really cool application that I haven't thought much about.

NANCY LYNN: Yeah, and while I'm dreaming, it would also be nice if it could set up more places where people can volunteer because there's huge swaths of the country that don't have any clinical trial sites near them, which is really frustrating. Two questions quickly that are not related. But Darlene asked about trials where you don't need a study partner. And Darlene, I think that the trial we're going to talk about on June 11th would be one of those. But let us look into that and get back to you. And then Burton asked-- and I think this does actually relate to what you were talking about-- "What are the sensitivity and specificity of beta-amyloid plaques on the brain as a biomarker for Alzheimer's disease? And why I think it relates is because I know some of your work looks at people who have let's say, amyloid protein or other biomarkers and don't develop cognitive decline. And so I'll reread the question, "What are the sensitivity and specificity of beta-amyloid plaques on the brain as a biomarker for Alzheimer's disease?"

DR. TIMOTHY HOHMAN: Yeah, it's a pretty fundamental question in the field right now, is, how do we define these people who have a disease

process that's present in their brain, but they aren't showing the clinical manifestations that disease process? And there's debate right now about how to handle this because for a therapeutic to be successful, you want to start it before there's clinical manifestation of it. So to some degree, those individuals who are not yet manifesting the disease are probably the people we really want to be thinking a lot about and trying to impact. So I think of this in cardiovascular disease. So when I was 35, my LDL was 200, which is very high for somebody was 35 years old. And I went on a statin at an early age, to try to control cholesterol because I wanted to reduce my risk of eventually manifesting heart disease. So whether or not we approach Alzheimer's disease biomarkers in the same way is still a debate in the field. And I'm not going to put my flag in a position on it, but it's an important thing to think about. But when it comes to how many people who have amyloid pathology in their brain, remain cognitively normal. So it varies by population area of the globe genetic background, but in general that number is about 30% So about 30% of people who would reach our autopsy definition of Alzheimer's disease, meaning that they have both plaques and tangles in their brain, remain cognitively normal. So it's a big number. And that's a huge opportunity. That's an opportunity from a treatment perspective, but it's also an opportunity to identify, what is it about these really incredible people who can endure pathology in their brain for a long period of time and not manifest disease? I think there's incredible opportunity there.

NANCY LYNN: That's really interesting. I want to see, Mark, if you're willing to be unmuted and ask your question live. Can I have you ask your question live?

MARK: I was just asking about bias that gets built in to the data set if you're not careful and how easy it is to pivot back and forth if say they discover that inflammation is a bigger part than the beta-amyloid, like you mentioned before, maybe it's a hallmark or something. I've played with ChatGPT a lot like a lot of people have, but I know it's just a very small equivalent. I'm just trying to get my mind wrapped around how easy it will be to pivot and how easy it will be to have it build foundations in the wrong direction.

DR. TIMOTHY HOHMAN: Yeah, it's an incredible, incredible question and a really important consideration. So most of the work that my team does is what I think of as data preparation for AI models. So what we're thinking about all the time is, how can we take data that are collected in different ways across the globe and get it into a format where it can be read into an AI model? So that means I'm always thinking about how representative is the data that we have, how well can we jointly analyze the data that we have? Because at the end of the day for every one of these models, you're exactly right, the model is only as good as the data that goes into it. So if there's bias in the data that goes in, there's bias in your model that comes out. So one of the things that we try to think about to mitigate this as best we can is out of the gate we're going to try to set up a benchmarking data set and not allow ourselves to shift that based on our modeling because what you can end up doing is what we call overfitting to your data set where now my model is perfectly predictive, but it's not going to be predictive in the absence of this current scenario. So as a field, we can set up benchmarking data sets to help us with that. But you're also right that you don't know what you don't know. So if didn't to include these markers of immune function or perhaps we just don't have them yet, then there's always a good chance that you may not see signals from that particular marker. So I think it comes down to what you're trying to do with the model and making sure that the data that go in are appropriate for the type of conclusion that you're trying to draw.

The other challenge I think that's really different now with these large language models from where we were even five years ago is that the models themselves are starting to reflect the data that are in them. You can make such incredibly accurate generative statements from the data that are read into these large language models. And now we have to be thinking about privacy and security for our models as well, which is pretty different from when I first got in the field when we're thinking about privacy and security just on the data side. Now, I think we have to be thinking about that on the model side as well. So that's a big change. But I think it all comes down to, what are the data that are going into your model? And you need to make sure that you have things built into both evaluate and hopefully, confirm in some gold standard data set that your model is performing the way you want. Definitely a challenge.

NANCY LYNN: I think that's a good segue to a question I was going to wait till the end, but let me throw it out now. People are nervous about AI, especially here in Los Angeles in the entertainment industry. But people are nervous about AI. Is there anything about AI that we should be nervous about in the dementia space?

DR. TIMOTHY HOHMAN: Yeah, absolutely. I think blind application of any model is very dangerous because you can-- just coming back to that last question, if there's already bias built into your data set, a model like this could just amplify any of those biases. Maybe I'll give a really simple example. If we build a model that can do great clinical prediction in one population and we roll out an AI model for that and it turns out that model is not predictive in a population that wasn't represented in the data set and wasn't evaluated, well, now you've just enhanced every disparity of the disease just by ruling the model out. So yeah, there's absolutely-- and I think as a field, we want to move fast. Certainly, that's true on the therapy side as well. People want to move fast. It's true on the clinician side we want to move fast, but sometimes moving fast can come at the expense of accuracy. So it's important that we think carefully about these things and that we don't just apply it to the first data set that we have and then roll that answer right out into the clinic until it's been evaluated in a pretty comprehensive way. So I think that's certainly something that the folks who work in AI at least that I work with are thinking a lot about and talking a lot about, certainly, something that our funding organizations are thinking a lot about and talking a lot about. But yeah, it is a concern for sure.

NANCY LYNN: We have about eight minutes left. And so I want to switch over to the post-diagnostic side and the caring side and the living with Alzheimer's side. So can you talk about-- I thought it was really cool seeing these AI-powered robots and all these tests there or all these trials and studies of how robots may be able to interact with and care for people with dementias. Can you tell us a little bit about where that research is at?

DR. TIMOTHY HOHMAN: Yeah, sure. Yeah, that's a really exciting area of application. I think both in terms of caregiving support that can be

really beneficial. And also when you think about-- so maybe ChatGPT as an example of this. Right now you can go into ChatGPT and you can ask a question about Alzheimer's disease. But the input data for ChatGPT is the whole internet. So the output that you're going to get may or may not reflect reality. But we can build tools like that with a very informed data set of good clinical information and good clinical advice that could become a tool that patients could log into and ask questions to and get responses from that are informative and include things like citations and links. And I think you'll see those types of tools come forward more and more as that technology becomes available. So that's just an example of, in the language domain, what you could imagine. But certainly to your point with robotics, you could imagine a lot of support for caregivers and for patients who have mobility issues or need additional support around the home or getting around. So yeah, I think there's some really cool potential there as well. That's not a space that I personally work in, but certainly I'm excited to see where things go.

NANCY LYNN: I thought you would like one that I saw that's meant to emotionally interact, which is really interesting. And the though that the-- but that the person with dementia was saying, this is not good. The robot interrupts when I'm talking. So it was really interesting to see how they're working through some of those complicated problems. And I also am very interested in obviously there's other ways to do this, but what about for actually making sure someone is taking their medications, watching their gait or there's ways to do this now, but can you talk maybe a little bit about digital wearables and that type of--

DR. TIMOTHY HOHMAN: Yeah, absolutely. Yeah, so I've got my Fitbit on right here. I wear that every day. And at the end of the night I get a summary that tells me how my sleep was, my sleep patterns. It gives me a sleep animal. I think I'm a parrot. I don't know what that means, but that's what I am. So that's a way that data can be rapidly analyzed with AI tools to give you usable and actionable information very quickly. Certainly, that's the case in dementia where you start to have changes in your mobility, you start to have changes in your cognitive function that can be picked up on by models that are noticing small changes in the way that you interact with your devices, the way that you move about throughout

your day. Yeah, I think there's absolutely huge opportunities there in the AI space as well.

NANCY LYNN: And before I ask you my wrap-up question, I would also mention I was thinking about how AI will also impact all of the risk factors that lead to dementia, like hearing loss and/or not being able to sleep, you're talking about the sleep sensors. And ultimately, all of those things, the risk factors for Alzheimer's that can be modified are pretty well known. And I think AI will play a big role in all of those things once it's up and running. And speaking of it being more up and running, I decided my last question would be something like this, it's the year 2040, 16 years from now. You can make it 2050 if you want. How has AI affected our experience with dementia? What's different now 15, 25 years from now because of AI?

DR. TIMOTHY HOHMAN: Yeah, great question. Well, hopefully, the number one thing is that we have therapeutics that are slowing or halting disease.

NANCY LYNN: You think that's possible?

DR. TIMOTHY HOHMAN: Very possible. So hopefully, that's first and foremost, what's happening. But I also think being characterized or identified early on from some of these tools is very likely as well. Whether that's from a combination of wearable technology and blood-based biomarkers or even some other technologies for biomarkers that haven't come out yet. I think there's a really good chance that you'll know early on that you're at either very high risk for disease or that you are going to within the next five years go on to disease. And that early screening makes such a big difference. But I think one of the points that you just made that I absolutely love is that so many of the factors that drive Alzheimer's disease-- I'm a geneticist, so I'm thinking about heritability and genetic drivers all the time, but the reality is so many lifestyle interventions have an enormous impact on disease. And the way that AI can do things improve your hearing or improve your vision, reduce your risk for heart disease, reduce your risk for strokes, help encourage good health behaviors, good dietary behaviors, good lifestyle behaviors. I think all of those are the areas that you're really going to see AI having a big

impact because those data are complex data. It's hard to characterize, am I getting enough activity? Am I getting enough sleep? Is my hearing working as well as it was before? But those are things that AI is actually quite good at picking up on. So I think that's where you'll see a lot of the big strides. But have a lot of hope and I really do believe that you're going to see big strides in the therapeutic side as well. I think we're at the beginning of the disease modifying stage of Alzheimer's disease and you're going to start to see more and more therapies that are tailored for an individual patient and really do slow or halt the disease.

NANCY LYNN: I think that's a really optimistic note to end on. And I think it's a moment also, for me, to recognize when I started in this field about 15 years ago, the government, the NIA was spending about $400 million on supporting research into Alzheimer's and dementia and now we're around the $4 billion mark. And that's really, really significant. And I know a good portion of that is supporting AI-related research. I want to thank, Dr. Hohman, so much. This is really an interesting area for me that I don't know anything about and I wish we could have a bunch of episodes on this. But we'll stay tuned and hopefully have you back.

If your question wasn't answered today or you have a follow on question that you think of for Dr. Hohman, you can email us at reply@brightfocus.org. And I did want to say that BrightFocus Foundation has been funding research for, we're just going into our 51st year. And so along with our big sister, the NIA, we've funded about $300 million worth of research globally, about 60% of that in the dementias. So hopefully, we're all the organizations contributing to finding therapeutics and treatments and cures. We offer free resources that you can find at BrightFocus.org/Alzheimers. And then the resources and recordings of all of the episodes of this program Zoom In is at brightfocus.org/ZoomIn or on our YouTube channel. And our next episode for this main series will be on Thursday, June 20 and it will cover the impact of genetics on early detection. Sounds like you could teach that one too, Dr. Hohman. Maybe he'll join us. So please join us for that on June 20. And we'll also be sending around a separate invitation for the clinical trial episode on June 11th, that I mentioned, which I believe will be on a trial. The website is, in case you want to take a look ahead of time, retainyourbrain.com, retainyourbrain.

com. And when Dr. Richard Isaacson was on talking about risk reduction and lifestyle interventions, he mentioned that trial, but it wasn't recruiting yet and now it is recruiting. So we're going to walk through how we can all participate in that study. So thank you all so much for joining us today. Again, you can email us at reply@brightfocus.org if your question wasn't answered. Have a wonderful month. And really appreciate your joining us. And Dr. Hohman, thank you so much for sharing.

DR. TIMOTHY HOHMAN: Thanks for having me. Thanks, everyone.