REDEFINING CARE—INNOVATING HOPE: CHARTING THE NEW ERA OF ALZHEIMER'S AND OTHER DEMENTIAS

Announcer 00:00

Thank you for joining us. Please welcome the panel to the stage.

Allison Aubrey 00:16

Good morning. I'm Allison Aubrey of NPR News. Thank you to the Milken Institute for having me and to this amazing panel. I think the scariest part of a dementia diagnosis is the slow, irreversible process of losing the person you love while simultaneously managing the escalating challenges of caring for them. I watched my father-in-law go through this with my mother-in-law, who died from Alzheimer's, and the question I have is, how would her journey have been different if she were being diagnosed today, right? When there are two drugs approved by the FDA, more opportunities for early detection, and a lot more known about the 14 modifiable risk factors of how people can change their habits to reduce their risks. I want to start with you. Dr. Howard Fillit, with the Alzheimer's Drug Discovery Fund, you have raised millions of dollars for more than 700 different drug discovery programs after decades of failures. Why did these new drugs break through?

Howard Fillit 01:25

Well, for one thing, their target is the beta amyloid that's in the plaques. So the history of research on that particular target goes back the furthest, because we started—we saw the plaques there was clearly a target there. And so I think that billions of dollars have been spent. And finally, we've got a validated target that works clinically. So I think that was one reason that beta amyloid became the primary target for all the development. And one of the other things that's happened is with—through the biomarkers that you

mentioned, we've been able to do modern, really precise clinical trials, so we get good answers. It used to be said you could have a or—it still is that you can have a failed trial or a failed drug, and if you don't have a good trial, then you don't know whether there was a failed drug or not. So I think one of the big advances has been with the new biomarkers. We're able to do much better clinical trials and get good answers. And I think that was something that led to this success. I could talk more about it, but maybe that's a brief answer.

Allison Aubrey 02:26

Yeah. So the trials are better because the biomarkers are better. I want to move over to you, Jesse Fahrbach of Eli Lilly. Eli Lilly remained in the space when a lot of other pharmaceutical companies sort of dropped out after failures. What are we likely to see in drugs going forward, both in the clinical trial pipeline, also when people start taking these drugs?

Jessie Fahrbach 02:46

Sure, so—thanks Allison, and it's an honor to be here amongst these experts and to be a part of this really important conversation. So it's—thanks for having us. So I think, you know, as Dr. Fillit said, there's definitely been a lot of exciting developments, and there's definitely a renewed energy amongst the Alzheimer's community, and especially amongst researchers. And one of the key areas that we're looking at next is earlier in the continuum of Alzheimer's, and really looking in those earlier stages before people develop symptoms of Alzheimer's. And so let me highlight a couple of key things within that area. So the first is, is what some people call preclinical Alzheimer's, or stage one and stage two. And this is when people have that amyloid biomarker where they're positive for it, but they do not yet have symptoms of Alzheimer's disease. And so here there are studies ongoing, Lilly has studies as do others, and really asking the question of, if we can treat people earlier on, before they're symptomatic, are we able to delay progression to that symptomatic stage of Alzheimer's disease? Or said another way, are we able to delay that cognitive decline? So that's one exciting area that we're looking at. And then the second is, moving even a little bit earlier and looking at primary prevention. And so, so this is really looking to see if we're able to identify people who are at high risk and treat them. Can we treat them even before they get that pathology? So another exciting area. And I think for both of these, we'll have to follow the science and ultimately see what the data shows us. But this is definitely the next frontier in our fight against Alzheimer's.

Allison Aubrey 04:33

Great. Dr. Richard Isaacson, you are a neurologist and lead Atria Precision Prevention, really focusing on shifting from sick care to preventive models. I watched a video of you give the ABCs of Alzheimer's prevention, and I was struck by the B, the blood biomarkers, the blood markers. And as we just heard, there's this opportunity for earlier detection. You talked about some very sophisticated markers, but also common markers, things that you'd be tested for at an annual physical, your glucose, your cholesterol. Talk about that.

Richard Isaacson 05:09

Sure. So, you know, there's no magic pill and there's no perfect one test for Alzheimer's disease. I want to be, you know, pretty clear on that. I think there's a lot of excitement in blood-based biomarkers, and I share that. But the baseball analogy I give is, you know, we're in the first inning of a nine-inning game when it comes to blood biomarkers for brain health. And when I think about brain health and biomarkers, I think of cholesterol markers, traditional ones, like HDL, LDL, ApoB, Lp(a). If you haven't heard of some of these, you should, because everyone needs to check track these things, not in their 60s and 70s and 80s, but their 20s, 30s, and 40s, because these diseases start early. So I think about brain health, and I think about heart health, and there's a difference, but they're similar. So I think about cholesterol panels. I think about inflammatory panels. I think about metabolic health, metabolic markers, not just about your hemoglobin A1C, that's a big term, glycosylated hemoglobin, HBA, fasting blood sugar. Everyone should know these numbers. Everyone should know they're fasting, insulin, insulin resistance, fast forwards Alzheimer's pathology. I also think about hormones, two out of every three brains affected by Alzheimer's are women's brains. Dr. Roberta Brinton, pretty cool you're here. I follow your work. I quote your papers. You know, there's this rapid withdrawal of estrogen during the perimenopause transition in women with one or more copies of a gene hormone replacement therapy. Ooh, it's bad, right? Black box warning, maybe not so much. These are the types of precision-based care that we need to provide, and we must provide based on using these blood tests. And then we have the brain biomarkers in our group, we're trying to develop the cholesterol test for the brain. And I think if people think that if this magic amyloid test is going to be the breakthrough, or the magic p-Tau 217, or 181, it's going to change everything. It's not because every single person out there is a little bit different. And we can't just follow one marker. You have to follow a panel. Mrs. Smith may need panel A, B, and C, but Mr. Jones may need panel X, Y, and Z, and just like me, know, HDL, LDL, triglycerides, total cholesterol, do we ever check just one? On brain health, we have to check the panel. And this is why we're in the first inning of a nine-inning game, and we're getting there, and I'm excited.

Allison Aubrey 07:11

Kris Engskov, you are the co founder of Rippl, and you have a sense of urgency about the need to change the way the care is delivered. How do you use technology? What do you see as the role of technology to improve dementia care?

Kris Engskov 07:25

I thought you're gonna ask me the AI question.

Allison Aubrey 07:29

Technology or AI [laughter.]

Kris Engskov 07:31

Separate them today, and maybe I'll do that. You know, we are—at Rippl, we adopted a virtual model. I mean, we are dependent upon technology every day to deliver the care that we're trying to deliver to patients and caregivers. And I would say, you know, technology—let me talk about AI first, because I think we don't—I mean, I work in this every day, and I don't think we have any idea what's coming. I mean, I think it's moving so, so quickly. And in many ways, dementia is perfectly positioned to take advantage of AI. I think it's there's the opportunity to, I think, work upstream, you know, using data and and predictive analytics to do a lot more work to identify dementia earlier and get these interventions in front of patients. I think there's a much bigger opportunity. We're doing this today at Rippl, where we're building navigation to really help our care teams decide the next best step, because obviously AI can go and understand that medical record in a much deeper way, a much quicker way, and really help guide the protocols that are personalized for that patient. And I mean, I think that's like just the beginning. I don't want to, though, miss the opportunity just to talk about basic technology, because I think the advent, since COVID, of just being able to get to people in a virtual telehealth model, is giant breakthrough for dementia. Today, we deliver our model 100 percent virtually. Much of our model came from UCSF that were the OGs and kind of proving that that was possible. And, you know, basic things like telehealth and just better, two-way communication are like a new lifeline to patients and caregivers who live, particularly in rural areas, but even people living in cities who just can't get out of their apartment or—so, I don't, I don't want to be too old-fashioned, but there's just a lot of basic technology that we can bring to medicine today. Particularly for this patient, that is going to be as breakthrough as AI in the short term.

Allison Aubrey 09:29

Joanne Pike, I want to move to you. You are CEO of the Alzheimer's Association, the leading advocacy group. As you listen to all this, what do you think is the biggest barrier to care? I mean, we've now got about 7 million people suffering with Alzheimer's. The estimate is that will double by 2050. What is the biggest barrier to care?

Joanne Pike 09:49

I think there's a couple. The fact is, you know, you started, Allison, with your own personal story. I think there are multiple people, whether in the room or—not a day goes by that we hear about the structural barriers that we see within Alzheimer's care today. The fact is that the system is fragmented. We don't have a comprehensive line that goes from all of the new innovations to delivering that at the community level, and then thinking about the innovations that are available within care models as well, and the importance of ensuring that post-diagnosis care is as integrated and as community-based as possible. We know that there are needs for not only the person who is receiving care as someone diagnosed with a dementia or Alzheimer's, but the needs of the caregiver within that dyad are incredibly important as well. So we have a fragmented system. We have a workforce that does not have the confidence to be able to care for those with Alzheimer's or another form of dementia. And then we also have IT challenges between interoperability and the infrastructure for a system to be able to communicate from PCP to

specialist. Right now, we have an opportunity, though, to really bring the best-of-care models forward. And one of those is through the initiative that the Center for Medicare and Medicaid Innovation has launched with the GUIDE Model, and the importance of bringing all of that work together. I was hoping that Kris was going to have a second to talk about this, because the Alzheimer's Association is partnering with Rippl on how we build that GUIDE Model together, and certainly Rippl has been doing amazing work on that front. But the same structural barriers that we see across the system apply within the GUIDE Model as well, where we're trying to bring an alternative payment model to incentivize comprehensive, coordinated care, but we have to go provider by provider in order to educate them about this opportunity. We have to be able to enroll individuals who qualify based on their Medicare enrollment, and then we have to be able to think about what that means from an IT perspective, to ensure that everyone across the system understands both diagnosis all the way to the care needs. Now there's some other structural barriers that we're seeing within this alternative payment model, and that's at the community level. We need respite for caregivers, and the payment that we are seeing right now out of Medicare within this is not enough to cover the respite costs at a basic level, at the community side. We also are running into the fact that we don't have enough dementia care providers within this country. We know today, as of this moment right now, that we need an additional 900,000 dementia care providers in order to meet the need. And that doesn't speak for 5 to 10 years from now, when we're going to see a bigger population needing the work that we're doing. So we have some structural barriers, but I think if we implement some of the evidence-based programs and models that we know of we can make a difference between now and the near future.

Allison Aubrey 13:04

Let me come back to you, Kris, on a couple of those points. I know that we're at a time when the lifetime cost of treating someone with dementia or Alzheimer's is about $400,000 to $500,000; the majority of that is the unpaid care. She talked a little bit about the GUIDE Model. If I'm correct, there's a sort of pay for caregiver support built into that model. Talk a little bit about this.

Kris Engskov 13:28

Wow. Okay, you ready to go? You know, it is go time for dementia. And I think it was—we talked—there's a lot of science being talked about, and this is the expert panel. I am not the scientist. I am the care guy. And I think that we got into this because—look, I'll give you an Alzheimer's Association fact. At age 85, you got a one in three chance of having just Alzheimer's. That is a staggering statistic. The other thing that Eli Lilly knows very well is that a lot of those folks that—a lot of the 72 million Boomers that are going to need care. You know, senior care over the next few years will never benefit from the drugs that are on the market today. They just won't, because you have to be pre-symptomatic, and many of them will be past that point. So let me just tell everybody we got a giant care tidal wave that we have got to embrace and figure out really quickly, because, you know, we're going to have lots of people who need to stay at home. I think the other facts are, right—people tell me all the time, if my mother gets Alzheimer's, well, maybe I'll just, you know, I'll put her in memory care. Well, that's great if you're rich and you can get a place, because that demand is going to outpace supply by 30x in that space, right? So we got to find a way to keep people at home. And I'm going to get to the GUIDE Model. So, you know, there was some really pioneering work

done at UCSF and UCLA. We use the UCSF science that came from that model. They ran a model for about 10 years called Care Ecosystem that had really impressive clinical outcomes, and even more impressive, total cost of care outcomes, which is what matters to getting paid right for these things, and it's what the GUIDE Model is based on, and I think the opportunity now is—I mean, the message I have is we know how to do this, and now we need to go do it. And as you all know better than anybody, it's it's how you get paid that matters. That's how we get care out there. It's the care available today. GUIDE is a new program, but we know how to do it. It's pretty, I wouldn't say easy, but we can deliver it. It's high touch, it's effective, it's working. I mean, we just delivered our own results in the GUIDE Program, and we showed that we could reduce ED visits by 30 percent and hospitalizations by 15 percent. I mean, those are astounding numbers. And I know other folks who are executing the GUIDE Model have had similar results. But as Joanne said, very well, and you went through the list, because there are a number of things that we could do to get that going much, much faster, because it's moving too slow. And that's just honest. The other thing I'll just add, and then I'll close up, is we also have a really elegant way to bring this to Medicare Advantage payers, right? Because that's half the country, right? GUIDE's great for Medicare, but that's only 50 percent of the folks out there. And we can bring a really elegant program to Medicare Advantage. But again, we're moving so slow, and we don't have time to wait. So we got to make this happen a lot, lot quicker.

Allison Aubrey 16:25

All right, I want to go back to personalized prevention. Howard, talk a little bit about some of the advances. For instance, speech detection we're hearing more about.

Howard Fillit 16:36

So speech is a product of the mind, and some of the earliest clinical changes that happen are changes in speech. They're very subtle. Sometimes we see them on TV with people that we know, and we—

Allison Aubrey 16:50

Repeating things.

Howard Fillit 16:51

Repeating things, sentence—changes in sentence structure, changes in prosody, which is the emotional tone of someone's language. And we have a $100 million project to look at this kind of issue. We have a speech consortium where we're developing a database, sort of, speech through the continuum of normal with aging to people that develop early Alzheimer's. And it's one of the earliest predictors, and it's a clinical predictor. So we have a database now from various sites that were sponsoring about 2,000 patients with with their speech patterns. And then the way that's going to work is that this database will be able to be

licensed by anybody who, you know, agrees with the way we license and signs the contract. They can go off and develop their own intellectual property. So this core database can then be used in many creative ways to help, to help diagnose early, and find the clinical symptoms early. And I think that that's a way that digital technology is really going to advance the early detection of Alzheimer's. You know, I think care is really important. I'm a geriatrician. I've been taking care of Alzheimer patients for over 45 years. So I know a little bit about caring for them and all the needs, but I think that the really big changes are going to happen when we develop effective drugs to prevent the disease. And it's been modeled that if we had an effective drug that could delay the onset of symptoms, and you were talking about that by about five years, we would reduce the number of cases by 40 percent, so I think, you know, these people that are getting out into the middle and later stages of disease, they need a lot of care, but I think slowing all that whole process down with drugs is really where we're going to have a big breakthrough.

Allison Aubrey 18:37

Richard Isaacson, back to you in your ABCs of prevention. C was sort of looking for cognitive decline. When you hear him talk about the ability to look at speech and changes in speech as an early sign, is that one of the things that's built into your personalized prevention model?

Richard Isaacson 18:56

So, people can take different roads to Alzheimer's, and that's the way I believe things are, and I think if you're on one road, you're going to need one instruction manual to get you off that path. And if you're on a different road, you're going to need a separate set of suggestions and recommendations. In our 2019 paper that we published, on average, people got 21 different recommendations per person. That may sound overwhelming, it's a lot, but that's good. That's a lot of things that we can do. And some of these are drugs, prescription drugs, to treat modifiable risk factors. Some of these are lifestyle changes. But the key here is that everyone needs a different path and a different plan. So that's what we study, and then we use the biomarkers, the blood tests, to evaluate the effectiveness. So I think a lot of us in the Alzheimer's community think about blood testing for diagnosis. Oh, someone has symptoms. I want to know if those symptoms are due to Alzheimer's pathology, so I'm going to do a blood test. Ah, tau. Aha, it's probable. So then we know it's Alzheimer's. That's not what these tests are going to be used for, in my opinion, because 47 million Americans today have Alzheimer's disease, starting silently in their body and brain before symptoms. Seven million affected. That's bad, but 47 million Americans today, one out of four people in this room, are at increased genetic risk, and there are hundreds of millions of people globally where things are starting, and that's when we need to intervene. We should be treating dementia when they have dementia. We should be, shouldn't be treating a person when they have a heart attack with a statin. We should be treating before, and that's the way I believe we need to do this. And how do we assess? Well, we do this through software. We funded an NIH—we had a NIH-funded clinical trial. Retainyourbrain.com, it's all free. It's 100 percent free, always will be free, where people can do a risk assessment. They can type in their Apo-E. I see 23andMe, something in there, nothing to disclose, no relationships with 23andMe. But you can get your Apo-E. And someone's scared if they have an Apo-E, right? No. Type it into the software, and the software will tell you what to do. And each person needs a targeted plan, omega-3 fatty acids. Oh, fish oil, right? That's good for the brain. If you have an Apo-E 4 variant. Oh, B vitamins, those are good,

right? Well, no, only if you have elevated homocysteine, which is a marker in the blood. So this is the concept and the core of precision prevention, you can take all the vitamin D you want. If you don't have vitamin D deficiency, it's not going to help. So that's the precision prevention approach.

Allison Aubrey 20:28

Dr. Jessie Fahrbach, as you listen to this, this idea of the personalized prescription, does that relate to the development of pharmaceuticals? So right now, the two big drugs remove amyloid plaques from the brain. Will there be a time when mechanisms of action are tied to various, you know, risk factors that might be genetic or might vary from patient to patient?

Jessie Fahrbach 21:32

Yeah, I think there certainly could be. And, you know, today we have treatments that target early, symptomatic Alzheimer's, and as we talked about, there's others. I think one of the keys, and one of the things that really keeps me up at night is, you know, a little bit what Joanne highlighted, is we really need to make sure that the health-care systems are ready and that they're prepared for what's approved today, but also for future advances that may come. And there are truly reasons to be hopeful today, but we do need to work together across industry, government, advocacy, health-care systems, to make sure that the patients can really have what's available today and to treat and diagnose people earlier. I think another thing that we haven't really touched on yet is we need to work to really destigmatize Alzheimer's disease, so that people will go in and see their doctors and get assessed. And this is both when people are starting to have memory and thinking issues, or they have a loved one that's starting to have those because we do know that the earlier you're able to identify it, the more impact you can have with interventions. And so it really is critical to get in there early. And that's not just when people are having symptoms, but really it needs to be part of our overall wellness plan. Brain health needs to be one of the things that we're tackling. And certainly, Dr. Isaacson has focused on this a lot, but it's really critical, you know, it should be a part of your overall wellness plan, going to talk to your doctor, understanding your risk factors, having a cognitive assessment, and you don't need to wait until something feels off in order to do that.

Allison Aubrey 23:09

I think that previously, there was maybe a fear. People thought, well, I could find out this information. Then there's this huge treatment gap. Do you think we're at a pivotal moment where as you look at what can be done with personalized prevention and with drugs that the treatment gap is closing, there are steps that you can take right away? Howard, yeah.

Howard Fillit 23:29

Well, I think what we're seeing we've gotten success. We know how to do clinical trials. We can get drugs approved for Alzheimer's disease. That's a huge breakthrough. We've never had disease-modifying drugs before, but what we've seen is also the limits of disease-modifying drugs, because they slow it down by about 30 percent, they slow the decline in function by maybe 45 percent. Some people actually get better. So in the in the population, the average is 30 percent, but some people have been reported to get better. It depends on your genotype and all that. But I think the next phase, which is really exciting, is combination therapy. Because like cancer, Alzheimer's is a disease of aging with multiple mechanisms. Each patient is a little bit different in their pathways getting to the pathology, and that's where the field is finally moving. It used to be five years ago that 75 percent of the clinical trials were beta amyloid trials. It's shifted now that 75 percent of the trials going on, out of about 150 trials, are drugs that are attacking inflammation in the brain, misfolding of proteins in the brain. We know now that Alzheimer's disease actually doesn't always occur as a pure illness, that there's multi morbid pathology. You've heard of Lewy body dementia, about 40 percent of people at pathology, at autopsy, have Lewy bodies and Alzheimer's disease, and those people tend to progress a little bit faster. So we have to recognize we need biomarkers. We're starting to get biomarkers, blood biomarkers for or spinal fluid biomarkers, or skin biopsy biomarkers for alpha-synuclein. And because that's the protein that's in the Lewy bodies, that would be a drug target if we went after that pathology. And there's other forms of dementia that contribute as well. So I think we're—we've gotten through the first phase. We saw the plaques, we treated the plaques, we got rid of the plaques. It works. We validated the first target, which was the obvious one, but in terms of thinking—in terms of like, okay, it all starts with beta amyloid. I think we have to think in terms of what happens before the beta amyloid that drives the beta amyloid plaques, and those would be more, I think, prone to prevention, because those are the things that are driving the pathology. And I say—as I say, inflammation of the 75 percent that are non-amyloid programs, about 25 percent are inflammation, because we know that inflammation really affects the brain and also probably causes cells to make the beta amyloid nexus and things like that. So it's the next era, and it's going to be combination therapy, and I suspect in five years or so, we might have a couple of new drugs approved, at least, where people will be studied and they'll be on two or three drugs for Alzheimer's disease, not just one.

Allison Aubrey 26:09

Yeah, Joanne, I want to go back to you. There's a lot more known about how lifestyle can improve brain aging. They, the Lancet Commission pretty much concluded that there are 14 modifiable risk factors that could play a role in preventing or delaying the onset of dementia. Tell us a little bit about the POINTER study that the Alzheimer's Association was behind. What did it find? And why are you hopeful, given these results?

Joanne Pike 26:39

The Alzheimer's Association took the idea of modifiable risk factors and basically applied that at the personal level. So we knew what could work at the population level, we applied it at an intervention level for here in the US, really looking at a diverse population, both in people characteristics, but also locations and the type of individuals that could benefit from this. So we invested, over time, about $50 million in running a rigorous research study looking at nutrition, physical activity, social and cognitive engagement,

along with medical care management of heart health, basically high blood pressure, over the course of two years, enrolling over 2,000 individuals in five cities across the US and those—we randomized these individuals to two different groups, a group that received self help and a group that received a highly engaged, accountable group to receive those interventions over time. What we found is that both groups, the self help group and the engaged group, increased their cognitive scores, so they both benefited. But the group that had the highest intervention, the engaged group saw a benefit of one to two years of cognitive benefit. One to two years is pretty incredible for what we knew could potentially work. The theories around the heart, what is good for the heart being good for the brain, we were able to prove that out within this intervention. So now it's important to think about, and what excites me as a public health professional is, how do you take research and change that now at the community level? Because you know, the work that we need to do needs to bridge back down to making it a reality. And quite honestly, there is personalized medicine, but there's also personalized prevention and risk reduction that can happen before you even get into the physician's office, that you can control. So what we've taken from that original investment is now looking at what is the future of the POINTER study in terms of implementation planning. We were, over the next several years, investing an additional $40 million in implementation projects to really look at bridging research to community intervention, but also studying that cohort for a couple of more years to see what continues to change about those individuals, and can we continue that progression of cognitive savings over that risk reduction intervention time period and extend that a little bit longer? It's an incredibly empowering opportunity for us as we think about the future of all of this, these great innovations that we're hearing about, we have the biological side of these innovations. We have the care side of these innovations, and now we also have the risk reduction side as well.

Allison Aubrey 29:54

One of the things about the POINTER study that I found fascinating is that one of the interventions was called the MIND diet, which was developed in Chicago by researchers at Rush University. It really is, sort of—as I looked at it, kind of Mediterranean pattern of eating with doubling down on greens, that kind of thing. And when you think about the 14 modifiable risk factors, many of them do come down to simple choices that people make every day. So for the MDs on the panel, when people start talking about these lifestyle changes that are important to improve brain health, if they say, you know, "Doctor, what's the most important thing? Is it the MIND diet, or is it these other 13 factors?" How do you communicate that there's sort of a "both and" component to taking care of your body and your brain?

Richard Isaacson 30:45

So, I get pummeled with this question probably every day, including last night at dinner and now today, and I'll probably get it on the train going back to New York when I'm visiting some friends. There is no one magic pill. And if anyone out there thinks that they can eat a magic blueberry and prevent or cure Alzheimer's, it ain't gonna happen. You heard it here first. It's the combination of things, and it's the biological principle of synergy. So one plus one equals three. Certain people need to exercise and they have to exercise, but if you exercise one way, it ain't gonna do it. As the belly size gets larger, the memory center in the brain gets smaller. I was on Peloton during COVID. Remember that? Remember COVID? We were stuck in the house. I still had a belly because I was doing it wrong. Lower intensity cardio, steady

state, zone two, where your heart rate is 60 percent of its max, not going all out. That's how you lose body fat. And doing it fasted, if your doctor says it's okay. I was making my heart stronger, and I was making my pulse rate lower, and I was probably going to live longer because of it, thanks COVID—benefits of COVID, but I wasn't losing my belly fat. So you have to change the game, and it's about precision exercise. Leafy greens? Absolutely. Fatty fish, lake trout, mackerel, herring, albacore tuna, wild salmon, sardines, omega-3 fatty acids, protective. Blueberries, half a cup. Nurse's Health Study showed you could delay cognitive decline by two years by eating berries. Just has to be twice a week, because the half life of the antioxidants and berries is long. There is no one magic anything. It's about stress reduction. It's about sleep. If you're burning the candle at both ends and you want to loosen up that amyloid by exercise, but you're sleeping five hours a night, well that's when the trash gets taken out. So you have to do all these things. And if you're not seeing your doctor on a regular basis. High cholesterol, diabetes, high blood sugar, fast forwards Alzheimer's pathology, and fast forwards vascular cognitive decline. We need to think about these things. We need to have these conversations. We need to know our numbers. We need to talk to our doctors. And there are so many free resources out there, from the Alzheimer's Association to the work that all of us are doing. There's so much out there in brain health. Brain Health Matters, I think, is a site that Lily's working on. I mean, literally, it's out there. It's in the zeitgeist. We can grab the bull by the horns, but it's not one magic pill.

Allison Aubrey 32:51

Howard, I heard you mention that you saw your first patient back in the late 1970s. What can you tell people in a clinical setting today that you couldn't tell them back then about the importance of these lifestyle choices?

Howard Fillit 33:04

Back then—I mean, actually, let me just back up a little bit more than that. Senility was always thought throughout millennia to be a normal part of aging. And so what changed that? Actually, it was in 1968-1970, three pathologists working in London, Blessed, Tomlinson, and Roth did a very similar, very simple study. They looked at the brains of 75-year-olds who died, who were senile, and they looked at the brains of 75-year-olds who are not senile, and they stained those brains with the same dyes that Alzheimer used in 1906 to see for the first time the plaques under the microscope at autopsy. And it was on that day in human history that senility went from being thought of as a normal part of aging to being recognized as a disease of old age. So I started medical school in 1970, I can tell you that for sure, I never heard the word Alzheimer's in medical school. It wasn't in the textbooks. When I did my clinical training, I saw many, many older people that I'm sure had Alzheimer's disease. Never bothered to—we didn't know how to do it, basically. So the initial criteria were really a diagnosis of exclusion, which means, you know, you excluded B-12 problems, thyroid problems, strokes. As neuro imaging became more available, we could do better at scans to see if people have vascular disease in the brain. And so the initial guidelines and diagnosis were diagnosis of exclusion. And then as we develop better imaging techniques, particularly the beta amyloid scan. So we funded the development of the beta amyloid scan around to beginning around 1998-99, and that really changed the world, because now people could go to the radiology office, get a PET scan with the same dye that Alzheimer's used pretty much in 1906 but almost 100 years later. It goes into the brain,

it binds the plaques, and you see the plaques on a PET scan. This was how the first disease-modifying drug was approved by the FDA, because, the first antibody, which isn't on the market anymore, showed that you could remove the plaques. I remember sitting at a meeting, and the thing was, Eisai Biogen, actually, at the time, showed us a scan of people before they got the drug, and it was filled with beta amyloid plaques and then after treatment, the plaques were gone. And everybody sort of gasped, you know, how could you do that? And the next question was, does it have a clinical benefit? And this is where I say we know how to do modern precise clinical trials. And the fact is that it had a clinical benefit to remove the plaques. So it's been a real, it's taken about 30-40 years to get where we are today, but we're really at a place where the next stage of research is going to be really exciting, because we really know how to do it. And we're following cancer. We have a lot to learn from cancer. The Imperial Cancer Trust, which really started cancer research in the world, was established in 1905. The National Institute on Aging, which has been the primary source of Alzheimer's research funding, was started in 1975. So we've come a long way in just 30-40 years, and I think we're poised to make big breakthroughs. And in terms of combination therapy and lifestyle management, we're funding a study of the leading anti-aging drug, which is also, in part, at least, sort of a GLP-1 agonist, which is semaglutide and those drugs, a combination of lifestyle interest, a lot like POINTER study in the US, and metformin, which is taken by many people as an anti-aging drug. Because we want to start saying—if you think about heart disease, we're treating people with lifestyle interventions, but they're also getting a statin. And I think that's the way that prevention will go with Alzheimer's disease. Also we'll have precision prevention, we'll recognize what people need, and what the pathways are that are predominating in those patients, and then treating those alongside lifestyle issues.

Allison Aubrey 33:27

Jessie, as you as you listen to that and hear about GLP-1s, Eli Lilly, obviously, is involved in both and there's a lot of anticipated enthusiasm about a coming announcement. Do you at Eli Lilly view the GLP-1s as anti-aging drugs, as brain health drugs? Given that so far, the evidence is clear, people lose weight, they reduce their A1C, but the benefits seem seem to go much further.

Jessie Fahrbach 37:27

Yeah, no, certainly the incretin therapies or the GLP-1s, have broad benefits for health, and we've seen that, and we're evaluating that, and certainly there are studies externally ongoing, looking at incretins for brain health. So I think there are some opportunities there and and we're not announcing anything like that, but certainly would do so when appropriate, if we decided to go into that field as well.

Allison Aubrey 37:53

Yeah, Kris, as you listen to all the ways in which you know, the POINTER study gave insights into how people can manage lifestyle. Talk about how continuing to manage these lifestyle choices can help in the disease care model, even after people have already been diagnosed. How do healthy habits, you know, change the trajectory, and why is that important to make that part of the care model?

Kris Engskov 38:22

Well, I'm grateful to the Alzheimer's Association for lots of reasons, but because of the POINTER study, I feel like I read that with a lot of intention. You know, because one thing, Allison, that we haven't talked very much about is caregivers. And you know, the science is not going to impact them, but I'll tell you that what we know today from the care side, and I'm going to answer your question, I think, is that the caregiver is fundamental to keeping somebody at home. And I think that we have not—that's been part of the funding issue. I probably should have gone into that in more depth a minute ago. We've not really put the funding into making sure that the caregiver has the kind of support they need to actually, you know, take care of their patient. And the caregiver, you know—the fact is, the caregiver often declines as fast or faster than the patient they're taking care of. There are lots of reasons to pay attention to this space, and I think it applies to the work in the POINTER study, because a lot of these caregivers are—this is, you know, this is a lot of us, right? Right in middle age, we've got young kids, and we are the sandwich generation. We got young kids, and we've got parents that are moving in this zone. And I think it is go time for dementia like I've—you know, I've been working on the last few years, and I've never seen the level of attention now that's focused in the momentum we have, you know, on the science, on the care, but we're still moving really slow. And I think the POINTER study gives us a lot of hope that actually for many of us that are paying attention here, there is a real opportunity to slow that progression. You know, because age 85 is pretty amazing. What I didn't say earlier, too, is that 85—many of us are going to live to 85 now. Like, that's not going to be uncommon. So to think that that's actually—and that's, again, an Alzheimer's Association statistic, that you get a 33 to 30 percent chance of getting just Alzheimer's at that age, you know, we got a big challenge ahead of us, and it's got to involve that caregiver.

Allison Aubrey 40:26

Thank you. Yeah, Joanne, as you listen to Howard talk about this trajectory, and talk about in the 70s, that you didn't hear the term Alzheimer's. Talk a little bit about, you know, the momentum that you have now as an advocacy organization at this pivotal time when there are these opportunities of treatment and earlier detection and focusing on these modifiable risk factors.

Joanne Pike 40:51

Yeah, there's—Allison, there's so many directions right now from an advocacy perspective, we can, we could think about, but I—honing in on a couple of things in terms of the momentum we have right now, and how do we sustain or accelerate some of that momentum? In the last a little bit over a decade, we've seen incredible momentum in the US government around investment in research. We went from in 2014 around $400 million from the US government, invested into Alzheimer's and dementia research, to now today, fast forward, it's $3.8 billion being invested out of the National Institute on Aging. And it's not about just protecting that, but also continuing to grow that pool of dollars. And right now, we have—we are seeing proposals to increase that by another over $100 million. So we're getting close to, potentially a $4 billion mark on Alzheimer's and dementia science out of the US government. We have to maintain that momentum. And I think that the fact is we're seeing progress today because of the increase on shots on

goal, and that goes for multiple places. Whether it's biomedical or the care pathway, or on the risk reduction side, we're able to see the results today because of some of that dramatic investment, whether it's government, venture, or philanthropic. Another great example just happened last night in terms of momentum, if you're a Texan, congratulations to all of you. We did pass the Dementia Prevention Research Institute of Texas, funded last night. For those of you who don't know what I'm referencing, the state of Texas committed $3 billion over the next 10 years to fund research across the continuum into Texas institutions. Now let's compare what that means. That's $300 million a year. The Alzheimer's Association as the global funder and nonprofit research funding, funded last year $112 million. That triples the amount that the Alzheimer's Association commits globally into institutions in Texas alone. Texas did this years ago with the cancer CPRIT model, and as a result, they've seen Texas become a destination for cancer treatment in the last decade. We—Texas intends to do that with dementia, but also with research as well. That type of momentum, where we're seeing both advances and continued investment, is important to maintain. But also think, how do we apply this to all of the areas that we know need to be applied towards, that is care. Even the best models right now where we are seeing the changes within the research landscape in terms of treatment, we still need to ensure that the care that is delivered, both in the health system and at the community level, meets an evidence-based guideline around how that can be delivered. So we need to continue to innovate and not just think about the front end of treatment and diagnostics, but also as someone progresses, what do we need to continue to do with that individual and their family to make sure that they receive the best of care?

Allison Aubrey 44:25

Richard Isaacson, as you listen to her talk about this big investment happening right now. How does that translate? How do these investments translate into better precision prevention programs? And now is the time to ask your questions. We have about 10 minutes left. I've got an iPad here, so if you want to put them in, we can probably get a few questions in.

Richard Isaacson 44:48

So, I'm deeply appreciative of all of the investment. It's just, you know, I've had challenges in prevention, you know, I haven't had grants to apply for. You know, right now there is a government shutdown, and I can't even apply for an NIH grant if I wanted to. We have a grant all ready to go and I can't submit it anywhere and everything's closed online. So I think, you know, focusing the funds, you know, as you said, on this dementia prevention initiative that's new. You know, there, again, were not grants to apply for the things I wanted to do 10 years ago. And there's—or 15 years ago, and there's still, you know, is a paucity, and I think, I think treatment is critical, but I still think over 90 percent of the funding, if not more than that, is going to treatment with symptoms. And that's good. That's great. They need it. I have four family members with Alzheimer's. We need it, but we have to shift the funding earlier. You know, we're a nonprofit, ind.org is where we, you know, focus our efforts, and we're trying to develop scalable, democratizable access, low-cost, at-home testing to panels of blood tests that, in our estimates, should be like, you can get 100 blood tests for, I don't know, about $100 that's pretty good, at home. And that's our goal. And, you know, funding needs to go there, and people need to partner. You know, we need to talk. We need to have panels like this, the ADDF and the Alzheimer's Association, Lily and Rippl Care and us.

We need to all talk. We need to collaborate. We need to, you know, go arm in arm. We got to stop with not agreeing. And we need to agree to go forward and partner and win this together.

Allison Aubrey 46:22

Dr. Howard Fillit, do you agree with this assessment that there needs to be more going towards prevention?

Howard Fillit 46:29

Yeah, and I was thinking about the model, you know, as people decline, somebody comes into the office and I say, "Well, if you exercise and if you eat the diet and so on, you'll slow your rate of decline, but in a year or two, you're going to be worse, but maybe you'd be worser if you didn't actually do these things."

Allison Aubrey 46:47

So inevitable, but you're slowing the process, right?

Howard Fillit 46:50

But I think for the individual patient, you can't really tell them. You don't really know what the trajectory would have been anyway. And I think the heart disease model would give people lifestyle management. We measure their cholesterol, so they don't know that taking that statin prevented a heart attack for them. I mean, it's, there's a metric, and this kind of thing called the numbers needed to treat. How many people would a doctor have to treat with a statin for five years to prevent one heart attack? And it's something like 100 people. So, you know, I see 100 people. How do I know which one is actually benefiting from the statin? Well, we use the biomarker. It lowers your cholesterol. We know high cholesterol is a risk factor for heart disease, so they come in this paradigm, and I say, "This is great. You know, your cholesterol went from 250, now it's down 150 and your LDL is below 40. And this is great." But I don't know if that's really going to prevent them from having a heart attack, and neither do they. And I think we're going to have the same paradigm in prevention. I think Richard alluded to this, where we have biomarkers now, for the first time, blood biomarkers, where clinical diagnosis and care will enter the mainstream of what a primary care doctor does by measuring these biomarkers. We talked about p-Tau 217, which predicts, to some degree, the cognitive decline and the fact that whether or not patient has beta amyloid in their brain. So imagine a world where we put people into exercise and their blood biomarkers for Alzheimer's disease improves. Now I can say, tell the patients you know this is doing good for you, and if you keep doing this, then the chances are you're going to prevent the onset or delay the onset of cognitive impairment. So I think we're just seeing the integration of these various pieces, the blood biomarkers, which are going to change—they've already changed clinical trials and the changing clinical care. It's just beginning. These blood biomarkers are just being started to be available from Quest

and LabCorp, and I think it's going to be a big change in terms—70 percent of prescriptions for the currently available drugs that are used to treat the symptoms of Alzheimer's disease are prescribed by primary care physicians, and they're the ones that also get involved in holistic care, and not just the neurology groups, where they're primarily interested in diagnosis and maybe need to be the people that prescribe and manage these infusion products, which are quite complicated. But 70 percent of the diagnoses the patients come to the primary care doctor with complaints, "My memory isn't the same." We can't have 70 percent of those patients going to neurology when it can be done in a primary care setting with a blood test. And that's the main, that's the mainstream of care for other chronic diseases of aging. So it really is a revolution.

Allison Aubrey 49:07

I want to end with the moments we have left with a lightning round. We heard you say, in five years, there will probably be new drugs. Given this five-year window for each of you, whether you're focused on sort of prevention for care, new drugs, give us a sense of what we could expect to see in 2030 that we don't see now in terms of advancements in care, in prevention and in drugs. And we'll start with you, Joanne.

Joanne Pike 49:23

I would say an advanced understanding that we have to build the medicalization of Alzheimer's and dementia care, and that is inclusive of what we consider evidence-based, guideline-based, care all the way through the way we treat end of life. And I think the next five years are going to be pivotal to building that type of model based on things we already know from the cancer community to the heart disease community, that it requires that level of rigor to ensure that we are delivering against the promise of innovation.

Allison Aubrey 50:37

Dr. Richard Isaacson?

Richard Isaacson 50:39

Within five years, I hope to be retired, and I have already moved from New York to Boca Raton, Florida, from Brooklyn to Boca, as Seinfeld would say, I live literally down the block from Seinfeld's parents. I don't know where I'm going to retire to, but I hope to be retired because I believe that automated care and low-cost care is possible. I believe that through the comfort of a person's own cell phone, someone could take a risk assessment at no cost. They can get targeted advice. They can get in the mail a little card where they do a couple of finger pricks and, no, it's not Theranos. This stuff is real. The technology is actually much better now. And for less than $100, you can process the card, because cards are like 10 bucks, the processing of the blood samples at cost is very inexpensive. Believe it or not, for 100 bucks, you can get a

risk assessment and get automated care, and then you track it from home, because there's not enough doctors, there's not enough nurse practitioners, there's not enough physician assistants. We can do this in an automated way, as long as we promise not to overpromise, we're transparent about what we can and can't do, and I believe we can do this all through software. AI is hot, AI is cool, but it's not that complicated.

Allison Aubrey 51:49

Dr. Howard Fillit, he makes it seem easy. Is it that easy?

Howard Fillit 51:53

Well, I think one, we're going to see a few things. We're seeing the proliferation of brain health clinics, and we need some guidelines, let's say around what they do. We see we have specialized clinics all over the country for other diseases. I think we're going to start seeing them well—what we call brain health, but in many ways, they're memory centers, where the the multidisciplinary need of that patient is going to be centered in one place by people that, at least at some degree, have experts. I think that's one thing that I think we're going to see. And also communities. We're starting to see the proliferation, because right now it's assisted living and then long-term care, with not much in the middle there, but we're starting to see communities where, you know, patients with memory loss and so on, can be in a larger community that's built—it's dementia-built communities. And I think that that will be really exciting. I don't know how expensive it'll be, but it allows people, you know, Alzheimer patients might like to wander in New York City, they'll get lost, and you know, it'll be terrible, but in these communities, they can wander and, you know, it's a nice thing. I think that is going to change the scene a bit also. And I hope Richard doesn't retire, because we're gonna need more of this stuff. So I think that—and I think we'll have more drugs, and again, the brain health clinics will be able to do the kind of work that Richard and the Alzheimer's Association is doing in identifying people's risk factors and then treating them with combination therapy.

Allison Aubrey 53:22

Dr. Jessie Fahrbach, do you think in five years, people will be taking medicines pre symptoms?

Jessie Fahrbach 53:29

So, I think there's—you know, we've heard from across the panel, there's amazing reasons to be very hopeful, and we truly have the opportunity to rewrite the story of Alzheimer's disease. And Howard was talking in the hall, you know, he's been at this for 40 years, and think about the amazing changes that have happened over those 40 years. So as I think five years out, you know, I think we can be very hopeful that there will be more treatments available across the continuum of Alzheimer's, and certainly we're studying pre-symptomatic as well. And then I hope that we're also able to destigmatize Alzheimer's, so that people

do get treatment earlier, and so that they can have the maximum benefit, and that we're able to continue to work to make sure that health systems are prepared and ready to receive and treat these patients early.

Allison Aubrey 54:15

Thank you. All right, Kris, you have the final word. We know that is go time.

Kris Engskov 54:18

It is go time.

Allison Aubrey 54:20

Yeah, you take the floor.

Kris Engskov 54:22

Well, I was just, I was just thinking about Dr. Isaacson talking about, we should all work together in this town. The chair that's missing here is actually who pays for this care. That's the chair that I'm realizing really missing. Because without that, none of this works right? We have to get paid to be able to hire these teams and build the technology and do all the things that we need to do. So—and the other observation I have, and I'll get to my five years, is listening to Dr. Fillit talk about five years being like—that seems like a lifetime to me. Right now, the number of people who will need care in the next five years is going to be gargantuan, and it's going to have impact way, way beyond those families. It's going to have, Diane Ty and I were just talking about, employer impact, right, and getting employers focused on this. So for me, in five years, my God, I hope we built a national infrastructure, working with the Alzheimer's Association to really get hands-on care to patients and caregivers. And you know, we've really, you know, really employed—because it is easy, Richard, and in some ways, we already know how to do this. We just got to get the right people to pay for it and really care enough, I say all the time. We don't like old people in America. If we did, we'd have way better infrastructure for it, and that's got to change. So that's what we're working on. And I hope in five years, we are light-years ahead on the care space and the science space. So that's where I land.

Allison Aubrey 55:40

All right. Thank you to this amazing panel, and thank you to a great audience.

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