



BREAKTHROUGHS RESHAPING AGING AND LONGEVITY

Announcer 00:01

Please welcome the panel on “Breakthroughs Reshaping Aging and Longevity,” moderated by Richard Lui, anchor MSNOW, Principal CAREGenome, Chief Impact Officer Caregiving Moonshot.

Richard Lui 00:24

Well, good morning, everybody. I hope you are having a good day three, if that's right on count. We have a fantastic gathering of—what I like to say—big brains in this topic. And we are going to try to dig down into the very title today: “Breakthroughs Reshaping Aging and Longevity.” Sitting on the panel today is Joe Betts-LaCroix, co-founder and CEO of Retro Biosciences, working to develop therapeutics to help people add 10 years to healthy human lifespan by reversing age-related diseases, which we will get into very soon. I know a lot of you are probably asking, how's he going to get this ten years, right? Or even five. Next to him, Tom Hale, CEO of Oura Health, the company behind that ring that many of you are very familiar with, which helps people track their sleep, activity, overall health, and better understand how their bodies function, as well as make us a little bit more OCD when it comes to that data.

Tom Hale 01:23

[Laughs]

Richard Lui 01:25

Tom, you laugh. You know. Richard Isaacson, director of Atria Prevention Program and neurologist whose life's work is preventing Alzheimer's before symptoms can begin. As well, Carina Kern, co-founder and CEO of LinkGeivity, who is running clinical trials with compounds targeting the root cause of aging itself.

And finally, John Whyte, CEO of the American Medical Association, the institution that will ultimately determine how longevity medicine enters mainstream practice. So a big round of applause to our panelists today, please. You know, I do want to start with a bit of a lightning round to all of the panelists, and I'll start with you first, and then we'll just go down the line here. What is the biggest thing standing between us and breaking through to extend healthy human lifespans by a decade? Which was the prophecy of Joe, but we'll let you go last, Joe, on this one. What would you say first? Is it biology, money, regulation, or medicine?

John Whyte 02:31

Richard, I'd say it's a combination of those. But the other element I'd add, since this is a lightning round, is that—

Richard Lui 02:38

—Yeah, it is—

John Whyte 02:39

—in medicine, we're not focused on the right things.

Richard Lui 02:41

Yeah.

John Whyte 02:41

We're focused on how do we open up that blood vessel that's closed. How do we find the best medication for diabetes? We're not focused on prevention. And if we focused more on prevention, having early diagnosis, then we would extend lifespan that way.

Richard Lui 03:01

So your answer is prevention.

John Whyte 03:02

It is.

Richard Lui 03:02

Very good.

John Whyte 03:03

I don't think that was on your list, but—

Richard Lui 03:04

—It wasn't. That's okay. It can be other than. Richard, what do you say?

Richard Isaacson 03:07

So to piggyback off that, we live in a sick-care system, not a healthcare system, and that's the problem. We need to get ahead of things. Heart attacks, strokes, Alzheimer's disease, other neurodegenerative conditions start silently decades before. So that's when we need to intervene. In our medical system reimbursement codes, we get paid, doctors like me get paid to treat a symptom, to help a sick person, not to prevent disease. People don't get paid for that. I don't get paid for that. So that's where I think we need to intervene.

Richard Lui 03:36

Carina?

Carina Kern 03:38

I would say medicines for sure, but not just developing new medicines. I think what we need is a paradigm shift in medicine development. Let me just explain that. So open even the latest medical textbook, and what you will see is kidney disease is a distinct topic to, say, cardiovascular disease, neurodegeneration. So diseases are treated in silos, and yet that is not how biology works. Aging is far more complex. Multiple diseases are interconnected, and multiple diseases arise simultaneously, meaning the standard approach that we've taken, the status quo, to try and identify single therapeutics for single targets for single

diseases, does not work. And so what you need is to identify therapeutics that can tackle multiple diseases simultaneously, which is really what we focus on.

Richard Lui 04:35

Medicines.

Carina Kern 04:37

Correct.

Richard Lui 04:37

Very good. Tom?

Tom Hale 04:39

I'll plus one all the work on prevention and moving away from sick-care. I think that's totally right. My addition would be actually behavior change, because behavior change is the hardest part of prevention. How do you get someone to really do the things that are going to yield a better outcome over the long term? The last thing, I'll throw in just a little bit of a word on prediction. As a purveyor of a wearable that you wear continuously, we see all these patterns. We can start to make predictions about when you're heading towards a direction where you might get a medicine or visit a doctor. That's the power of something like a wearable, is that it sends you down a path with maybe more time to make an intervention that could help.

Richard Lui 05:17

Joe?

Joe Betts-LaCroix 05:19

I think that prevention, obviously, we would rather not get sick than have to be cured and go to the doctor. I think that lifestyle is important, and a lot of people are killing themselves and don't need to be. But we also have ideal lifespans, ideal behaviors on the planet, and that people still die for some reason. So around 85 percent of all the diseases we treat in hospitals are age-related diseases. And that means that prevention—and to Carina's point about finding common causes—the way to deal with all of that disease is to go upstream, to ask where does it come from? And it comes from aging. And understanding what aging

is and why it gives rise to all of this disease. Basically, \$4 trillion worth of healthcare, just in this country, comes from understanding aging, which very few of us are actually working on, and that's what I've devoted my life to.

Richard Lui 06:19

So understanding, is that correct?

Joe Betts-LaCroix 06:21

Understanding and then intervening.

Richard Lui 06:23

Got it. The title of this conversation is "Breakthroughs Reshaping Aging and Longevity." What are each of you working on specific to the title of this conversation that is interesting to you, that you don't sleep on, you're worried about it, right? Tell me about something you're working on right now. It could be early on, it could be later stages. But when you think about breakthroughs reshaping aging and longevity, based on where each of you sit, what's keeping you up in an exciting way, like you can't wait to put on your boots in the morning? Tom, we'll start with you.

Tom Hale 06:57

I would say for us, actually, blood pressure is this really interesting new horizon. Blood pressure traditionally is measured in an episodic way. There's all these factors that'll affect your blood pressure. The time of day, did you drink coffee, did the doctor come in and scare you? All those things. And I think measuring blood pressure continuously is going to be really powerful for the same reasons we just talked about, which is that, one, it's a good predictor.

Richard Lui 07:21

Yeah.

Tom Hale 07:22

Two, it's also largely undiagnosed if you have hypertension or hypotension. And then ultimately, it's the kind of thing that actually will save a bunch of lives.

Richard Lui 07:30

Can you do that with a ring?

Tom Hale 07:32

You can. Now, whether or not we're allowed to do it is another one, and we'll probably get to this. But the FDA has been very clear about this new guidance that they put out that says actually, as long as you follow their guidelines about how you talk about it—

Richard Lui 07:45

Sure.

Tom Hale 07:45

—you can. And so I think you'll see that from us very soon.

Richard Lui 07:47

Theoretically, what's the accuracy percentage, theoretically, here?

Tom Hale 07:51

Well, when you look at the theoretical data that we're looking at today—because we have a study called the Blood Pressure Profile Study, 400,000 people involved, hypotensives, hypertensives, all sorts of people in between, different shapes, colors, healths, ages, genders, all the things. What you see is we can probably get within 5 percent.

Richard Lui 07:47

Within 5 percent.

Tom Hale 07:51

Which by the way is practically clinical grade. Now, again, going back to what we can say about that and how accurate we can be—

Richard Lui 08:15

Sure. I got you.

Tom Hale 08:15

—that's something else—

Richard Lui 08:16

—Copy.

Tom Hale 08:17

And by the way, maybe that's another reason for your lightning rounds.

Richard Lui 08:20

That's right.

Tom Hale 08:20

Actually, the industry and government, they have a—

Richard Lui 08:23

—Yeah—

Tom Hale 08:23

—huge role to play in changing the nature of healthcare.

Richard Lui 08:25

Yeah. What are you working on this—

John Whyte 08:26

—Yeah, Tom—

Richard Lui 08:27

—that we don't know about?

John Whyte 08:28

Yeah. Tom was glancing at me because we had a feisty discussion beforehand. What keeps me up is this great opportunity we have with wearables in terms of really moving healthcare that's being provided in the hospital, in the healthcare setting, to the home, and that's continuous in nature. But Richard, what keeps me up is that the guidance that Tom referenced talks about that these general wellness apps basically don't have to be clinically grade. And since when do we live in a world when if we measure blood pressure, it's good enough? Or that it's not that reproducibility within 5–10 percent? That's the real risk that keeps me up at night, because patients are going to make decisions, despite how things are marketed, that that number is accurate and that reflects them. And doctors are going to have to base decisions on tools that may not be as accurate. So we really need to create a system that wearables are clinically grade, that provide us the data that consumers expect. Otherwise—

Richard Lui 09:35

—What—

John Whyte 09:35

—we're at the supplement industry.

Richard Lui 09:36

What wearables specifically, in 30 seconds, are you looking at? Of course, you're looking at Tom's, but other than Tom's?

John Whyte 09:43

I think it's all wearables in general.

Richard Lui 09:46

Any type?

John Whyte 09:46

Not any specific product.

Richard Lui 09:48

Fall prevention?

John Whyte 09:50

What we're particularly interested in are things that have big impact. Fall prevention does, and you could say that's more easily able to calculate. If we address blood pressure, everyone's focused on their steps. We're joking about HRV. If I could get people to monitor their blood pressure continuously, that's how we're going to reduce heart disease. That's how we're going to reduce stroke.

Richard Lui 10:14

Okay.

John Whyte 10:14

It'll be the biggest impact.

Richard Lui 10:16

Joe, what is something we don't know about related to breakthroughs and the title of this conversation that you might want to tell us about?

Joe Betts-LaCroix 10:25

It would be great if I knew all of what you knew, so I could answer that.

Richard Lui 10:31

Scientist. Here we go.

Joe Betts-LaCroix 10:35

Yeah, I'm a nerd CEO. I'm reasonably okay with that. I think that one of the things that keeps me up is that, well, I guess I see my role as part of this overall arc of aging being understood by explorations in labs, in academia, and then moving its way through early stage clinical, and eventually being rolled out into medicines through biotech. That's my job, the biotech part. And we've been doing that. So now we have a molecule in clinical trials, and it's most of the way through its first clinical trial, and so I'm just like—

Richard Lui 11:21

—Have you given—

Joe Betts-LaCroix 11:21

—biting my nails, waiting for the data to come out.

Richard Lui 11:24

What's the name of the molecule?

Joe Betts-LaCroix 11:26

We call it RTR242, and it restarts the autophagy process, especially in aged neurons, where it is often halted. And it leads to the buildup of aggregates, toxic components inside those cells, which have to last us our entire lifetimes.

Richard Lui 11:49

So, in high school language, RTR242, what does it do, in a sentence?

Joe Betts-LaCroix 11:54

It cleans out your brain cells.

Richard Lui 11:56

Ah.

Joe Betts-LaCroix 11:58

I mean, I can go—

Richard Lui 11:59

—That's great—

Joe Betts-LaCroix 11:59

—further if you want.

Richard Lui 12:00

Just like sleep. Sleep does the same thing.

Joe Betts-LaCroix 12:01

Yeah.

Richard Lui 12:03

That's great. Thank you for sharing. Carina, what is something you're working on that we might not know about when we talk about breakthroughs reshaping aging and longevity?

Carina Kern 12:14

Well, in terms of what I see with aging as the real challenge, right? It's a systems-level challenge that needs a systems-level solution. And the way we've gone about it is—in this sheer complexity with all of these interacting elements—can you identify key nodes giving rise to the greatest level of degenerative change, and intervene there? And what we've actually managed to identify is a first-in-class drug to tackle unregulated cell death, or necrosis, which underlies tissue degeneration and is one such node. And we're taking that as a next step, looking to take that into phase two clinical trials, and have partnered with the UK NHS, or the National Health Service.

Richard Lui 12:58

What do you call that node?

Carina Kern 13:00

Necrosis.

Richard Lui 13:01

Necrosis.

Carina Kern 13:01

I can explain it a bit more as well, if you like.

Richard Lui 13:04

In a sentence.

Carina Kern 13:07

In a sentence, it is—

Richard Lui 13:08

Yeah.

Carina Kern 13:08

—negative cell death.

Richard Lui 13:10

I do that as a cable guy. Sorry. Yeah.

Carina Kern 13:12

In a sentence, it is undesirable cell death that underlies tissue degeneration.

Tom Hale 13:16

Is there desirable cell death?

Carina Kern 13:17

Oh, yes. There's several types, lengthy lists. So, genetically regulated forms of cell death, you have apoptosis, pyroptosis, lengthy medical terms that you don't want to go into. But in short, in contrast, cell death that arises purely from damage, it is unregulated. There's no benefit. It's not there to take out cancers or for wound healing. That is necrosis.

Richard Lui 13:41

Very good. Richard, a lot of stuff in your space, when we talk about Alzheimer's and dementia, to be excited about. Tell us about some of the things that you've seen—as you're a doctor—that you can share with us, that might be "wow" when it comes to breakthroughs.

Richard Isaacson 13:58

Yeah. So I think two things. Our mission is to democratize access to brain healthcare, full stop. And I'm not going to stop until we achieve that. I see patients as a clinician at the Atria Health Institute, and it's great, and I can see patients. But we need to see many patients and tens of millions of patients, and we're going to do that through two ways. Number one, democratizing access to brain health education and information in a valid way. We've completed an NIH-funded randomized controlled trial. It's under review at *Nature Medicine* right now, so fingers crossed. Tough journal. We'll see. Anyone right now, today, from the comfort of their own cell phone, can go to retainyourbrain.com for free and get a risk assessment, take a memory test. Everything that we do in our clinic, we've put that online, and we've studied it in a six-month randomized controlled trial and shown that people that use this free software today can reduce their Alzheimer's risk by 16 percent, with no drug, just behavior change and learning.

Richard Lui 14:52

16 percentage points.

Richard Isaacson 14:53

16 percentage points in six months, the people that were the most compliant. That's a breakthrough. The second breakthrough is what we're really going for, and that's on the biological front, and that's developing a cholesterol test for the brain. Everyone here knows what their HDL, their LDL, their triglycerides. Every 6-12 months, you talk to your primary care doctor to prevent heart attacks or strokes. Well, this summer, we hope to fully validate what I believe to be the first cholesterol test for the brain. And instead of HDL and LDL and triglycerides and all these terms, it's going to be a different set of brain proteins that anyone can access. And our goal is to democratize this by an at-home fingerprint card test that we're working on today.

Richard Lui 15:31

What's the working name that you're calling this test?

Richard Isaacson 15:34

So I like cholesterol—

Richard Lui 15:35

—The Richard test?

Richard Isaacson 15:36

No.

Richard Lui 15:36

Oh, okay.

Richard Isaacson 15:36

No, definitely not. We've called it Neuro Insights. we've called it Neuro Longevity, but to me, it's a cholesterol test for the brain because it's—understandable by the public.

Richard Lui 15:44

What will the cost be, roughly?

Richard Isaacson 15:46

Well, the goal, less than \$150. That's the goal. At-home testing cards is a few dollars. Processing the test is a little bit more, mailing in the cards. Right now, the costs are more, \$2,000 to \$3,000, but we're trying to get those costs down.

Richard Lui 16:00

Fantastic. Thank you all for sharing what you're looking at right now when it comes to breakthroughs. Joe, when we look at the idea of longevity and the biology of it, describe to me the distinction between reversing, if that's possible, versus extending.

Joe Betts-LaCroix 16:15

Yeah. Well, it's usually not that controversial to people that they want to not die and suffer. And the converse is that they would like to live a longer, healthier life. And there's—essentially, my job is to take action on that. How do I create therapeutics and medicines that can intervene in aging to create more of that health? There are two fundamental ways of doing that. One is to slow down aging, which seems obvious enough. And the other is to reverse the aging that has already occurred, so turn back the clock a bit. So from a purely utilitarian perspective, either one or the other can create the same amount of sort of overall population happiness or wellbeing, right? But my job is action. So if I want to go out and perform interventions in a legal way, I need to be able to then measure the result of those interventions and decide whether I've done an okay job or not, and whether this drug should be moved on to the next stages. And the only way I know how to do that is aging reversal. Because if I'm slowing aging, if you slow aging by 12 percent, this would be a massive contribution to humanity and the whole globe and everybody on it. But I can't run a 50-year clinical trial. I can't run a 10-year clinical trial. The cost of a clinical trial eats almost all of the money in biopharma as it is. So the cost is proportional to the length of the trial. So even running a one-year clinical trial is pretty heavy metal. So if I can create interventions that reverse aging, and they're relatively quick to perform on the person, then that means I can just do before intervention, after, and decide did it work or not? So, that's everything we're focused on, is a reversing aging intervention, and that's why.

Richard Lui 18:36

Thanks for that explanation. Carina, to you and the blueprint theory of aging. What is it? Build on what Joe was saying.

Carina Kern 18:44

Absolutely. So, this is what I was saying. You need a paradigm shift in how you tackle diseases, age-related diseases in particular, and how you then develop therapeutics to do that. And the approach we have taken, as I was saying, is akin to factor modeling in finance. In this system, once you identify a key node that is conserved across multiple different diseases, is driving the greatest level of change, then you're going to stabilize the system as a whole and have a vastly protective effect. And going back to necrosis, because you need an example here. So the drug that we're taking into clinical trials as the next step. To bring to life what that's treating, think about what the fundamental building block of all of biology is. It is the cell. How your cell lives, how it dies, that determines all of biology. That determines your health or your lack of it. So you can see why it is so fundamental to so many different diseases. And once you identify that target, then identifying a therapeutic to take into clinical trials to get your good scientific data. And of course, in our case, the ambition is to get this approved as the first drug for aging. And going back to Joe, who made a very good point—how do you prevent having to do those decade-long clinical trials? And there, key is really to identify the first key disease or key model to begin with. And in our case, the first indication or the first disease we're going for is kidney disease. We're doing that really for two reasons. One, vast unmet medical need. It's really sad. All you have is dialysis or transplants. To put it into perspective, 24 percent of Medicare's annual budget goes into kidney disease. But the second reason—and this was our strategy—it is an accelerated aging model. It's one of the organs to age the most rapidly. In other words, ideal as a starting model to gain that invaluable data

Richard Lui 20:57

Richard, for you in Alzheimer's, the idea of reversal is probably pretty hopeful. For so many decades, you've been looking at just extension or longevity within the journey of Alzheimer's and/or dementia. How do you discuss that?

Richard Isaacson 21:18

Yeah. So reversal is not usually a word that—pops off my tongue, and I don't like that word. I don't know if it's a pet peeve, but to treat, to try to prevent, to reduce risk, to improve symptoms, those are more medical terms for me. If we can delay cognitive decline, if we can slow pathology, promise not to overpromise.

Richard Lui 21:43

Right.

Richard Isaacson 21:44

We've had amazing progress. We've had people's brains grow, repeatedly. I've lost count. We've had normalization, it's a word I like to use, of amyloid protein, a sticky protein that builds up in the brain and

blood of a person with Alzheimer's and a person at risk. We've had normalization of tau protein. Again, brain cells grow, proteins come down, cognition, cognitive function improves. Something's working.

Richard Lui 22:12

What do you mean by normalization?

Richard Isaacson 22:13

Normalization means to me—everyone has an amount, just like everyone has LDL cholesterol in their blood, or HDL cholesterol or triglycerides. Everyone has an amount. But as we age, our brains age, too, and those numbers change. Normal amyloid levels in the blood suggest that you are not at risk of developing cognitive decline related to Alzheimer's pathology within the next 10 or 12 years, for example. As the amyloid level changes and goes in the wrong direction, you're at increased risk for cognitive decline. We've shown that through lifestyle interventions, behavior change, drug treatment for modifiable risk factors, treating cholesterol, diabetes, especially GLP-1s, all sorts of medical risk factors—I believe Alzheimer's is actually a medical disease. I need to come work for you at the American Medical Association, if you're taking applications, because to me, that's what brain disease is. It's a medical condition that causes changes in brain pathology. We talk about end organ, where I couldn't agree with you more. If your medical conditions aren't well controlled, your kidneys fail, or your eyes fail, or you get numbness in the toes, you have a heart attack. It's the same thing, but with the brain. And the end organ of damage is the brain. So to me, if we improve risk factors, treat risk factors, reduce risk, then we can improve or normalize biological markers that suggest if a person is going to be on or off the road to Alzheimer's.

Richard Lui 23:40

So, you don't need LinkedIn anymore. He just applied for a job.

Joe Betts-LaCroix 23:44

Richard, I think we're violently agreeing here. In that Alzheimer's, dementia is the result of these risk factors going too far, going off the rails, and ultimately the brain starts dysfunctioning. Those are some of the upstream causes, or at least intermediate upstream causes. And if you can restore them to more normal healthy levels, that's what I call reversal. Our first drug that's in a clinical trial right now is specifically for Alzheimer's disease. My dad died of Alzheimer's disease three weeks ago. I wish it had been ready for him, but I literally could not legally dose him with it, unfortunately. But the hope that I would have, and that I do have for it, is that we'll change these risk factors that are inherent in the cells, that are not yet causing disease even. That's the ultimate dream, to go back that far. If it's removing intracellular aggregates by restarting autophagy, then it's reversing something that isn't necessarily showing up yet, but it's reversing something that's a risk factor. If left unchecked, it results in pathology.

Richard Lui 24:53

So prevention related. Tom, I want to move into our next section, which is this discussion about data, which is certainly a topic on many of the panels here at Milken. I'm part of a project at the University of Michigan called CAREGenome. It's a physical primary data set initiative across several schools. You have a lot of data. Tell me about—

Tom Hale 25:16

Not me personally.

Richard Lui 25:17

Yeah. Well, it's right in your pocket, right? But your company does. How much do you have, and do you have enough for what you want to do?

Tom Hale 25:25

The power of data, especially in this age of computing and pattern recognition through machine learning techniques, I think is actually a huge unlock. We're already seeing that in drug discovery. We're seeing that in new compound creation. The ability to have a study of millions of people and understanding what some kind of impact might be on them, I think it's unprecedented. So we are in this incredible moment. Just to answer your question, we have over 30 billion hours of human data. Okay. And that's across every age, gender, skin color, ethnicity, position on the globe, health condition, all the things. And being able to understand that, there's a couple of really powerful impacts. One of which actually relates to research, which is that we can provide populations for study that are narrowly phenotyped against the thing you're trying to fix. So if you're looking for hundreds of thousands of people who might have obstructive sleep apnea—or tens of thousands who are on the pathway to early Alzheimer's because of fragmented sleep—we can identify that phenotype and provide that to the clinical investigators so they can actually do research on that population. Many Oura members raise their hands and say, "I would like to be studied. I have a long-tail illness that is underfunded. I would like to reduce the cost of finding me because I want this to be solved." So that kind of citizen science is one really interesting dimension. The other really interesting dimension is there's patterns in the data that frankly have yet to be discovered. One of the things that we're looking at, going back to blood pressure, is the sort of shape of your blood pressure through the night. People have different dipping—is what it's called—over the course of the night. What happens? Do they dip deeply? Do they not dip? Do they actually rise? And what does that correspond to? And that sort of understanding of that across a large data set is really powerful because all of a sudden science learns something they didn't know before. What does it mean to be a deep dipper? Well, that's quite good. You want to be a deep dipper. What does it mean to be somebody who doesn't? Well, that's not good. You want to understand what that means. So the power of data, properly used, appropriately managed, managed for privacy, managed for security, I think is a game changer because—and we haven't even mentioned AI once this panel. It's been a good 30 minutes—

Richard Lui 27:41

—Yeah.—

Tom Hale 27:41

—which I think is kind of a miracle. But the reality is that things have yet to be uncovered that will be uncovered.

Richard Lui 27:47

Yeah. The blood pressure standing versus sitting versus laying down. My mother, who has an orthostatic issue, it's a difference of about 50 percent.

Tom Hale 27:55

Yeah.

Richard Lui 27:55

And that's a deep dip, right?

Tom Hale 27:58

Yeah.

Richard Lui 27:58

And when you look at the variance, what is the objective?

Tom Hale 28:03

Well—

Richard Lui 28:04

—I'm just curious—

Tom Hale 28:04

—I think it would be to sort of see, is there a predictor—that this kind of pattern might yield? We know actually, going to Alzheimer's for a second, fragmented sleep is a really strong predictor of Alzheimer's. If someone has a long, decades, history of fragmented sleep, they're probably at higher risk for Alzheimer's than not. So seeing that kind of pattern in the data, and then being able to say, "This pattern corresponds to this outcome," it allows systems like Oura Health to make a prediction about your health that is not what's going to happen a minute from now or a week from now—

Richard Lui 28:37

—Sure—

Tom Hale 28:37

—But years from now. And then what can you do about it now that'll have a positive impact on both the health and the wellness of the individual?

Richard Lui 28:45

John, as CEO of the AMA, before that you were at WebMD. At AMA, what? 300,000 physicians that you have as part of your membership? But also talk about your experience adding that in at WebMD. Talking about digital data, you were probably one of the earlier platforms to get data on a large scale before we had large application and adoption of wearables.

John Whyte 29:10

And that's exactly right. And because it's really about that more information typically leads to better health. But it has to be the right information. What I think is really interesting about the discussion, as we talk about data in the context of digital health in wearables, historically, say when I was at WebMD and other places, as physicians we were trained, you look at kind of this population data. Basically look at your demographic data, your age, your sex, your race, and then a few lab data points that we could utilize, particularly cholesterol. And then we make a predictor about your risk of cardiovascular disease or stroke, or even of Alzheimer's. But now with the collection continuously of different data points that we had not thought about, we're actually going to be able to have an opportunity where we're truly going to be able to make a personalized recommendation for you based on your data points instead of this population-based predictions. That's not something we talk enough about, but I think that's one of the most powerful predictors that we will have. And when we want to talk about longevity, I'm not just making it on that population data applied to you, but truly utilizing your continuous personalized data over time, and then I'm going to make recommendations for you.

Richard Lui 30:42

How did WebMD handle digital data related to health?

John Whyte 30:44

And the other issue I'd say—and WebMD was a leader on this—is really issues of privacy—particularly in terms of data and protection. And there still are some bad apples out there. Much of it relates around people forget, kind of in the weeds of HIPAA, of what's a covered entity. Most of these tools that we're talking about, they're not covered entities. And basically what that means—you should have no expectation of privacy of your data. But Richard, I'll say there are some generational differences, I find. I find younger patients—and up until seven months ago, I still saw patients, they're willing to put everything in generative AI tools. And the kind of response is, "Well, what's the harm?" It's like, your health is some of your most sensitive data, and you're just willing to upload it to get a recommendation. So that's something that we have to think about. But back to your point—

Richard Lui 31:40

—Yeah—

John Whyte 31:40

—I think how we think of data today is going to be drastically different in just three to four years, because of the ability to collect these new data points continuously.

Richard Lui 31:52

Joe, you've got three things happening, big things happening at the same time. Yes. And don't go through all of them necessarily, because they're very, very important. More importantly, when it comes to data, how do you manage? What's your philosophy of managing data around clinical trials, around the data that you need to move these three projects forward? What's your philosophy?

Joe Betts-LaCroix 32:18

There's so many classes of data in that respect. There's the scientific data that motivated the creation of that program in the first place. There's the pre-clinical data that we develop in our labs. We have 90 brilliant people in California grinding away all day, doing experiments. I think we've done maybe 4,000 experiments now. Then there's data about which patients to select from the population to bring into our clinical trials. There's data generated during the clinical trial. There's blood tests and various kinds of assays performed on the people, and all that data needs to be collected. It's a lot. I would say for all of the stuff before reaching the clinic, the AI coding systems are so amazing now. We just write all of our own internal

software. Well, write is a strong word. We ask one of these magic genies to write it for us. So we have our own internal software suite that does all of our data management and computation, and deducing of results called Retro OS. Then once we get to the clinic, it gets kind of gummed up. And so far in our first clinical trial, this has been managed by these legacy—I would say, I call them fear-based software suites, where there are these entrenched providers that have been approved by health authorities, and follow these certain sets of complicated regulations, like 21 CFR in the US. And they charge ridiculous quantities of money for doing essentially nothing. But they work. It's great. But why—to use something that I would pay \$10 for if it were something doing a similar amount of heavy lifting, just in the normal day-to-day sphere—am I paying \$100,000 during a few months of a clinical trial? So I'm damn well determined to, in our next clinical trial, to take that on ourselves.

Richard Lui 34:42

Got it.

Joe Betts-LaCroix 34:43

It's going to be a heavy lift, but—

Richard Lui 34:42

—Very quickly, give me the percentage number, just roughly, that you believe—you were talking about generative AI and some of the LLM-empowered tools they're using right now in your clinical trials and managing data. How much has it sped up your ability? 5 percent? 90 percent? What number would you roughly tell us?

Joe Betts-LaCroix 35:04

Right now, it's feeling like about double.

Richard Lui 35:07

About double. Two X.

Joe Betts-LaCroix 35:08

I mean, we're—we're a pretty AI native crew. Our company is seed funded by Sam Altman, and we're—

Richard Lui 35:19

—Who's he?

Joe Betts-LaCroix 35:23

Let me ask ChatGPT.

Richard Lui 35:23

Yeah. Just, yeah. Ask Claude.

Joe Betts-LaCroix 35:28

And we've done very close research collaborations with OpenAI directly, creating new models that can generate completely new proteins, which the world really hasn't been able to do before, and that kind of thing. So—

Richard Lui 35:40

—About 10 times

Joe Betts-LaCroix 35:40

—in some respects, just day-to-day life, I would say it probably doubles our productivity right now. But obviously going to increase as we have scientist agents that we can let loose on problem.

Richard Lui 35:50

Yeah.

Joe Betts-LaCroix 35:51

But from a scientific development perspective, there are a couple of research programs we have now where they just wouldn't be there if we couldn't generate our new proteins.

Richard Lui 36:02

Got it.

Joe Betts-LaCroix 36:02

So the ratio is kind of infinite.

Richard Lui 36:04

Right. Sam, I was just kidding, by the way. Alright, I'm going to move into investments and breakthroughs. Let's say I'm the managing director of a \$1 billion fund. I'm coming to you. Where should we invest, and where would you invest in terms of breakthroughs in longevity and aging? Carina, I was going to ask you. Oh, Tom, go ahead. Where would you go?

Tom Hale 36:29

Well, I was going to say, we're heavily invested in a pharmaceutical, and it's a great one because it's free and it's universally available. It's called DWYMTY. DWYMTY is, like most pharmaceuticals, they've run out of vowels, so they have to use all consonants in the name.

Richard Lui 36:45

Right.

Tom Hale 36:29

But what it is, it's actually understanding that the greatest and most effective tool for longevity is to do what your mother told you—DWYMTY. Which is basically a recognition that if you sleep well, eat well, avoid stress or manage stress well, you exercise, you move your body, you have social connection—these are the things that, across the broadest population, for the least amount of cost, are going to have the biggest impact. So I think I'm a proponent of this, but it is hard because behavior change is the biggest part of this puzzle. It's why prevention, which we've known about for decades in medical science, is still so hard to accomplish.

Richard Lui 37:25

So this would be an awareness training program across—

Tom Hale 37:27

No, I think—

Richard Lui 37:27

—various levels of society?

Tom Hale 37:29

—I think actually AI plays a role because AI is where people are going and saying, "What's going on with me?"

Richard Lui 37:33

Right.

Tom Hale 37:34

"I've got this rash," whatever. So there's this opportunity for education there.

Richard Lui 37:37

Got it.

Tom Hale 37:37

But I think there's the opportunity for people to be held accountable. I think one of the things that wearables do is they sort of give you a little bit of a push that says, "Hey, you should do this," or, "You shouldn't do that." And that accountability, it's actually the role that the clinician usually plays. "Hey, if you don't stop drinking, smoking, and staying out all night, you're going to die soon."

Richard Lui 37:55

We're going to get to your questions. Thank you all who have put it into the app. We are going to get to that shortly. Carina, a billion dollars. I'm running the fund. In 60 seconds, where would you invest? What's your suggestion to me?

Carina Kern 38:07

Yeah. So I tell you two things. First, Swiss army knife therapeutics, as I like to call them. Right? In other words, this paradigm shift where you're not just trying to develop a single drug for a single disease. If you want to move the dial, you need to identify a means to target multiple diseases simultaneously.

Richard Lui 37:37

Two, at least?

Carina Kern 38:28

The second point—

Richard Lui 38:29

—Would you say two? What's multiple? Two or five or ten?

Carina Kern 38:32

Multiple would be, well, think of how many age-related diseases you have. How many would you need to really move the dial?

Richard Lui 38:39

Yeah.

Carina Kern 38:39

I would say a good number, taking necrosis as an example, list the diseases. And we have done extensive reviews on this, from neurodegeneration, cardiovascular disease, liver disease, kidney disease—the list goes on. Right?

Richard Lui 38:52

The reason why I ask is I know as you start to add to that, it gets more complex. That's why I was asking that. The second investment space that I should look at.

Carina Kern 39:00

Well, less an—well, an investment space, but also a warning, right?

Richard Lui 39:06

Yeah, sure.

Carina Kern 39:06

A point I think all of us need to pause and think about for a moment is the fact that to date, not a single therapeutic has been approved by any of the major regulators for aging. Right? Not one. In other words, we don't have the level of scientific data and the level of scientific rigor to get a drug approved for aging, yet. And I think where we need to focus is on therapeutics that are going into clinical trials that are able to generate that bar of rigor and that bar of data because ultimately you follow the data.

Richard Lui 39:46

A billion dollars here, Tom. Where are you going to put it? What should I do with it?

Tom Hale 39:53

Talking to me?

Richard Lui 39:53

Oh, sorry. I meant John. Tom. Please, go ahead.

John Whyte 39:53

So I think part of the challenge is we already know many of the things that we have to do on longevity. We have these areas of the world called the blue zones, where they have the highest number of centenarians. So if I could invest in some blue zones areas, I would do that. Because all too often, again, we're trying to find that magic pill, that magic intervention, where if we want people to live longer, we have to invest in education. We know that people who have higher levels of education, that have graduated high school, live longer. We know that people that have access to fresh fruits and vegetables are going to live longer. We forget those elements. It's to what Tom's point is, people don't want to do what their mother told them to do. They don't want to have behavior change. So I'd want to invest in how we're going to create this behavior change. That's where I think we'll see the greatest advancements in longevity.

Richard Lui 40:52

Richard, 60 seconds.

Richard Isaacson 40:54

The next giant unlock in brain health does not take a billion dollars. We're talking low eight figures, \$12-15 million, for example, which the NIH, or the organization formerly known as the NIH—it's just hard nowadays. And I guess what I would say is if there's someone out there that wants to make a difference, invest in clinical research, where you have clinicians and researchers working together with real-life patients. Brain proteins and proteomics is the next unlock for me.

Richard Lui 41:22

Fantastic. Joe.

Joe Betts-LaCroix 41:24

Well, behavior change is very difficult. I think industries all over the world have spent many, many more than billions of dollars trying to change people's behaviors. I think if I were a VC with a billion dollars, I'd look for a team that is working on some of the highest leverage interventions in the space. So things that are very upstream from all the diseases and—to Carina's point—one making therapeutics that can treat multiple downstream age-related diseases, that operates in a scrappy, cash-efficient manner; that is all passionate about their work, because that gets more productivity and excitement out of them. And, yeah, for whom speed is one of their primary characteristics. So, I think it would probably be best just to invest it in Retro.

Richard Lui 42:33

I want to move now finally to the system itself. The system can be defined in many different ways. I'll let you decide what that might be, in its ability to accept change of breakthroughs in these spaces. If you can give me one to 10, one being not good at all, 10, fantastic and perfect, and then why. If you could do that one to 10. Carina, I'm going to start with you, in 60 seconds, please.

Carina Kern 42:59

Just repeat the question. So, one to 10—

Richard Lui 43:02

—One is it's not ready, the system, whichever way you define it, not good. It could be a governmental agency, it could be a societal issue, it could be a local space. Ten means it's perfect. It is absolutely ready for breakthroughs. It's ready to go. So tell me about systems and their readiness for breakthroughs in longevity and aging.

Carina Kern 43:24

So I would say around a three.

Richard Lui 43:26

Three.

Carina Kern 43:24

And the reason I would say this is, put it like this: a paradigm shift is coming and are the different sectors, including the financial world, is it prepared? Right? Are the various sectors prepared? And if you speak with pension funds, if you speak with insurance companies, if you speak with various different industries, what you find is they're relying on data we have generated that is in effect looking in the rear view mirror.

Richard Lui 43:58

Yeah.

Carina Kern 43:59

And the reason for that is we have never had a therapeutic, we have never had an intervention that can have a significant increase when it comes to human health span and lifespan. All we've had is incremental beneficial effects. If you have a true Swiss army knife therapeutic that's able to take out multiple different diseases by hitting a key note, say like necrosis, then you're going to see two things. First, you will see a large increase in health span and lifespan. But significantly, that increase is going to be rapid. And if you're not prepared for that, there are going to be risks. But also, don't get me wrong, because there are going to be vast benefits as well. And this isn't just the benefits in terms of, for instance, the vast burden on healthcare systems. You see, if you truly increase health span and lifespan, it's not going to be individuals that are living longer but decrepit. Instead, what you are going to find is potentially an opportunity, what you could even call a window of economic opportunity, similar to ones we've had in the past, where we've managed to increase the percentage of economically active.

Richard Lui 45:18

Right.

Carina Kern 45:19

Right? Which is central to productivity.

Richard Lui 45:22

Richard, 60 seconds, one to ten.

Richard Isaacson 45:28

3.726.

Richard Lui 45:29

There we go. Excellent precision. [Crosstalk]

Richard Isaacson 45:33

Yeah. And we were like 3.1 last Milken.

Richard Lui 45:36

Rounded up four.

Richard Isaacson 45:37

Yeah. So, there's just so much broken, but I want to end this on a good note. Awareness about brain health is, I think, step one. But then when a person that's interested in brain health or prevention goes to their physician, they're stuck. And they're stuck because the system is just still broken. There are no diagnostic codes to reduce risk for Alzheimer's. There are diagnostic codes to treat medical risk factors. And we started the first Alzheimer's prevention clinic in the country in 2013, and we struggled because of this. So I think what I would say is, the customers are supposed to drive the business, right? Well, the patients in this sense are the customers, and they're going to their clinicians, but I have empathy for the clinicians.

They get 15 minutes to do all these different modifiable factors that one day we'll have a drug to hit across the multiple risk factors, great. But until that time, it's bespoke and it's personalized and it takes time.

Richard Lui 46:35

Joe, 60 seconds, one to 10, and what is it that you'd improve to get the number higher in terms of systems?

Joe Betts-LaCroix 46:43

Well, I'm going to obviate the second part of your question because I think right now we're at a 10, and that's because there's nothing in the way now other than the breakthroughs. The regulators are fine. We've already had two clinical trials approved by US FDA for aging, which are essentially basket trials of age-related diseases. We have what you would say an Overton window in the population that compared to where it was when I started around 2010, 16 years ago, in this field people were like, "Mm, aging, that's for these weird kind of fringe science fiction strange people." And now we're ready for it. You can feel it everywhere. You say longevity, and they're like, "Oh, which one? How does it work?" So the regulators are ready, the people are ready, and the science is just there's so much ready to try to take through. I would also say that the path to clinic works now because, only if you work on mechanisms that are upstream of age-related disease, to your point, then that means there are multiple downstream diseases, which means you can pick one as a proxy to work on, to go through regulations even, and make measurements.

Richard Lui 48:13

60 seconds.

John Whyte 48:14

Sure. I was going to give it a six, but because you gave it a 10, which I vigorously disagree with, I'm going to give it a four.

Richard Lui 48:21

That's why we put you on opposite ends. Yeah.

John Whyte 48:22

Because I don't think the regulators are at the right place. I don't think it's the best FDA at this time in the review of data, the review of science, and having the best folks. I think the system, in terms of the

healthcare system, is set up that doctors aren't training to focus on prevention. They're not interested in doing prevention, and it's not incentivized to do that. I'll end with the reason why I think it's going to be so hard is, we're too focused on where the puck is instead of where it's going. We want to change the current system instead of thinking of the ideal system and create it there. Everybody wants to focus on the EHR. We should be focused on what is the system without the current EHR that allows patients to have better outcomes.

Richard Lui 49:02

Okay. Tom?

Tom Hale 49:04

So I'm going to say six, and I'm going to say a six because actually there's a really interesting dynamic of agency. We talked about democratizing it. We talked a lot about the social determinants of health. There's actually the social determinants of longevity. Right now, information is more accessible than ever before. Tools like Oura, not freely available to every person on the planet, but are available to people. And the agency that people have in taking control of their health journey, I think that actually is something that's moving us forward. We're better educated than ever before. More people are reading scientific papers and understanding them. More people have access to more things. We've got more experimental ways to provide experimental therapies to people than ever before. I think we're at a really interesting moment. I think it might be a moment of creative destruction. We talk about the old system constraining us. I think the new system, what we need is a way to understand what health is versus what sickness is. Today, reimbursement, the system is all about, let me put you in a box for what illness you have, and then I could give you a therapeutic. I actually think doctors are willing to accept it. And I think if we were able to propagate a definition of what health is, you might be able to find that the insurers would say, "You know what? It's in our interest to keep you healthy. Let's do it."

Richard Lui 50:12

So our highly reviewed study and poll here came out to an average of six, altogether. So above water, above the midpoint. I want to go to some of your questions, and I thank you all for putting them in. First off, it reads, "How should investors and consumers tell the difference between longevity science that's ready for broad application and what's still emerging or speculative?" We'll take two responses very quickly. Go ahead.

Tom Hale 50:37

If it's on Instagram, I wouldn't follow it.

Richard Lui 50:41

Good call.

Joe Betts-LaCroix 50:43

I'd say it's based on evidence. It depends on how they're talking about it. If they're saying, "This increases vitality, and we've shown that the toenails grow faster on laboratory rats," or whatever, it's like, okay, but so what? What is the actual evidence that this will make you healthier? And if it just stays kind of hand-wavy like that, they're probably trying to make \$1,000 off of you.

Carina Kern 51:04

Yeah, I think just to add to that, it's really important when you talk about aging and longevity to talk about tangible degenerative changes, not talk about it in abstract, fluffy terms. And I think exactly as you say, you follow the data and you see those tangible changes.

Richard Lui 51:20

Let me add to the questions. "How do we make access to all of the novel aging innovations accessible and affordable, especially to marginalized populations who oftentimes lack access to healthcare?"

Joe Betts-LaCroix 51:34

I would call that the biotech social contract. First of all, it depends on what you're referring to by these. If you're getting red light therapy or a hyperbaric chamber or something, I don't think the evidence is very strong on those yet, so I wouldn't necessarily worry about distributing them to all socioeconomic regions of the planet. But for some of the most amazing therapeutics we've generated as a civilization, they always start off in expensive and being distributed in developed countries that can actually afford to produce them, because it's extremely expensive to make a medicine. And then they get distributed more widely. The costs fall. Eventually, they go off patent, and then you can go to a pharmacy in Nigeria and get an antibiotic prescription for 18 cents. And it'll save your life. That is the biotech social contract. That's how it cascades.

Richard Lui 52:33

Any other quick reactions? Go ahead. You didn't go yet.

John Whyte 52:37

I think we have to democratize access to personalized data. I do think insurers actually should cover wearables that have demonstrated certain thresholds. Otherwise, you can make the argument that we're only making the healthy healthier. So I think insurers should think about covering some of these services.

Richard Lui 52:54

Next question. "For those on the panel focused more on aging as a whole as opposed to a specific disease, should we pivot from all of the Alzheimer's research, or is your work complementary to that work and other more specialized work?" Richard, I'm actually going to go to you on this one.

Richard Isaacson 53:07

Well, what is aging and geroscience versus preventive health versus longevity versus cognitive health versus—the list goes on and on. I think, thinking broadly and stepping back, preventive health to me is a path towards longevity. Modifying risk factors for medical conditions extends lifespan, which is longevity. It improves health span, which is the quality that we have based on our medical conditions, and forestalls and probably improves brain span, which is cognitive health. So to me, they're all interrelated. There's multiple legs of the stool, and I'm not a reductionist. I think we can think broadly in these terms.

Richard Lui 53:51

Yeah. They're all a lot of overlaps. Carina, go quickly. I think you wanted to say something?

Carina Kern 53:56

Well, that was in the last question. All I was going to add to that one was, when you talk about the cost of a longevity intervention, and I think you need to flip that and think of the cost of aging itself and all of these debilitating diseases that ultimately end up robbing us of our human dignity. I mentioned kidney disease. 24 percent of Medicare's annual budget. Put that into perspective. It's five times the annual budget of NASA, right? So just going back to the previous one, I think it's a question of how much can we actually save from these.

Richard Lui 54:31

Joe, is it an either/or on aging and Alzheimer's, or they're all in the same boat together?

Joe Betts-LaCroix 54:36

Our first therapeutic that's currently in clinical trial is—we're going to be taking it up specifically for Alzheimer's. But it is a more general mechanism than that and can apply to other forms of neurodegeneration. So I think it depends on where you're trying to intervene. If in a typical biotherapeutic pharma mindset, you're going specifically for the disease, and okay, there are these tau tangles that are a hallmark of this particular disease, and we're going to try to somehow anti-tau it, you're going to end up with a pretty specific therapeutic. But if you're going upstream and saying, all of these neurodegenerative diseases involve accumulating toxic products over time, then you could have an effect on Parkinson's—

Richard Lui 55:26

—Is it—

Joe Betts-LaCroix 55:26

—Lewy body dementia, and all the—

Richard Lui 55:28

—Is it fair to say then, sometimes funding should be redirected from Alzheimer's into aging? That was the question.

Joe Betts-LaCroix 55:34

Well—

Richard Lui 55:34

—From the audience.

Joe Betts-LaCroix 55:35

—I think it depends on how mutually exclusive they are. I think that the highest leverage funding is going to be as far upstream as you can bear to move it. So if you can fund something that also affects Alzheimer's as well as other diseases...

Richard Lui 55:49

Alright. Very quickly from each of the panelists here, name it, and then one sentence as to why. For everyone on the panel, what is one supplement we should all take and one surprising behavior we should all practice to extend our lifespan? Pick one or the other, the practice or the supplement. Who would like to go first? Okay. Joe, beat you to it there, Tom.

Joe Betts-LaCroix 56:10

The best therapeutic we have for aging right now is, most people hate it, but, is exercise.

Richard Lui 56:18

That's a supplement. That's a practice.

Unidentified speaker 56:20

Every day.

Richard Lui 56:20

And a supplement. Go ahead, Tom.

Tom Hale 56:23

Mine is to set an alarm clock for when you go to bed. And the reason why is that actually regularity in sleep is actually a really profound predictor of the quality of your sleep, which then has all these downstream effects. So set an alarm clock for when you want to go to bed.

Richard Lui 56:36

Okay, Carina?

Carina Kern 56:37

Okay. So again, just to reiterate, no drug has been approved for aging, right? So the best you have is lifestyle choices and whether or not you think that's going to extend lifespan. Certainly, what we do know

is poor lifestyle choices can accelerate age-related change and degeneration. So for that reason, definitely lifestyle.

Richard Lui 56:59

Okay. Thank you. Richard?

Richard Isaacson 57:01

That question's broken. I'm sorry. You can't ask for what's the one—come on, people. You've been to how many of these longevity things? It's not about one thing. It's everyone needs something different. And if we're expecting a magic pill, yes, supplements may help in people that are deficient in certain things. And if there's one thing, if you're going to force me, as we age, it's harder to absorb B vitamins, so yeah, maybe a B complex vitamin. But, yeah, it's the wrong, broken question.

Richard Lui 57:26

Yeah.

John Whyte 57:26

The only thing I'd add to that with the B complex vitamin is vitamin D for many people.

Richard Isaacson 57:32

Yeah, vitamin D.

John Whyte 57:32

But the other element I'd add to follow up on your point is lab tests, particularly as it relates around lipids. We've seen more and more data about the impact on lipids, on managing both dementia as well as cardiovascular disease.

Richard Lui 57:48

Fantastic. And my final question for the panelists here is when we think about breakthroughs in longevity, as well as aging, how do you feel about the next five years from where you sit, and the experience? All of you bringing, as I said earlier, your big brains to the conversation. How do you feel about the next five years, in a sentence? And we only have 41 seconds to do that. And I'll start with you.

John Whyte 58:12

Yeah. I'm going to give it a nine. You didn't ask, but I feel very excited.

Richard Lui 58:16

A nine. Okay, you're bullish.

John Whyte 58:16

A nine. I feel very excited about the possibilities we have, particularly over the next five years.

Richard Isaacson 58:21

Yeah. Without capital constraints, I'm a ten. With capital constraints, I'm a 5.63.

Richard Lui 58:26

Hmm. Carina?

Carina Kern 58:29

So very excited because hopefully we can bring that change and for the betterment of humanity as a whole.

Richard Lui 58:35

Tom?

Tom Hale 58:35

I'm optimistic because we can cover a massive population and not practice our medicine on the averages.

Joe Betts-LaCroix 58:42

Super excited because we will already have one approved therapeutic on the market and a total of four that'll be in human testing. So it's going to be good.

Richard Lui 58:52

Thanks to our audience and thank you to our panel. So, a warm round of applause. Thank you.

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